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CHANGES IN RED MEAT CONSUMPTION AND MORTALITY

A large body of evidence has demonstrated that a higher consumption of red meat, especially processed red meat, is associated with an increase in several medical conditions. This study investigated the health effects of replacing red meat with equivalent amounts of other protein sources.

Data were obtained from The Nurses' Health Study, a prospective cohort of registered female nurses ages 30 to 55 years at enrollment, and the Health Professionals Follow-Up Study, including U.S. male health professionals, ages 40 to 75 years at enrollment. In both studies, food frequency questionnaires were completed biannually after baseline. Questionnaire items addressed unprocessed red meat intake, included beef, pork and lamb, as well as processed red meat, including bacon, hot dogs, sausage, salami, bologna and other processed red meats. The authors compared short-term (four-year) and long-term (12-year) changes in red meat consumption with total mortality.

In the pooled meta-analysis an increase in red meat consumption was associated with a higher risk of death. An increase of one serving per day of processed red meat was associated with 17% higher risk of all cause mortality, while a similar increase in unprocessed red meat was associated with a five percent increased risk. A substantially lower mortality risk was noted with a decrease in red meat consumption if accompanied by a simultaneous increase in the consumption of nuts (HR 0.81), fish (HR 0.83), whole grains (HR 0.88), poultry without skin (HR 0.90,), vegetables without legumes (HR 0.90), dairy (HR 0.92), eggs (HR 0.92) or legumes (HR 0.94).

Conclusion: This study, including longitudinal data from two, large, prospective studies, found that changes in the consumption of red meat, especially processed red meat, significantly effects long-term mortality.

Zheng, Y., et al. Association of Changes in Red Meat Consumption with Total and Cause Specific Mortality among U.S. Women and Men: Two Prospective Cohort Studies. **BMJ.** 2019; 365: 12110.

RECOVERY AFTER MILD TRAUMATIC BRAIN INJURY

Controversy exists surrounding the expected course of recovery for patients with mild traumatic brain injury (mTBI). The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI) study was designed to better understand recovery in community acquired TBI.

Subjects were patients seen in the emergency departments of one of 11 level I trauma centers between 2014 and 2016, each with a mTBI (defined as a Glasgow Coma Scale (GCS) score of 13 to 15). A control group (C) included patients with an orthopedic injury, without evidence of altered consciousness or head trauma. The primary outcome measure was the Glasgow Outcome Scale-Extended (GOSE). Secondary outcomes at one year comprised self-reported TBI related symptoms, using the Rivermead Post-Concussion Symptoms Questionnaire (RPCS).

Data were completed for 1,154 patients with mTBI, and 199 orthopedic control patients. At two weeks post-injury, limitations in one or more areas of function of the GOSE were noted in 87% of the mTBI group and in 93% of the C group. At 12 months, these rates fell to 53 % of the mTBI group and 38% of the C group. At 12 months, 47.2% of the patients with mTBI and 62.3% of the C group reported full return to preinjury levels of day-to-day functioning (p =0 .001).

Conclusion: This study of patients with mild traumatic brain injury seen in emergency departments of level I trauma centers found that, at 12 months, only 47.2% had fully returned to preinjury levels of day-to-day function.

Nelson, L et al. Recovery after Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK–TBI) Study. **JAMA Neurol**. doi:10.1001/ jamaneurol.2019.1313.

LASMIDITAN FOR ACUTE MIGRAINE

While triptans are considered the gold standard for acute treatment of migraine, these medications are not efficacious for all patients. This study assessed the migraine treatment efficacy of lasmiditan, a centrally-penetrant, highly selective and potent 5-HT1F receptor agonist.

This randomized, double-blind, placebo-controlled trial was completed at 125 headache centers in the United States, United Kingdom and Germany. Subjects were adults with a one-year history of disabling migraine, with or without aura, with three to eight migraine attacks per month. Subjects were randomized to receive lasmiditan (200 mg, 100 mg or 50 mg) or placebo. Headache severity was recorded by the patients at specified times up to 48 hours after the first dose. The primary outcome was the proportion of patients with headache pain freedom or freedom from the most bothersome symptom (MBS), as identified by the patient, from the associated symptoms of nausea, phonophobia and photophobia

Data were completed for 2,156 patients with an average of 18.3 years with migraines, and an average of 5.3 attacks per month. Compared to placebo, headache pain relief at two hours was significantly better for the groups taking lasmiditan, 200 mg (OR 2.3, p<0.001), 100 mg (OR 1.7, p<0.001), and 50 mg (OR 1.5, p=0.003). In addition, compared to the placebo group, the proportion of

patients who were MBS-free at two hours was significantly higher for all doses of lasmiditan.

Conclusion: This double-blind, placebo-controlled study of patients with chronic migraine demonstrates that lasmiditan is superior to placebo for eliminating headache pain within two hours.

Goadsby, P., et al. Phase 3 Randomized, Placebo Controlled, Double-Blind Study of Lasmiditan for Acute Treatment of Migraine. **Brain.** 2019, July; 142 (7): 1894-1904.

TRENDS IN ANTICOAGULATION IN PATIENTS WITH ISCHEMIC STROKE AND ATRIAL FIBRILLATION

Atrial fibrillation (AF) is an independent risk factor for stroke. While anticoagulation with warfarin has long been the mainstay of treatment for stroke prevention in patients with AF, it has been underutilized. This study was designed to identify the temporal trends in anticoagulation in patients with AF after the introduction of direct oral anticoagulants (DOACs).

The Florida Puerto Rico Atrial Fibrillation (FLiPER-AF) Stroke Study used data from the stroke registry of the Florida-Puerto Rico Collaboration to Reduce Stroke Registry (FL-PR CReSD). Data were collected from 86 hospitals from January of 2010 to December of 2016. Subjects' diagnoses included ischemic stroke (IS), transient ischemic attack, subarachnoid hemorrhage, intracerebral hemorrhage and stroke not otherwise specified. The use of aspirin, warfarin and DOACs was recorded, with temporal trends of utilization reviewed.

The sample included 24,040 patients with a mean age of 79 years. The overall proportion of patients with IS and AF who were prescribed anticoagulation remained stable over time, totaling 51.5% in 2010 and 53.5% in 2016. Between 2010 and 2016, the rate of aspirin use remained stable (41.7% to 40.2%), while warfarin use declined (51.5% to 17.3%) and DOAC use steadily increased (0% to 36.2%).

Conclusion: This study of patients with atrial fibrillation found that, between 2010 and 2016, the use anticoagulation was relatively stable despite the increased use of direct oral anticoagulants (DOACs).

Sur, N., et al. Disparities and Temporal Trends in the Use of Anticoagulation in Patients with Ischemic Stroke and Atrial Fibrillation. **Stroke.** 2019, June; 50(6): 1452-1459.

PREVALENCE OF COGNITIVE DYSFUNCTION IN YOUNG STROKE PATIENTS

Approximately 10% of all strokes occur in patients below 50 years of age. While early studies have suggested that motor recovery in this age group is superior to their older counterparts, cognitive dysfunction has been reported in over 60%. This study was designed to better understand the course of cognitive dysfunction in young stroke patients.

Between February of 2016 and April of 2018, consecutive patients 18 to 55 years of age, diagnosed with stroke, were invited to participate. A neuropsychological test battery was performed, including the Montréal Cognitive Assessment, the Symbol Digit Modalities Test, the Comprehensive Trail Making Test and two subtests of the Regensburger Wortflüssigkeitstest (RWT) word fluency test. All were repeated at three-month follow-up.

Neuropsychological follow-up was available for 87 patients, with a mean age of 44.5 years. At baseline, deficits in processing speed were noted in 56 %, in flexibility/executive function in 49.5%, in attention in 46.4% and in general cognitive function in 42.1%. At three-month follow-up, cognitive deficits were present in approximately one third of the patients.

Conclusion: This study of patients 18 to 55 years of age with ischemic stroke found that, at three months, one third demonstrated persisting cognitive deficits.

Pinter, D., et al. Prevalence and Short -Term Changes of Cognitive Dysfunction in Young Ischaemic Stroke Patients. **Euro J Neurol**. 2019, May; 26(5): 727-732.

GLOBAL BURDEN OF STROKE

The Global Burden of Diseases, Injuries and Risk Factors (GBD) study found that, although the age standardized death rates and prevalence of stroke have decreased over time, the overall burden remains high. Using data from the GBD, this study provides updated estimates of death prevalence and disability due to stroke.

Using data from the GBD, it was

determined that, in 2016, stroke was second to ischemic heart disease as a cause of death worldwide. In addition, stroke was the second most common cause of disability-adjusted life years (DALYs). Globally, the age-standardized rate of deaths due to stroke decreased by 36.2% from 1990 to 2016. The highest age standardized incidence of stroke was observed in East Asia, especially China with 354 per 100,000 person years. The lowest incidence was in central Latin America, with El Salvador demonstrating 97 per 100,000-person years. Metabolic risks (high systolic blood pressure, high body-mass index, high fasting plasma glucose, high total cholesterol and low glomerular filtration rate) accounted for 72·1% of stroke DALYs, while behavioral factors (smoking, poor diet, and low physical activity) accounted for 66·3% of attributable DALYs. Environmental risks (air pollution and lead exposure) accounted for 28·1%.

Conclusion: This study found that the global burden of stroke is high, with more than 80 million stroke survivors in 2016, and with behavioral factors accounting for 66.3% of stroke disability adjusted life years.

GBD 2016 Stroke Collaborators. Global, Regional and National Burden of Stroke in 1990 through 2016: A Systematic Analysis for the Global Burden of Disease Study 2016. **Lancet Neurol.** 2019, May; 18 (5): 439-458.

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MORTALITY IN YOUNG STROKE PATIENTS

Approximately 10 to 15% of all strokes occur in adults ages 18 to 49 years of age. This study was designed to better understand the mortality of this group.

Subjects were patients with a first stroke, identified through the Dutch Hospital Discharge Registry (HDR). Mortality was determined using the Dutch Population Registry, and the National Cause of Death Registry (CDR), from January 1, 1998, to January 1, 2017. The primary outcome was all-cause, cumulative mortality among those who had survived a stroke for at least 30 days.

Subjects were 15,250 adults, including 55.3% with ischemic stroke, 20.2% with intracerebral hemorrhage and 24.5% with stroke otherwise not specified. Of the group, 11.6% died in the first 30 days. In the thirty-day survivors, the cumulative mortality after any stroke increased from 3.1% at year one, seven percent at year five, 11.5% at year 10 and 17% at year 15. The standardized mortality rate compared with the general population was 5.1 for ischemic stroke and 8.4 for intracerebral hemorrhage.

Conclusion: This Dutch study involving individuals 18 to 49 years of age who were 30-day survivors of a first stroke found that their mortality risk, as compared with that of the general population, remained elevated up to 15 years later.

Ekker, M., et al. Association of Stroke among Adults Aged 18 to 49 Years with Long-Term Mortality. **JAMA.** 2019, June. 321(21): 2113-2123.

GABAPENTINOIDS AND SUICIDAL BEHAVIOR

Gabapentinoids are often used for the treatment of epilepsy and neuropathic pain. In 2008 the FDA reported an increased risk of suicide among those using gabapentinoids. Follow-up studies have produced inconsistent results. This study was designed to better understand the association between gabapentinoids and adverse outcomes.

This Swedish population-based cohort study identified individuals over the age of 15 who had received at least two prescriptions of gabapentinoids. Information was collected from the Swedish Patient Register on suicidal behavior, unintentional overdoses, head or body injuries, and road traffic incidents.

A total of 191,973 individuals received prescriptions of gabapentinoids. Gabapentinoid treatment was associated with an increased risk of suicidal behavior and death from suicide (Hazard Ratio (HR) 1.30), unintentional overdose (HR 1.24), head/body injuries (HR 1.13) and road traffic incidents and offenses (HR 1.10). The highest risk of suicidal behavior was found in the 15-24-year age group. Of the gabapentinoids, pregabalin was associated with an increased risk of all outcomes, while gabapentin treatment was associated with reductions in road traffic incidents and offences (HR 0.81), and arrests for violent crime (HR 0.80).

Conclusion: This Swedish study found that treatment with gabapentinoids is associated with an increase in suicidal behavior, unintentional overdoses, head/body injuries, road traffic incidents or offences and arrests for violent crime. No such association was found for those over 55 years of age.

Molero Y., et al. Associations between Gabapentinoids and Suicidal Behaviour, Unintentional Overdoses, Injuries, Road Traffic Incidents and Violent Crime: Population Based, Cohort Study in Sweden. **BMJ**, 2019; 365:l2147doi: 10.1136/bmj. l2147

CHRONIC TRAMADOL AFTER ACUTE PAIN PERSCRIPTION

With an increased focus on opioids, prescriptions of tramadol have increased, with the widespread assumption that this medication is safer than other short acting opioids. Data to support this assumption are lacking. This study assessed the risk of transitioning from acute to prolonged use among those prescribed tramadol for postoperative pain.

This retrospective analysis included medical claims recorded in the OptumLabs Warehouse, representing a diverse mixture of ages, ethnicities and geographic regions across the U.S. The records were reviewed for those undergoing twenty commonly performed surgical procedures. Discharge opioid prescriptions were placed into five, mutually exclusive categories; short acting opioids only (SAO), excluding tramadol (reference); tramadol only (T); tramadol and any other short acting opioids (no long acting) (T+SA); any long acting opioids (LA) or no opioids (NO).

Of the 357,884 with a prescription for one or more opioids, the *additional use* of *opioids* (one or more opioid fills 90-180 days after surgery) was found in 7.1% of the sample. One per cent of the sample met the criteria for *persistent opioid use* after surgery, (opioid use lasting 90 or more days). The most stringent criterion—the *CONSORT definition of chronic opioid use* (opioid use episode lasting at least 90 calendar days and including either 10 or more opioid fills or supply of 120 days or more) was present in 0.46%. The receipt of tramadol alone was associated with a 6% increase in the risk of *additional use of opioids* relative to those receiving other short acting opioids ($p=0.049$), a 47% increase in the adjusted risk of *persistent opioid* use $p<0.001$), and a 41% increase in the adjusted risk of a *CONSORT definition of chronic opioid use* episode ($p=0.013$).

Conclusion: This study of surgical patients receiving

prescription pain medications after surgery found that those prescribed tramadol had similar to somewhat higher risks of prolonged opioid use as compared with those receiving other short acting opioids.

Thiels, C., et al. Chronic Use of Tramadol after Acute Pain Episode: Cohort Study. **BMJ** 2019; 365: l1849

CENTRALLY DRIVEN OSTEOARTHRITIS PAIN

Many patients with osteoarthritis (OA) develop referred pain at sites distant to the initial joint damage and suffer from chronic pain resulting from a discordance between nociceptor activation and the resulting pain. Tapentadol is a centrally acting analgesic that activates descending opioidergic controls and increases the synaptic availability of noradrenaline producing analgesia through the activation of α2-adrenoceptors. This animal study investigated the effects of tapentadol and pregabalin on centrally mediated pain by using Diffuse Noxious Inhibitory Controls (DNIC) as a marker of changes in descending controls.

Male Sprague Dawley rats were randomized to receive knee injections of an OA producing chemical, monoiodoacetate (MIA), or a similar volume of saline. A laminectomy exposed the L4-L5 segments of the spinal cord, with extracellular single-unit recordings made from deep dorsal horn wide dynamic range (WDR) neurons during a variety of stimuli. Tapentadol injections included 1, 2 and 5 mg/kg. Pregabalin was injected at 10 mg/kg. After each individual drug dose as well as combinations of the two, neuronal responses to noxious stimuli were recorded.

After tapentadol injections, DNIC-induced neuronal inhibition was restored. Injections of gabapentin inhibited pre-conditioned mechanically evoked neuronal responses but did not restore DNIC. Given in combination, tapentadol and pregabalin restored DNIC expression and also inhibited spinal neuronal responses.

Conclusion: This animal study found that tapentadol and pregabalin target different mechanisms of centrally driven chronic pain associated with OA. The combination of the two may provide superior analgesia.

Lockwood, S., et al. A Combination Pharmacotherapy of Tapentadol and Pregabalin to Tackle Centrally Driven Osteoarthritis Pain. **Euro J Pain.** 2019;23(6): 1185-1196.

MORTALITY FROM FALLS IN THE ELDERLY

In the United States, 28.7% of adults ages 65 years or older fell in the year 2014. This study evaluated trends in mortality due to falls in the U.S. population, 75 years of age or older, between 2000 and 2016.

Data were extracted from the US National Vital Statistics System mortality files. Unintentional deaths from falls for persons ages 75 years or older were documented and compared between the years 2000 and 2016.

The absolute number of deaths from falls among those 75 years of age or older increased from 8,613 in the year 2000 to 25,989 in the year 2016. Mortality due to falls increased in those 75 years of age or older from 51.6 per 100,000 in 2000 to 122 per 100,000 persons in 2016. Age-adjusted mortality rates among adults aged 75 years or older increased from 60.7 per 100 000 men in 2000 to 116.4 per 100 000 men in 2016 and from 46.3 per 100 000 women in 2000 to 105.9 per 100 000 women in 2016. Mortality from falls was dramatically higher among those 95 years of age or older (590.7/100,000) than among those 75 to 79 years of age (42.1/100,000).

Conclusion: This nationally representative study of individuals 75 years of age or older found an increase in the number of, and mortality due to, falls between the years 2000 and 2016.

Hartholt, K., et al. Mortality from Falls among U.S. Adults Aged 75 Years or Older, 200-2016. **JAMA.** 2019, June 4; 321(21): 2131-2133.

PHOSPHODIESTERASE INHIBITORS AND STROKE PREVENTION

Given that antiplatelet agents differ from each other in the mechanisms that they effect, a combination of agents should be able to produce more effective stroke prevention than a single agent. The Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) was designed to determine whether combining cilostazol with aspirin or clopidogrel would be superior to either aspirin or clopidogrel alone in reducing the risk of recurrent ischemic stroke in the chronic stage.

Subjects were 20 to 85 years of age, all with non-cardioembolic ischemic stroke. The participants were randomized to receive monotherapy (with aspirin or clopidogrel at 50 mg or 75 mg once per day) or dual therapy (with cilostazol at 100 mg, twice per day), in combination with either aspirin (81 mg or 100 mg) or clopidogrel (50 mg or 75 mg), once per day, for a period of six months. The primary efficacy outcome was the first recurrence of symptomatic ischemic stroke.

At a median follow-up of 1.4 years, of the 1879 patients, three percent of the dual therapy and seven percent of the monotherapy group experienced an ischemic stroke (p=0.001). A composite of stroke, myocardial infarction and vascular death occurred in four percent of the dual therapy group and in eight percent of the monotherapy group (p=0008). No significant difference in adverse events was noted between groups.

Conclusion: This study of patients at high risk for non-cardioembolic ischemic stroke found that the addition of cilostazol to single antiplatelet therapy reduced, by almost half, the rate of a composite of stroke, myocardial infarction and vascular death.

Toyoda, K., et al. Dual Antiplatelet Therapy Using Cilostazol for Secondary Prevention in Patients with High Risk Ischemic Stroke in Japan: A Multicenter, Open Label, Randomised, Controlled Trial. **Lancet Neurol.** 2019, June; 18 (6): 539-548.

PERIPHERAL ARTERY DISEASE AND STROKE

The rates of stroke among those with peripheral artery disease (PAD) have not been well studied. This sub-study from the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial evaluated the factors associated with stroke among patients with PAD, and compared the treatment efficacy of clopidogrel and ticagrelor, with the recurrence of stroke or transient ischemic attack (TIA).

Patients were 50 years of age or older with symptomatic lower extremity PAD. Those subjects were randomized to receive antiplatelet monotherapy with ticagrelor or clopidogrel. The subjects were followed for a median of 30 months. The primary outcome variable was a

composite of cardiovascular death, myocardial infarction and/or ischemic stroke.

Of the 13,885 patients enrolled, 458 cerebrovascular events occurred in 424 patients (2.4%) during the 30 months of follow-up. The cumulative rates were 0.87/100 patient-years for ischemic stroke, 0.11/ 100 patient-years for hemorrhagic stroke and 0.27/ 100 patient-years for TIA. A baseline ankle brachial index (ABI) of <0.60 was associated with an increased risk of all-cause stroke. After adjusting for baseline factors, the rates of ischemic stroke (p=0.032) and all-cause stroke (p=0.038) remained lower in patients treated with ticagrelor than in those receiving clopidogrel. No significant difference was seen between groups for myocardial infarction, major bleeding or hemorrhagic stroke.

Conclusion: This study of patients with peripheral artery disease, all over 50 years of age, found that an ankle brachial index of <0.60 was an independent risk factor for stroke, and that this risk was lower among those treated with ticagrelor as compared with clopidogrel.

Kolls, B., et al. Stroke in Patients with Peripheral Artery Disease. Insights from the Euclid Study. **Stroke.** 2019, June; 50(6): 1356-1363.

CURCUMIN SUPPLEMENTATION ENHANCES SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR

Studies have shown that a reduction of brain-derived neurotrophic factor (BDNF) adversely affects cognitive function and behavior. Several randomized, controlled trials have examined the neuroprotective effects of curcumin and its ability to increase BDNF levels, with inconclusive results. This literature review was designed to better understand the impact of curcumin supplementation on serum BDNF levels.

A systematic review of the literature included placebo controlled, randomized investigations assessing the effect of curcumin supplementation on serum BDNF levels. The mean change in serum BDNF levels was used to estimate the overall effect of the intervention.

From the search, four studies were chosen, including 139 subjects with a mean age of 41 years. A pooled analysis revealed that curcumin supplementation significantly increased serum BDNF levels (p<0.01). This increase was noted in women, those over 40 years of age, those taking doses over 500 mg per day and those with supplementation for 12 weeks. Significant effects were not found for men, those under 40 years of age, those with doses below 500mg/day or those with treatment durations of less than eight weeks.

Conclusion: This meta-analysis found that curcumin supplementation of at least 500mg/day can increase serum levels of brain-derived neurotrophic factor.

Sarraf, P., et al. Short-Term Curcumin Supplementation Enhances Serum Brain Derived Neurotrophic Factor in Adult Men and Women: A Systematic Review and Dose-Response Meta-Analysis of Randomized, Controlled Trials. **Nutr Res**. 2019. https://doi.org/10.1016/j.nutres.2019.05.001

TRANSCRANIAL DIRECT CURRENT STIMULATION AND CIGARETTES SMOKED

Globally, cigarette smoking is estimated to cause over $500 billion in economic damage per year. Studies have shown that repetitive transcranial magnetic stimulation can modulate focal cortical activity, reduce craving, and with treatment of several months, can reduce tobacco abuse. This study reviewed the effects of a short treatment with direct current stimulation (DCS) for reducing tobacco abuse.

In this randomized, parallel, double-blind, sham controlled trial, subjects received three days of 20-minute sessions of sham tDCS or active tDCS with the cathode placed over the right and the anode over the left dorsolateral prefrontal cortex. Subjects recorded smoked cigarettes for seven days before, during and up to four months following the end of the treatment. The level of nicotine dependence was assessed through the Fagerstroms Nicotine Dependence Test (FNDT).

During the interval of 15 days, both the active and the sham groups demonstrated a significant reduction in cigarettes smoked. At follow up, compared to pre-tDCS, there was no significant difference in the number of smoked cigarettes in the active (p=0.806) or the sham (p=0.573) groups.

Conclusion: This study of 21 male tobacco abusers did not find that three sessions of transcranial direct current stimulation could reduce the number of cigarettes smoked per day to a greater extent than could sham stimulation.

Alghamdi, F., et al. Effect of Transcranial Direct Current Stimulation on the Number of Smoked Cigarettes in Tobacco Abusers. **PLOS One.** 2019. https://doi.org/10.1371/journal.pone.0212312.

EFFECTS OF PLYOMETRICS

Plyometric training (PLY) is most often performed as unloaded jumping exercises with high-speed execution. This literature review was designed to better understand the effect of lower body plyometric training on jumping, sprint performance and lower body muscle strength in healthy adults.

A systematic literature review and meta-analysis included studies of healthy, adult subjects. Studies were included with training of four or more weeks, that utilized a control group to compare changes in jump height, sprint performance and lower body muscle strength.

The literature review identified 25 studies including 751 subjects. In the meta-analysis, as compared to the control group, significantly better improvement was noted in the plyometric group for jump performance, with increases ranging from 3.4% to 26.3% (as compared to -6 to 8% in the control group). In addition, compared to the control group, improvements were superior in sprint performance and lower body muscle strength (p<0.05 for all comparisons).

Conclusion: This meta-analysis found that plyometric training is an effective modality for improving jumping, sprint performance and lower body muscle strength.

Oxfekdt, M., et al. Effects of Plyometric Training on Jumping, Sprint Performance and Lower Body Muscle Strength in Healthy Adults: A Systematic Review and Meta-analysis. **Scand J Med Sci Sports**. 2019:1-14.

PLATELET RICH PLASMA FOR PATELLAR TENDINOPATHY

Patellar tendinopathy is common among sports involving jumping and can result in substantial pain and reduced performance. This study addressed the effect of injections with platelet rich plasma (PRP) as a treatment for patellar tendinopathy.

This parallel, randomized, single blind, controlled study was conducted at three sports centers in separate countries, involving patients between 18 and 50 years of age. All were diagnosed with patellar tendinopathy, with symptoms present for at least six months. The participants were randomized to receive injections, placed adjacent to the patella tendon defect, of 3.5 mL of leukocyte poor PRP (LP–PRP), leukocyte rich PRP (LR–PRP) or normal saline. The primary outcome measure was the change in the Victorian Institute of Sports Assessment Patellar Score (VISA-P) at 12 weeks, with pain scores measured with a 10-point numeric pain rating scale.

At 12 weeks, 58% of the patients experienced improvement in VISA-P scores, with no significant difference noted between treatment groups. At six weeks, participants who rated themselves as worse included five from the LP-PRP group, three from the LR-PRP group and none from the saline group.

Conclusion: This study of patients with patellar tendinopathy found that exercise, combined with platelet rich plasma injections, does not provide superior relief than exercise combined with saline injections.

Scott, A., et al. Platelet Rich Plasma for Patellar Tendinopathy. A Randomized, Controlled Trial of Leukocyte Rich PRP or Leukocyte Poor PRP versus Saline. **Am J Sports Med.** 2019; 47 (7): 1654-1661.

PATIENT SUBGROUPS AND BENEFITS FROM MENISCAL SURGERY

Research has shown that arthroscopic partial meniscectomy for painful meniscal tears is often not beneficial. Some have argued that, despite these data, subgroups of patients may benefit from this surgical intervention. This study was designed to determine the veracity of this argument.

Data were obtained from the Knee Arthroscopic Cohort Southern Denmark (KACS) prospective cohort study of patients undergoing knee arthroscopy for a meniscal tear. Subjects were consecutive adult patients recruited from one of 14 hospitals in Southern Denmark. All underwent arthroscopic surgery for a repair of a suspected meniscal tear. The outcome variable was change in the Knee Injury and Osteoarthritis Outcome Score (KOOS) from baseline to 52 weeks after surgery. To develop a prognostic model, 26 factors in the KACS were considered.

Subjects included 641 patients, of whom 600 received a resection and 33 underwent a repair, with the remaining receiving a combination of the two procedures. The average improvements in KOOS scores from before surgery to 52 weeks post-surgery were 18.6 for the entire cohort, 16.2 for those younger and 19.2 for those older than 40 years of age. The strongest prognostic factors were previous meniscal surgery, level of education and knee-related symptoms such as difficulty twisting/ pivoting and inability to straighten the knee fully.

Conclusion: This study of patients undergoing meniscal repair does not support the existence of subgroups who have favorable outcomes after surgery.

Pihl, K., et al. Wild Goose Chase, No Predictable Patient Subgroups Who Benefit from Meniscal Surgery: Patient Reported Outcomes of 641 Patients One Year after Surgery. **Br J Sports Med**. 2019. doi.org/10.1136/bjsports-2018-100321.

FEMOROACETABULAR IMPINGEMENT AND NERVE INJURY AFTER SURGERY

Hip Arthroscopy (HA) is thought to be safe and less invasive than open surgery. This study was designed to determine the rate of nerve injury after hip arthroscopic surgery for femoroacetabular impingement (FAI).

Subjects were consecutive patients at a single institution, each treated by HA for FAI between January of 2016 and January of 2018. During surgery, pincer and labral lesions were treated by acetabuloplasty and refixation of the labrum with suture anchors. All participants were queried about sensation at 24 hours, three and six weeks and then at three- and six-months post-surgery.

Data were collected for 110 patients with a mean age of 36 years. At four hours post-surgery, 60% to 77% reported abnormal sensation in at least one area. At three weeks, 39% still reported abnormal sensations in the perineal area, with 3.6% reporting such a disturbance in the lateral thigh. At six months, only one patient reported continued symptoms.

Conclusion: This study of patients with femoral acetabular impingement who underwent arthroscopic surgery found that over 60% reported symptoms of nerve dysfunction at 24 hours post-surgery, with nearly all resolved in six months.

Martinez, J., et al. Femoroacetabular Impingement: Prospective Study of Rate and Factors Related for Nerve Injury after Hip Arthroscopy. **J Orthop**. 2019, Sept-Oct; 16(5): 350-353.

PHARMACEUTICAL INDUSTRY PAYMENTS TO NONPHYSICIAN CLINICIANS

Studies have shown that payments from pharmaceutical companies to physicians are associated with an increase in healthcare costs. Restrictions to such payments have been implemented in the United States and in other regions of the world. This Australian study assessed the nature and extent of payments to nonphysician clinicians.

Since 2015, companies have reported payments to all health care professionals in Australia, including nonphysicians. For this study, the authors downloaded the "168 *Payments to Healthcare Professionals"* reports from October 1, 2015, to April 30, 2018. By matching recipient names with registered health care professionals, payment recipients were identified by health care role.

Nonphysicians accounted for 22.1% of the recipients. Nurses and pharmacists were the primary nonphysician recipients, with nurses receiving 8.3%, and pharmacists receiving one percent of total spending. A total of 75.9% of the payments to nurses and pharmacists supported meeting attendance. Of the most highly paid individuals, most were found to be involved with chronic disease management, practiced in hospitals, held positions of clinical seniority, participated in research or were influential in professional organizations.

Conclusion: This Australian study found that a large percentage of nonphysicians receive money from the pharmaceutical industry. As the scrutiny of these healthcare providers is far less that of physicians, the authors suggest a need to better understand the extent and import of such payments.

Karanges, E., et al. Understanding the Nature and Extent of Pharmaceutical Industry Payments to Nonphysician Clinicians. **JAMA Intern Med**. 2019, June 10. E1-E3.

DELAYED THROMBOLYSIS FOR SALVAGEABLE TISSUE

For patients with acute ischemic stroke (AIS), the time window from symptom onset to thrombolysis is traditionally limited to 4.5 hours. It is unknown whether extending this window in patients with at-risk but not infarcted tissue on neuroimaging offers a greater chance of neurologic recovery, without increasing the risk of adverse events.

This randomized, placebo-controlled, multicenter trial assigned 225 patients with AIS to receive either intravenous alteplase or placebo. The time from onset to treatment was between 4.5 and nine hours, with patients eligible if they had had excellent functional status, as determined by a Modified Rankin Scale (MRS) score of below two prior to stroke, and had ischemic, but not infarcted, brain tissue, as detected by computed tomography perfusion or perfusion-diffusion magnetic resonance imaging. The primary outcome measure was an MRS score of zero or one at 90 days. Safety measures were death or symptomatic intracranial hemorrhage within 90 days.

Compared to those in the placebo group, a significantly greater increase in the percent of patients who achieved MRS <2 at 90 days was found in the alteplase group (29.5% and 35.4%, respectively, p=0.04). Symptomatic intracerebral hemorrhage was noted in 6.2% of patients in the alteplase group, as compared to 0.9% in the placebo group (p=0.05). No significant difference was found in 90-day mortality between groups.

Conclusion: Among patients with acute ischemic stroke who demonstrate at-risk, but not infarcted, penumbra on neuroimaging, thrombolysis with alteplase up to nine hours after symptom onset resulted in a higher percentage of patients that achieved a significant neurological improvement.

Ma, H., et al. Thrombolysis Guided by Perfusion Imaging Up to 9 Hours after Onset of Stroke. **N Engl J Med.** 2019, May 9; 380(19):1795-1803.

CORTICOSTEROID INJECTIONS AFTER ROTATOR CUFF REPAIR

After rotator cuff repair, most patients have pain and pain related difficulty during rehabilitation. While one treatment option is an intra-articular triamcinolone injection, some have expressed concern that corticosteroid injections may hamper tissue growth, particularly after surgery. This study was designed to better understand the efficacy and safety of intra-articular corticosteroid injections after arthroscopic rotator cuff repair.

Subjects were patients undergoing arthroscopic rotator cuff repair, with a standardized postoperative rehabilitation protocol. Eight weeks after surgery, patients were randomized to receive a glenohumeral joint injection with either a placebo (normal saline) or a corticosteroid (one ml of triamcinolone 40 mg/mL, combined with 1.5 mL of 2% lidocaine). Before surgery the clinical status of each patient was assessed, including measures of pain, ROM, and function, measured by the American Shoulder and Elbow Surgeons (ASES) and the Constant at three, six and 12 months.

At one-month post injection (three months post-surgery), the treatment group had significantly lower pain scores (p=0.02) and improved ASES scores (p=0.02) as compared to the control group. In addition, at three months, the treatment group was superior to the control group in measures of forward flexion (p=0.05), external rotation at the side (p=0.04) and external rotation at abduction (p=0.05). No such differences were noted at six months. At 12 months, the rate of re-tear, as determined by MRI, did not differ between groups.

Conclusion: This study of patients undergoing repair of a rotator cuff tear found that intra-articular corticosteroid injections after surgery can help improve short-term pain and function, without increasing the risk of damage to the rotator cuff.

Kim, Y., et al. Is It Safe to Inject Corticosteroids into the Glenohumeral Joint after Arthroscopic Rotator Cuff Repair? **Am J Sports Med.** 2019, June; 47 (11): 1694-1700.

ONE-STAGE CARTILAGE REPAIR OF THE KNEE

For patients with cartilage damage of the knee, there are limited treatment options to restore the knee with durable tissue. This study investigated the long-term clinical outcomes of a one-stage, cell-based cartilage repair of the knee with a hyaluronic acid-based scaffold embedded with bone marrow aspirate concentrate (HA-BMAC).

Patients with a full-thickness chondral injury of the knee (>1cm^2) who were treated with HA-BMAC between April of 2007 and January of 2012 were followed prospectively for a median of eight years. All had received a scaffold composed of an HA-based material (Hyalofast) size matched to the cartilage lesion. The activated BMAC clot was implanted into the cartilage defect, with the scaffold secured by polydioxanone suture and/or fibrin glue. Clinical outcomes were examined with the patient-reported scoring instruments the Tegner Activity Scale, the International Knee Documentation Committee (IKDC) subjective score, a visual analog scale and the Knee IInjury and Osteoarthritis Outcome Score (KOOS).

Subjects were 23 patients with a mean age of 48.5 years. The median cartilage lesion size was 6.5 cm^2. The median Tegner score before surgery was two, improving to four at a final follow-up (p<0.001). The median visual analog pain score at final follow -up was 0.3, significantly improved from a median score five at baseline (p<0.001). No significant difference was found in outcome between those older than, and those younger than, 45 years of age.

Conclusion: This study of 25 patients undergoing a single stage repair of a knee cartilage defect found a good to excellent outcome at eight-year follow-up.

Gobbi, A., et al. Long-Term Clinical Outcomes of One Stage Cartilage Repair in the Knee with Hyaluronic Acid-Based Scaffold, Embedded with Mesenchymal Stem Cells Sourced from Bone Marrow Aspirate Concentrate. **Am J Sport Med**. 2019, July; 47(7): 1621-1628.

CEREBRAL MICROBLEEDS AND STROKE RISK AFTER ISCHEMIC STROKE

Cerebral microbleeds are a neuroimaging finding, thought to be associated with an increased risk of stroke. It is not known whether cerebral microbleeds, found in patients with a recent ischemic stroke (IS) indicate an increased risk of intracranial hemorrhage (ICH) that are magnified when treated with antithrombotic drugs. This meta-analysis was designed to better understand this association.

This literature review and meta-analysis included studies of patients with a recent IS or transient ischemic attack (TIA), that included documentation of cerebral microbleeds. The analysis was completed using 38 studies, including 20,322 patients, with a median of

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20,322 patients, with a median of 1.34 years follow-up.

During follow-up 189 ICHs, 1,113 ischemic strokes and 172 composite events were documented. The hazard ratio (HR) of the composite of any intracranial hemorrhage or ischemic stroke, symptomatic intracranial hemorrhage (HR 2·45) and symptomatic ischemic stroke (HR 1·23) was greater in patients with cerebral microbleeds, than in those without (p<0.001 for all comparisons). No increased risk of ICH was found among those using antiplatelet medications (p=0.358), oral anticoagulants (p=0.717) or the combination of oral anticoagulants and antiplatelet medications (p=0.163).

Conclusion: This study found that, while cerebral microbleeds indicate an increase of stroke, even when they are treated with antiplatelet medications, the risk of hemorrhagic stroke is not excessively increased.

Wilson, D., et al. Cerebral Microbleeds and Stroke Risk after Ischemic Stroke or Transient Ischemic Attack: A Pooled Analysis of Individual Patient Data from Cohort Studies. **Lancet Neurol**. 2019, July; 18 (7): 653-665.

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