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EFFECTS OF GROWTH HORMONE ON FRACTURES AND QUALITY-OF-LIFE

In a previous study, women with postmenopausal osteoporosis, treated for three years with growth hormone (GH), were found to have increased bone mineral density (BMD) at one year after treatment termination. This study reviewed the BMD data and fractures, after 10 years, of women who had received growth hormone for at least three years.

This randomized, double-blind, placebo-controlled trial involved 80 postmenopausal women with osteoporosis. All women received 750 mg of calcium and 400 units of vitamin D and were randomized to receive either recombinant human GH at one unit per day, two point five units per day, or a placebo. The GH injections continued for three years. All women were followed for 10 years. The subjects were invited for reevaluation after a mean of 12 years' follow-up at the age of 67 to 76 years. At follow-up, measurements included body composition, bone measurements, quantitative ultrasound measurements, lifestyle factors and quality-of-life measures. A random population sample of 2,400 men and women served as population controls.

Before treatment, 56% of the women in the treatment group had sustained a fracture, while 28% sustained fractures in the 10 years of the study ($p=0.0003$). In the control group, three percent had sustained a fracture before the study and 32% sustained a fracture in the 10 years of the study ($p=0.0008$). At 10 years, BMD had decreased to similar levels as before treatment, but was still higher in the 2.5 U GH group than in the other two groups.

Conclusion: This long-term follow-up study of postmenopausal women with osteoporosis found that growth hormone treatment can

reduce the incidence of fracture seven years after treatment cessation.

Krantz, E., et al. Effect of Growth Hormone Treatment on Fractures and Quality-Of-Life in Postmenopausal Osteoporosis: A 10-Year Follow-Up Study. *The J Clin Endocrin Metab.* 2015, September; 100(9): 3251-3259.

MUSIC TREATMENT FOR DISORDERS OF CONSCIOUSNESS

Patients with disorders of consciousness (DOC), presenting as being in a comatose, vegetative or minimally conscious state, have demonstrated some ability to recognize and respond to external stimuli. This study evaluated the effect of music on the cerebral functions of patients with DOC.

Thirteen patients with DOC, and thirteen healthy controls were included. Each subject was read 10 sequences of 64 first names, including the subject's own first name (SON) and other first names (OFNs) either with or without having listened to their preferred music. An electroencephalogram (EEG) acquisition was obtained to determine the cerebral response to the names, comparing the music and the non-music conditions.

Seven patients showed a discriminative response (N2 and/or P3) to the SON, as compared with the OFNs. For all of them, the discriminative response was greater in the music condition as compared to the non-music condition ($p \leq 0.01$). Those seven gained supplementary behavioral responses in the following six months. The six patients with no response to the SON in either condition remained in the same state or died within six months.

Conclusion: This study of patients with disorders of consciousness suggests that having a patient listen to their preferred

music may improve residual cognitive function.

Castro, M., et al. Boosting Cognition with Music in Patients with Disorders of Consciousness. *Neurorehab Neural Repair.* 2015, September; 29 (8): 734-742.

AUTOLOGOUS PLATELET RICH GEL FOR REFRACTORY CUTANEOUS ULCERS

Diabetic ulcers are a serious clinical problem and are often difficult to treat. As the microenvironment of these ulcers suggests a deficiency of growth factors, this study explored the effect of autologous platelet rich gel (APG) for the treatment of chronic, refractory cutaneous ulcers in a group of diabetic patients.

This prospective, randomized, controlled trial included adult diabetic patients with cutaneous ulcers resistant to standard treatments. The participants were randomized to either a treatment group, receiving standard treatment plus topical APG, or a control group receiving standard treatment plus a placebo APG. In the treatment group, the APG was prepared and then mixed with thrombin and calcium gluconate before placement in the wound bed. The dressing in both groups was changed every three days. Both groups were followed for 12 weeks, with outcomes including wound healing grades, time to complete healing and healing velocity.

Subjects were 117 patients with an average age of 62.8 years. Intention to treat analysis revealed that the percentages of patients with complete healing, defined as healing grade 1, were 84.8% in the APG group and 69% in the control group. The mean times to healing were 36 days for the APG group and 45 days for the control group. The APG group had faster healing velocities than did the control group ($p=0.02$). No side

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effects were seen with APG application.

Conclusion: This prospective, randomized, controlled study of patients with chronic, refractory, diabetic wound ulcers found that a topical application of autologous platelet rich gel can accelerate healing.

Li, L., et al. Autologous Platelet Rich Gel for Treatment of Diabetic, Chronic Refractory Cutaneous Ulcers: A Prospective, Randomized, Clinical Trial. **Wound Repair Regen.** 2015, July/August; 23(4): 495-505.

COGNITIVE IMPAIRMENT AFTER SUCCESSFUL STROKE RECOVERY

Cognitive impairment is a common consequence of stroke. Traditionally, clinical outcomes in stroke studies have been measured with assessments of physical recovery or focal clinical syndromes such as aphasia and neglect. This study investigated the prevalence of domain-specific cognitive impairments three months after ischemic stroke.

In the Helsinki Stroke Aging Memory Study, 486 patients consecutively admitted to the acute care unit of the Helsinki University hospital were examined three months after ischemic stroke. All patients underwent extensive clinical and neuropsychological assessments, with impairment in nine cognitive domains determined according to age appropriate normative data. Functional disability was evaluated with the modified Rankin scale (mRS) at three and 15 months after stroke.

At three months, 80% of the patients remained impaired in at least one cognitive domain, including 20% in one domain, 14% in two domains and 50% in multiple domains. The most frequent impairments were memory, visuoconstructional and spatial functions, and executive functions and attention. In patients with excellent clinical recovery three months post-stroke, as determined by a mRS score of zero to one, some cognitive impairment was found in 71% of the cases.

Conclusion: This study of patients hospitalized with stroke found that cognitive impairment is prevalent in stroke survivors, even

among those with successful clinical recovery.

Jokinen, H., et al. Post-Stroke Cognitive Impairment Is Common Even after Successful Clinical Recovery. **Euro J Neurol.** 2015, June; 22(9):1288-1294.

FUNCTIONAL EFFECTS OF FAMPRIDINE FOR MULTIPLE SCLEROSIS

The potassium channel blocker 4-aminopyridine (Fampridine) has been found to improve nerve conduction in demyelinating neurons, and has been approved by the European Medicines Agency for the treatment of patients with Multiple Sclerosis (MS) with walking disability. This study investigated the benefits of Fampridine SR on parameters of gait, fatigue and quality-of-life among patients with MS.

This prospective, open label, cohort study enrolled 120 adults with MS. All were assessed for walking with the Timed 25 Foot Walk Test (T25FW), the Two-Minute Walk Test (2MWT) and the Self Perceived Multiple Sclerosis Walking Scale (MSWS-12) at baseline and at 14 days. Those in the treatment group received Fampridine SR, 10 mg twice per day, for 14 days, continuing for three months only among responders (at least 50% improvement by day 14 on one of these tests). Additional assessments included the Nine Hole Peg Test, a self-assessed fatigue visual analogue scale (F-VAS), the Fatigue Severity Scale (FSS), the GAITrite Walkway System for gait parameters and the 12-Item Short Form Health Survey (SF-12). Outcomes were compared between responders and non-responders at day 14.

Of the initial cohort, 112 completed drug treatment and measures at day 14. Of those, 74% were responders, with significant improvements on the T25FW ($p < 10^{-4}$), the 2MWT ($p < 10^{-4}$) and the MSWS - 12 ($p < 10^{-4}$). Responders also demonstrated improvement on the secondary outcomes for hand function ($p < 0.001$), fatigue ($p < 0.001$) and quality-of-life ($p < 0.001$). Findings were sustained at three-month follow-up.

Conclusion: This study of patients with multiple sclerosis found that treatment with Fampridine SR

can improve several parameters of gait, as well as hand function and fatigue.

Allart, E., et al. Sustained Release Fampridine In Multiple Sclerosis: Effects on Gait Parameters, Arm Function, Fatigue and Quality-Of-Life. *J Neurol.* 2015, August; 262: 1936-1945.

SPOUSES OF STROKE SURVIVORS AND LONG-TERM HEALTH-RELATED QUALITY-OF-LIFE

The effect of stroke on spouses as caregivers during the first two years has been well studied, indicating a negative effect on their health-related quality-of-life. Knowledge is limited however concerning this variable at long-term follow-up. This study was designed to explore the health-related quality-of-life of spouses, seven years after stroke onset.

Data on stroke survivors, controls and spouses were collected from a seven year follow-up of the Sahlgrenska Academy Study on Ischemic Stroke (SAHLIS). This study involved 600 consecutively recruited patients with ischemic stroke before the age of 70. From a seven year follow-up, spouses of stroke survivors and spouses of controls were recruited. Health-related quality of life (HRQoL) of spouses was assessed using the short form – 36 questionnaire (SF-36) with eight domains including physical functioning, physical role in bodily pain, and mental health. For stroke survivors, physical impairment was assessed using the National Institute of Health Stroke Scale with global disability assessed by the modified Rankin Scale. Cognitive impairment was assessed with the Mini Mental State Examination (MMSE).

At 7-year follow-up, 299 stroke survivors and 344 controls were available for this study. At follow-up, 16.5% of the stroke survivors had a recurrent stroke. The HRQoL scores showed that the spouses of stroke survivors scored lower on all of the mental domains ($p < 0.001$), physical role ($p = 0.006$), and general health ($p = 0.013$) compared with the spouses of controls.

Conclusion: This study of stroke survivors found that spouses of the survivors experience impaired health-

related quality-of-life even at seven years after the stroke.

Persson, J., et al. Spouses Of Stroke Survivors Report Reduced Health – Related Quality Of Life Even In Long – Term Follow-Up. Results from the Sahlgrenska Academy Study on Ischemic Stroke. *Stroke.* 2015, September; 46:2584-2590.

BETA-ADRENERGIC ANTAGONISTS AND IN-HOSPITAL STROKE MORTALITY

Animal studies have demonstrated that pretreatment with beta blockers can reduce infarction size after stroke. This study was designed to determine whether the use of β -adrenergic antagonists (β -blockers) before admission and during hospitalization can affect mortality after stroke.

This retrospective study collected data from the Joint Commission-Certified Comprehensive Stroke Center's clinical database. Subjects were 18 years of age or older, all admitted for acute ischemic stroke between September of 2005 and December of 2011. β -blocker exposure was defined as the patient's taking β -adrenergic antagonist at stroke onset and during the first three days of hospitalization. These patients were compared with those without such exposure. Variables associated with mortality or β -blocker use were included in the multivariable model.

Of the participants, 1,392 received home β -blocker medication, 721 received in-hospital β -blocker medication and 436 received both home and inpatient β -blocker medication. Multivariable analysis, performed after adjusting for differences between the groups on important variables, revealed that the use of β -blockers both at home and during the first three days of hospitalization was independently associated with reduced inpatient mortality ($p < 0.05$). No significant difference was seen in mortality rates between those using β -blocker only at home or only during the first three days of hospitalization.

Conclusion: This study found that continuation of home β -adrenergic antagonist medication during the first three days after hospitalization with ischemic stroke is

associated with decreased inpatient mortality.

Phelan, C., et al. Effect of β -Adrenergic Antagonist on in-Hospital Mortality after Ischemic Stroke. *J Stroke Cerebrovasc Dis.* 2015, September; 24(9): 1998-2004.

EXERCISE AND PATELLAR CARTILAGE IN WOMEN WITH MILD KNEE OSTEOARTHRITIS

Knee osteoarthritis (OA) is characterized by a loss of, and degeneration of, hyaline cartilage. This study investigated the effects of 12 months of supervised aerobic/step aerobic exercise program on patellar cartilage.

This 12-month, randomized, controlled trial included postmenopausal women with knee pain on most days, and grade one to two Kellgren-Lawrence radiographic tibiofemoral joint OA. The subjects were randomized to one of two experimental arms; an aerobic/step aerobic training group or a non-training control group.

The exercise group performed 55-minute sessions of an aerobic and step aerobic jumping exercise program three times per week, progressing in intensity for 12 months. The control group was asked to maintain their usual activities. Daily activity of all participants was measured with an accelerometer. Cartilage measurements were made through MRI, with the secondary outcomes including muscle force, muscle power and cardiorespiratory fitness.

At 12-month follow-up, the full patellar cartilage T2 relaxation time values had improved in the exercise group, suggesting improved cartilage quality ($p = 0.018$). Positive effects were noted in the lateral and medial segments of the joint, as well as in the total deep zone ($p = 0.013$). While the exercise group showed better improvement in pain, OA symptoms, and quality-of-life scores, the difference between the exercise and control groups did not reach statistical significance.

Conclusion: This randomized, controlled, high-impact exercise trial involving postmenopausal women with mild osteoarthritis of the knee found that T2 relaxation time decreased, indicating improved

patellar cartilage quality, after 12 months of exercise.

Koli, J., et al. Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. *Med Science in Sports Exer.* 2015, Sept; 47(9): 1767-1774.

ISOMETRIC EXERCISE FOR PATELLAR TENDINOPATHY

For patients with patellar tendinopathy (PT), eccentric exercise is commonly prescribed. However, this exercise is often painful to complete. This study was designed to determine whether isotonic or isometric exercise can induce pain relief in patients with PT.

This single blind, randomized, crossover trial included six, male volleyball athletes with PT. At baseline, tendon pain and quadriceps strength were tested. The single leg decline squat (SLDS) was used as a primary outcome measure. The athletes were asked to complete a Victorian Institute of Sport Assessment-Patellar Tendon (VISA-P) questionnaire of patellar tendon pain and function.

During a maximum voluntary isometric contraction (MVIC), the athletes completed five efforts of 45 seconds each, with a two-minute recovery between sets. During an isotonic condition, the subjects exercised at 70% of their one repetition maximum, with five sets of 45 seconds duration. Baseline measures of corticospinal excitability and short interval intracortical inhibition were obtained by transcranial magnetic stimulation.

At baseline, the participants had a mean VISA-P of 52.8, with isometric exercise reducing pain on the SLDS from a mean of 7/10 to 0.17/10, with the reduction sustained at 45 minutes ($p < 0.001$). During the isotonic condition, pain on the SLDS was reduced from 6.3/10 to 3.75/10 ($p = 0.04$), although this reduction was not sustained at 45 minutes. A significant increase in MVIC torque was observed immediately after isometric intervention ($p < 0.001$), and was sustained at 45 minutes after intervention, that was not significant in the isotonic group.

Conclusion: This small study of volleyball athletes with patella tendinopathy found that a single bout of isometric contractions can result in

immediate pain relief lasting for at least 45 minutes, with a concurrent increase in maximal voluntary isometric contraction.

Rio, E., et al. Isometric Exercise Induces Analgesia and Reduces Inhibition in Patellar Tendinopathy *Br J Sp Med.* 2015, October; 49(19): 1277-1283.

HIGH-VOLUME INJECTION FOR RECALCITRANT PATELLAR TENDINOPATHY

Preliminary studies of patients with recalcitrant tendinopathy and evidence of neovascularization have suggested that high-volume, image-guided injection (HVIGI) may decrease pain and improve functional activities. This study was designed to determine the short-term effect of HVIGI on patients with recalcitrant tendinopathy of the patellar tendon.

Patients were included if they had a clinical and imaging diagnosis of patellar tendinopathy, unresponsive to three months of eccentric exercise and other common treatments. All thirty-two participants underwent an ultrasound guided bolus of 40 ml of normal saline, mixed with 10 ml of 0.5% bupivacaine and 62,500 IU of apoprotein, placed posterior to the patellar tendon, immediately adjacent to the area of neovascularization. At 15 months' follow-up, an independent observer assessed the patients on the VAS scale of pain and the Victorian Institute of Sport Assessment-Patellar Tendon (VISA-P) questionnaire. The subjects were asked to rate the results of the procedure according to the presence of pain and to return to their sporting activity.

In all patients, neovascularization disappeared immediately after the injection. At last follow-up, the mean VISA-P, pain VAS and function VAS scores had significantly improved as compared with baseline. Of the 32 active patients, 72% return to sport at the same level as before the onset of symptoms. In twenty-five cases a further injection was performed at an average of 2.7 weeks. At final follow-up, 23 of 32 (72%) athletes were classified as good to excellent, and nine as poor.

Conclusion: This study of patients with recalcitrant patellar tendinopathy found that high-volume image guided injections can improve

pain and function scores, with improved return to sport.

Maffulli, N., et al. High-Volume, Image-Guided Injection for Recalcitrant Patellar Tendinopathy in Athletes. *Clin J Sp Med.* 2015 DOI: 10.1097/JSM.0000000000000242

SPLINTING FOR DE QUERVAIN'S TENDINOPATHY

Thumb spica splints are frequently prescribed for the nonoperative management of de Quervain's tendinopathy. However, no consensus has been reached concerning the best splint-wear protocol. This study reviewed the outcomes of full-time versus as desired splint wear.

This prospective, randomized trial included 83 patients diagnosed with de Quervain's tendinopathy. The participants were assigned to either a cohort that was asked to wear the splints at all times or to a group wearing splints as desired. At baseline the patients completed the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire as the primary outcome measure, as well as the Pain Anxiety Symptoms Scale (PASS) to assess anxiety regarding pain, the Center For Epidemiologic Studies Depression (CES-D) scale to measure depressive symptoms, the Pain Catastrophizing Scale (PCS) to measure a set of maladaptive cognitive conditions and the pain Numeric Rating Scale (NRS) to assess pain intensity.

At an average follow-up of 7.5 weeks, no significant differences were noted between the splinting groups in disability ($p = 0.77$), grip strength ($p = 0.82$), pain intensity ($p = 0.36$) or treatment satisfaction ($p = 0.91$). Bivariate analysis revealed that upper extremity debility was significantly related to CES-D ($p = 0.001$), PCS ($p = 0.001$) and PASS ($p = 0.008$) test scores.

Conclusion: This study of patients with de Quervain's tenosynovitis found that full-time splinting is not superior to splinting as needed, and that depressive symptoms are strongly associated with greater disability.

Menendez, M., et al. A Prospective, Randomized, Clinical Trial of Prescription of Full-Time versus as Desired Splint Wear for De

Quervain's Tendinopathy. **Intern Ortho.** 2015, August; 39(8): 1563-1569.

TLSO BRACES AND THORACOLUMBAR BURST FRACTURES

Treatments for thoracolumbar burst fractures often involve early bracing and return to activity. While thoracolumbosacral orthoses (TLSO) are commonly used for this injury, evidence concerning their efficacy is limited. This study compared the outcomes of patients treated with TLSO with those of patients without such immobilization.

This randomized, blinded, controlled trial included 96 patients with isolated burst fractures between T10 and L3. Patients in the TLSO group were placed on strict bed rest until they were fit with the TLSO, which was worn at all times for 10 weeks, except when in bed. Patients in both groups were cautioned to not exceed 90° of hip flexion or to lift more than 5 kg. The primary outcome measure was performance on the Roland Morris Disability Questionnaire (RMDQ) at three months. Secondary outcome measures included the mental and physical component scores of the Short Form-36 (SF-36), pain, satisfaction and kyphosis.

The average RMDQ scores at three months were 6.8 points in the TLSO group and 7.7 points in the non-bracing group. At two-year follow-up, the groups did not differ in RMDQ scores or on any of the secondary outcome measures.

Conclusion: This study of patients with neurologically intact thoracolumbar burst fractures found no difference between those treated with a TLSO brace and those treated without bracing.

Bailey, C., et al. Treatment with or without an Orthosis Is Equivalent for Thoracolumbar Burst Fractures. **J Bone Joint Surg (Am).** 2015, August 19; 97(16): 1374.

STAY ACTIVE ADVICE FOR SEVERE LOW BACK PAIN

As substantial evidence suggests that physical activity is beneficial for most musculoskeletal conditions, including low back pain (LBP), advice

for the patient to stay active is common. This study reviewed the effect of advice concerning activity among patients with LBP.

Subjects were 109 patients with acute, severe LBP of less than 48 hours' duration. At baseline, the patients underwent an extensive physical examination including radiographic imaging, and completed a battery of questionnaires, including questions concerning acute LBP, and a seven-day diary recording activity and pain. All were provided a digital pedometer.

The subjects randomized to the stay active (SA) group were advised to remain as physically active as possible, despite LBP. Those in an adjusted activity (AA) group were advised to adjust activity according to pain. For the 99 subjects included in the final analysis, the step count increased only in the SA group, with step counts of 9,865 steps on the last day of follow-up in the SA group and 6,609 in the AA group ($p=0.008$). While the SA group showed higher pain intensity and a slower decrease in pain intensity compared to the AA group, no significant difference was found between the groups in pain intensity change trajectory.

Conclusion: This study of patients with acute, severe low back pain (LBP) found that those advised to stay active despite LBP increased their activity more than those advised to adjust activity by pain level, with slightly higher, although insignificant differences in pain.

Olay-Contreras, P., et al. The Effect of the Stay Active Advice on Physical Activity and on the Course of Acute, Severe Low Back Pain. **BMC Sp Sci Med Rehab.** 2015; 7: 19 doi:10.1186/s13102-015-0013-x

STRESS INTENSITY AND MIGRAINE FREQUENCY

Patients with headache frequently report stress to be one of their main activators. However, evidence is lacking concerning the association between stress and headache frequency. This study investigated the association between stress intensity and headache frequency.

The Longitudinal Population-Based German Headache Consortium (GHC) involved 18,000 men and women, ages 18 to 65 years of age, who were randomly selected

from three German cities. Questionnaires were sent to the subjects to assess stress using a visual analogue scale (VAS). Questions were posed concerning the number of days associated with headache and the frequency of intake of acute pain medication. The participants were also queried regarding stress level, using a 100-point VAS. The subjects' headaches were classified through questionnaires as tension type headaches, migraines, migraines with coexisting tension type headaches, unclassified headache or no headache.

Of the 5,159 participants, tension type headaches were reported by 31%, migraine by 14% and migraine associated with tension type headache by 10.6%. An increase in headache frequency was positively correlated with increasing stress intensity, independent of headache subtype. The highest effects were observed in participants with tension type headaches, with each 10-point increase in stress intensity associated with a 6.4% increase in headache days per month.

Conclusion: This longitudinal population-based cohort study demonstrates that increasing stress is associated with increasing headache days for all patients with headache subtypes. This was particularly pronounced in participants with tension type headaches.

Schramm, S., et al. The Association between Stress and Headache: A Longitudinal, Population-Based Study. **Cephalgia.** 2015, September; 35(10): 853-863.

INFLAMMATORY MARKERS AND DEPRESSION AFTER BRAIN INJURY

Many patients experience depression after traumatic brain injury (TBI). Previous studies have demonstrated that non-responders to antidepressant medications often have increased inflammatory profiles. This study investigated whether inflammatory profiles, obtained during the acute phase of injury, can predict posttraumatic depression (PTD) symptomatology after TBI.

This prospective study included patients admitted to a level I trauma center with moderate to severe TBI. Serum and cerebral spinal fluid (CSF)

samples were collected to measure 12 inflammatory markers, with comparisons made to those of 15, healthy controls. Outcome variables included depression, assessed with the Patient Health Questionnaire-Nine (PHQ-9), administered at six and 12 months post-injury.

Subjects were 41 participants with CSF data and 50 with serum data, all with at least one PHQ-9 score. The patients' average, acute CSF inflammatory biomarker levels in the first week after TBI were significantly elevated compared to those of healthy controls for IL-1[β], IL-4, IL-6, IL-7, IL-8, IL-10, TNF-[α], sVCAM-1, sICAM-1 and sFAS ($P \leq 0.05$). No significant relationships were found between acute serum inflammatory biomarker levels and PTD at six or 12 months. The inflammatory cell surface marker, sVCAM-1, sICAM-1, and sFAS in the CSF, and the cytokine IL-8, were each positively associated with PTD at six months ($p < 0.02$), while the cytokine IL-7 was inversely associated with PTD at 12 months ($p < 0.05$).

Conclusion: This study of patients with TBI found that higher levels of the cytokine-induced proteins sICAM-1, sVCAM-1, and sFAS predicted a higher likelihood of post-traumatic depression (PTD) at six months post-injury.

Juengst, S., et al. Acute Inflammatory Biomarker Profiles Predict Depression Risk following Moderate to Severe Traumatic Brain Injury. *J Head Trauma Rehab.* 2015, May/June; 30(3): 207-218.

PHYSICAL EXERCISE AND NEUROINFLAMMATION, NEUROPLASTICITY, NEURODEGENERATION AND BEHAVIOR

The effects of exercise on the central nervous system in health and in neurodegenerative and cerebrovascular disorders have been a recent focus of research. This study reviewed the effects of different types of exercise on experimental models of neurodegenerative disorders, particularly Parkinson's disease and Alzheimer's disease.

This literature review used articles in PubMed from 1980 through August of 2014. The search focused on physical exercise, training,

neuroinflammation, neurodegeneration, intensity, high-intensity interval training, cytokines, behavior, cognition, in rodents and in humans. Exercise was found to lead to increased levels of neurotrophic factors, as well as changes in levels of different cytokines and altered microglial functions in different parts of the brain that could be beneficial for patients with neurodegenerative diseases.

Exercise was also shown to affect cell surface receptors, such as the TLR and adrenergic receptors, as well as intracellular signaling molecules involved in inflammatory pathways. Exercise intensity studies have demonstrated that high intensity training can increase anti-inflammatory cytokines and decrease pro-inflammatory cytokines. Moderate intensity exercise lowers levels of pro-inflammatory cytokines more than does mild intensity training in diabetes patients. No studies have investigated the effect of training intensity on neuroinflammation and neurodegeneration.

Conclusion: This literature review demonstrates that exercise is related to increased levels of neurotrophic factors, elevated expression of anti-inflammatory cytokines and reduced levels of pro-inflammatory cytokines and activated microglia.

Svensson, M., et al. Effects of Physical Exercise on Neuroinflammation, Neuroplasticity, Neurodegeneration, and Behavior: What We Can Learn from Animal Models in Clinical Settings. *Neurorehab Neural Repair.* 2015, July; 29(6): 577-589.

MIRROR THERAPY FOR MOTOR LEARNING AFTER STROKE

Over 50% of stroke survivors suffer from impaired motor function of the upper extremity. While many studies have reported on the positive effect of mirror therapy on motor recovery after stroke, the exact mechanism is not well understood. This study reviewed the effect of mirror therapy in the chronic stage of stroke recovery.

The study included 37 patients, at least six months post-stroke, with an upper extremity Brunström score of between three and six. The participants were randomized to

receive either action observation (AO) mirror therapy or control observation (CO) only. The subjects performed a set of 10 trials with the unaffected arm, which were recorded with a digital camera and used for AO. All were instructed to observe a video of the unaffected arm with the intention to reproduce the reaching task with the affected arm. Those in the CO group observed a slideshow of static photographs.

Movement time significantly improved in both groups, 18.3% in the AO group and 9.1% in the CO group ($p = 0.026$). An extended regression analysis found that baseline movement time and type of stroke were independent confounding variables, although the regression model that included these variables still showed a significant effect of the experimental condition ($p = 0.036$).

Conclusion: This study of patients with chronic stroke demonstrates that mirror therapy based action observation contributes to motor learning.

Harmsen, W., et al. A Mirror Therapy-Based Action Observation Protocol to Improve Motor Learning after Stroke. *Neurorehab Neural Repair.* 2015, September; 29 (6): 509516.

BLOOD PRESSURE AND RECURRENT INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhages (ICHs) present in two predominant forms; lobar (cortical-subcortical regions), which are associated with cerebral amyloid angiopathy, and non-lobar (deep structures), which are associated with arteriosclerosis. This study assessed the association between blood pressure control and the risk of recurrent non-lobar and lobar ICH.

This longitudinal cohort study enrolled consecutive patients 18 years or older, admitted to Massachusetts General Hospital with ICH between July, 1994, and December, 2011. The survivors or their caregivers were contacted and interviewed at three, six, nine and 12 months after the index ICH, and every six months thereafter. Blood-pressure control was assessed and classified according to the American Heart Association/American Stroke Association guidelines. The primary outcome measure was recurrent ICH.

Subjects were 1,145 patients with ICH, including 505 lobar and 640 non-lobar cases, with survival of at least 90 days. Inadequate blood pressure control was associated with an increased risk of both recurrent lobar and non-lobar ICH, with hazard ratios of 3.53 ($p < 0.001$) and 4.23 ($p < 0.048$), respectively. Systolic blood pressure was associated with increased risk of both recurrent lobar and non-lobar ICH. Diastolic blood pressure was associated with an increased risk of recurrent non-lobar, but not lobar, ICH.

Conclusion: This study reported on the associations between inadequate blood pressure control and recurrent lobar and non-lobar intracranial hemorrhage.

Biffi, A., et al. Association between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. *JAMA*. 2015, September 1; 314(9): 904-912.

TOTAL HOMOCYSTEINE LEVELS IN ACUTE STROKE

Numerous studies have demonstrated that plasma total homocysteine (tHyc) is a strong, independent risk factor for coronary heart disease and stroke. Further, elevated tHyc levels have been found to cause oxidative stress, endothelial dysfunction and atherothrombosis. This study investigated whether plasma tHyc levels in the acute phase of ischemic stroke are contributors of stroke recurrence and all-cause mortality.

Between September of 2005 and March of 2011, all patients admitted with a first ischemic stroke within 48 hours, were eligible for the study. Participants were classified by subtypes of large artery atherosclerosis and small vessel occlusion. All underwent blood sampling within 24 hours of admission, from which were measured levels of tHyc, high sensitivity C-reactive protein, triglycerides, fasting glucose, high density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein (Apo) B, and Apo A1. The primary outcome measure was all cause mortality at a median of 48 months' follow-up.

During a median follow-up of 48 months, 6.1% of the patients died. Mortality was higher among those in

the highest and second-highest tHyc quartiles, as compared to those in the lowest quartile ($p = 0.002$ and $p = 0.006$, respectively). The association remained significant for those in the fourth quartile after adjusting for risk factors. The risk of recurrent ischemic stroke was not significantly increased in patients with elevated levels of tHyc. In the subgroup analysis, the association was only significant for the large artery atherosclerosis subgroup.

Conclusion: This Chinese study found that elevated plasma total homocysteine in the acute phase of ischemic stroke can predict mortality, especially among those with large vessel atherosclerosis.

Shi, Z., et al. Elevated Total Homocysteine Levels in Acute Ischemic Stroke Are Associated with Long-Term Mortality. *Stroke*. 2015, September; 46(9): 2419-2425.

DIABETES AND AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease with approximately half of those patients dying within three years of onset. Recent reports have suggested a protective association between vascular risk factors and ALS incidence/survival. This study explored the association between diabetes and ALS.

Data for this retrospective, population-based study were obtained from the Danish National Register, with cases diagnosed from January of 1982 through December 31, 2009. The ALS cases were compared with controls selected from the Danish Civil Registration System, which includes administrative records on all persons living in Denmark. The records were reviewed for diabetes, obesity and lipid metabolism disorders. The main outcome measure was the adjusted odds ratio for ALS associated with diabetes, obesity, or both.

A total of 3,650 cases of ALS were identified, with a mean age at diagnosis of 65.4 years. From the records of the controls and the ALS patients, 9,294 participants were diagnosed with diabetes before the index date. In addition 4,536 participants were identified with obesity, and 4,168 with hyperlipidemia or

hypercholesterolemia at least three years prior to the index date. The adjusted odds ratio for the association between prior diabetes-related admissions and ALS was 0.61. This protective association increased with increasing age, with odds ratios of 1.66 for those less than 40 years of age and 0.52 for those older. While the effects of obesity were similar, the association was no longer significant when adjusted for diabetes (odds ratio 0.81).

Conclusion: This population-based study suggests that diabetes has a protective association with the diagnosis of amyotrophic lateral sclerosis.

Kioumourtzoglou, M., et al. Diabetes Mellitus, Obesity and Diagnosis of Amyotrophic Lateral Sclerosis: A Population-Based Study. *JAMA Neurol*. 2015, August; 72(8): 9059011.

SIDELINE BALANCE ERROR SCORING SYSTEM PERFORMANCE

Appropriate concussion management is predicated on timely symptom recognition. One symptom of concussion is impaired postural control, which is commonly tested with the balance error scoring system (BESS). This study examined the difference between BESS testing on the sideline and testing in quiet settings, in an effort to determine whether environmental factors influence those results.

Subjects were National Collegiate Athletic Association Division I female student-athletes (SA) involved in soccer, volleyball or softball at a single institution. Controls were recreational level athletic female college students. A BESS test was performed three times for each participant, once in a quiet setting and twice in either basketball or football settings. The SA group performed their baseline test during pre-participation physicals in a quiet, controlled environment, with the controls assessed in the same environment. The controls were then matched to members of the athlete group, and then tested in either a basketball or a football environment, with testing of the athletes during games, and that of the controls in the same venue when no game was occurring.

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*Ilya Igonnikov, M.D., M.S.
Michael Hodde, D.O., ATC
Paul Hurd, M.D.
Adam Mullan, M.D.
Temple Univ./UPenn., Philadelphia, PA

*Lindsey J. Beck, D.O.
Logan McCool, D.O.
Parisa Salehi, M.D.
University of Minnesota, Minneapolis, MN

*Jennifer Soo Hoo, M.D.
University of Washington, Seattle, WA

*Anne Eliason, M.D.
*Sean Stockhausen, D.O.
Greg Condie, D.O.
Dan Contract, M.D.
VCU, Richmond, VA

*Jeremy Hartman, M.D.
Prateek Grover, M.D., PhD
Rucha Kharod, M.D.
Elizabeth O'Keefe, D.O.
Washington University, St. Louis, MO

Executive Editor Emeritus
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Subjects ultimately included 38 athletes and 38 controls completing the testing. No significant difference was present between the athletes and controls in baseline BESS scores. At the football and basketball settings, the athletes increased BESS errors from baseline, while the controls decreased errors ($p=0.001$ and $p=0.005$, respectively).

Conclusion: This study found that, for student-athletes, Balance Error Scoring System performance worsened when determined during a live football or basketball game, suggesting caution when evaluating an athlete in those settings.

Rahn, C., et al. Sideline Performance of the Balance Error Scoring System During a Live Sporting Event. **Clin J Sports Med.** 2015, May; 25(3): 248-253.

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