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Video Presentation

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J Orthop Trauma Surg Rel Res, ISSN: 1897-2276

Finding an optimal time interval to maximize outcomes and minimize morbidity and mortality in staged bilateral total knee arthroplasty

Safa Fassihi
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Introduction: Demand for total knee arthroplasty (TKA) is projected to increase by over six-fold in the next decade. Along with that, the number of patients who are indicated for arthroplasty of both knees will likely increase at a similar rate. Several studies have compared the functional outcomes, perioperative morbidity, and complication rates of patients undergoing simultaneous bilateral total knee arthroplasty (BTKA) versus staged BTKA. Despite that, there remains a lack of consensus regarding how the various timing schemes in staged BTKA affect morbidity, complications, mortality, and outcomes.

Methods: The literature was queried using searches with keywords "bilateral total knee arthroplasty," "staged," "timing," "interval," "complications," "morbidity," and "mortality." Clinical outcomes, functional outcomes, complications, morbidity, and mortality data from selected articles were compiled and categorized by interval for staged BTKA. Resulting papers that met strict inclusion criteria were stratified by staged intervals: 7 to 21 days, 22 to 90 days, 91 to 180 days, 181 to 270 days, 271 to 365 days, and greater than 365 days. The clinical and functional outcome scores, complications, morbidity, and mortality data were compared among intervals to determine the optimal timing for staged BTKA.

Results: In total, 7 articles met the inclusion criteria and were included in this review. Overall, there was a lack of consensus regarding optimal timing for staged BTKA, as well as a lack of standardization when investigating the optimal time interval. There was no significant difference between time intervals for staged

Biography

Safa Fassihi is a US-based physician pursuing a career in orthopedic total joint arthroplasty. His research focuses on newer arthroplasty techniques and how they affect patient outcomes. In this specific analysis, he collaborated with a US board-certified orthopedic surgeon who performs a high volume of both simultaneous and staged bilateral total knee arthroplasty.

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The effects of neurokin1 receptor antagonist for arthritic pain in a rat model of osteoarthritis

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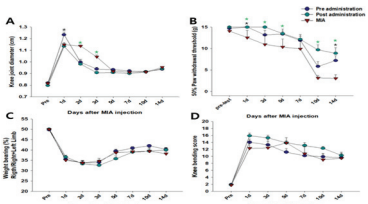
Statement of the Problem: Osteoarthritis (OA) cause inflammation in the joint and is a common degenerative disease in elderly people. Chronic pain is a main symptom in OA patients. However, medications for OA pain limited effects due to the side effects depending on long- lasting usage. Substance P is a neuropeptide release from nociceptive afferent fiber to peripheral and central nervous system that is responsible for neurogenic inflammation and pain transmission through the activation of neurokinin 1 (NK1) receptor. This study was designed to examine a possibility for the NK1 receptor antagonist to be a therapeutic agent for OA pain.

Methodology & Theoretical Orientation: Knee joint inflammation was induced by intra-articular injection of monosodium iodoacetate (MIA, 2mg/50ul). NK1 receptor antagonist (TOCRIS, GR92334, 10uM/30ul) injected before (Pre group) and after MIA injection (Post group). To assess edema, the knee joint diameter was measured by caliper. Paw withdrawal threshold (PWT) was used by von Frey filament to measure mechanical hypersensitivity, and weight bearing test, knee bending test were performed to evaluate the pain during knee joint move.

Findings: Both pre- and post-administration of NK1 receptor antagonist significantly reduced edema in ipsilateral hind-limb on days 2 and 3 after MIA injection. Significant decrease of PWT caused in the MIA group was observed from days 10. However, a single injection of NK1 receptor antagonist into the knee joint inhibited to develop mechanical allodynia in both PRE and POST groups. However, NK1 receptor antagonist in both PRE and POST group did not produce any significant changes in reduced weight bearing and increased knee joint score on the ipsilateral hind-limb after MIA injection compared with the MIA only group. Conclusion & Significance: Administration of NK1 receptor antagonist in early stage of OA inhibited the initiation of chronic pain through alleviation of inflammatory responses in the joints.



Effects of NK1 receptor antagonist on the behavior of OA rats. Behavior tests were performed on pre, 1, 3, 5, 7, 10, 14 days of MIA injection. (A) Knee joint diameter was measured by caliper. (B) Paw withdrawal threshold was measured by von frey filament test in mechanical allodynia. (C) Ipsilateral weight / (ipsilateral + contralateral weight) * 100 percent weight distribution. (D) Knee bending test was performed to measure knee bending score. (*) : MIA only vs Pre injection group, (*) : MIA only vs Post injection group, . All of this is p<0.05

Biography

Junesun Kim is P.T. and Ph.D. in Physiology. She is a professor at Department of Physical Therapy Korea University College of Health Science. Her major fields of academic interest are the peripheral and central mechanisms of chronic pain, and regenerative mechanisms governing spinal cord injury. She has several publications in in peer-reviewed journals. She provides continuing education lectures regarding neurological physical therapy for SCI and mechanisms of chronic and pathologic pain to student majoring in rehabilitation science at graduate program.

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Humanin treatment, a potential new strategy to prevent bone growth impairment in chronic inflammatory disorders

Yunhan Zhao
Karolinska University, Sweden

Statement of the Problem: Children with chronic inflammatory conditions such as inflammatory bowel disease (IBD) often suffer from bone growth impairment which has been linked to increased levels of pro-inflammatory cytokines, including IL-1β and TNF-α, and treatment with high doses of glucocorticoids. Humanin is an endogenous anti-apoptotic protein which in preclinical studies has been shown to prevent glucocorticoid-induced bone growth impairment, without interfering with the desired anti-inflammatory effects of glucocorticoids. We hypothesized that systemic levels of humanin are decreased in growth retarded children with inflammatory bowel disease (IBD) and that treatment with a humanin analogue (HNG) can prevent cytokine-induced bone growth impairment.

Methodology & Theoretical Orientation: Humanin levels were measured by ELISA in serum samples obtained from 40 short children with IBD and in gender-matched healthy controls. Ex vivo cultured fetal rat metatarsal bones were treated with the pro-inflammatory cytokines IL-1β plus TNF-α (10 ng/ml each) and/or HNG (300 ng/ml) while bone growth was followed for 12 days.

Findings: Serum humanin levels were significantly decreased in the IBD patients when compared to healthy controls ($p < 0.01$). The cytokines TNF-α and IL1-β acted in synergy to suppress metatarsal bone growth ($p < 0.001$ vs control) and this effect could be partly prevented when co-cultured with HNG ($p < 0.01$ vs cytokines only).

Conclusion & Significance: Our data suggests that systemic levels of humanin are decreased in patients with chronic inflammation who suffer from bone growth impairment. Interestingly, the human analogue HNG was found to partially prevent cytokine-induced growth impairment in ex vivo cultured rat metatarsal bones. Our findings suggest that humanin is a potential drug target for the prevention of bone growth impairment in conditions of chronic inflammation.

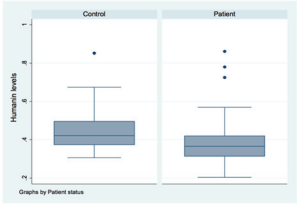

Fig. 1 Humanin levels are significantly suppressed in IBD patients (p<0.01, n=40). Serum taken from IBD patients (Laakso, Valta et al. 2012) already known to have decreased BMD, were analyzed for humanin levels by using ELISA.

Biography

Yunhan Zhao is a PhD student from Karolinska Institutet. His project is on Prevention of growth failure and osteoporosis in chronic inflammation. The aims of his studies are to explore the molecular mechanisms of GC-induced growth failure and osteoporosis, and to investigate the potential for humanin analogues, in combination with GCs to prevent osteoporosis and bone growth failure in inflammatory diseases.

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Evaluation of biocompatibility and myogenic differentiation of the transplanted myoblast using 3D cell printed muscle construct in rats

Jinju Kwon, Dongyeon Nam, Jinseung Lee, Junesun Kim
Korea University, South Korea

Severe skeletal muscle loss and long-term denervation lead to an irreversible degenerative process. In this regard, the development of engineered skeletal muscle including fusion of myoblast have investigated to promote muscle regeneration and functional recovery of injured muscle tissue. However, further researches are needed to mimic the structure and function of native muscle. In this study, we investigated 1) the differentiation of transplanted myoblasts (C2C12) using 3D cell printed muscle construct and 2) the aspect of behavioral changes in sensory and motor function after transplantation. 3D cell printed muscle (Artificial muscle) was constructed by printing of myoblast-encapsulated muscle decellularized extracelluar matrix (mdECM) bioink in nanofiber structure. To transplantation, artificial muscle was fixed to the gastrocnemius muscle. Tibial nerve transection was performed, and then the proximal end of transected nerve was implanted into artificial muscle (artificial muscle group) and into the gastrocnemius muscle (nerve implantation group) in male Sprague-Dawley rats. Behavioral test for mechanical sensitivity of the hind paw and motion capture to quantify motor function was conducted before and after artificial muscle transplantation. Immunohistochemistry was performed at the implanted nerve-muscle junction to confirm viability of transplanted muscle construct and differentiation of myoblasts. After implantation, paw withdrawal threshold was significantly decreased in both of the nerve implantation and the artificial muscle group. But it was still higher compared to those of tibial nerve injury only. Rats in both nerve implantation group and artificial muscle group showed a similar pattern with the increased range of motion (ROM) in knee joint while ROM in ankle joint decreased. Distance of strides did not show any significant changes in both groups. The present results demonstrated that the potential for myogenic differentiation of transplanted myoblasts. It suggests that possibility of creating customized functional muscle substitutes for the therapeutic treatment of the muscular injuries.

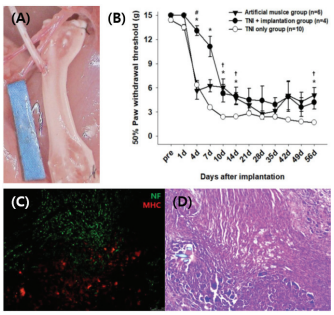

Figure 1 (A), (B) shows the surgical procedure with transplantation of artificial muscle and behavioral test in sensory function after transplantation. Immunofluorescence staining (C) and H&E staining (D) was performed.

Biography

Junesun Kim is P.T. and Ph.D. in Physiology. She is a professor at Department of Physical Therapy Korea University College of Health Science. Her major fields of academic interest are the peripheral and central mechanisms of chronic pain, and regenerative mechanisms governing spinal cord injury. She has several publications in in peer-reviewed journals. She provides continuing education lectures regarding neurological physical therapy for SCI and mechanisms of chronic and pathologic pain to student majoring in rehabilitation science at graduate program.

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e-Poster

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Sex estimation based on the clavicle measurements in Romanian population using TensorFlow

Madalina Diac
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In forensic anthropology, sex estimation is the grounds for an accurate identification of unknown human skeletal remains. This part is essential in establishing the individual biological profile. The objective of the study is to enhance the development of forensic anthropology in Romania by creating a formula for assessing sex based on metric analysis of clavicle. A total of 46 cases from Institute of Legal Medicine Iasi, Romania were included in the study. The maximum length of the clavicle, the maximum breadth of sternal end and the maximum breadth of acromial articular surface of the individual which age we knower were taken before autopsy. The method relies on a machine learning ensemble algorithm, TensorFlow, to classify the age of the metric analysis, which was used in this pilot study. The algorithm behind it is based on known algorithms in the field and creating a new one requires advanced research and mathematics. The result provided by the computer is a number between 0 and 1. Under 0.5 she's considered a woman and over a man. For better accuracy you can enter other help values as age or more numeric values that can group the dataset. That way, improving future predictions. The preliminary results obtained are good. The computer finds the correct number of men and women. Yet, the sample is still limited, and more research (more cases) should be done to verify these preliminary results. In the end, the program should be tested on skeletal collections.

Biography

Madalina Diac M.D., graduated University of Medicine and Pharmacy "Gr. T. Popa" in 2014 and Criminalistics Master of the Faculty of Juridical Sciences, University "Al. I. Cuza" Iasi in 2017. In present, Ph. D student in Forensic Medicine at the University of Medicine and Pharmacy "Gr. T. Popa" Iasi, Romania, from 2016. Currently MD, specialty Forensic Medicine, at the Institute of Legal Medicine Iaşi and also as assistant professor at the University of Medicine and Pharmacy "Gr. T. Popa" Iaşi, Romania. Author and co-author of various papers in journals and conferences.

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Variations in tibial tray locking mechanisms influence backside wear rates of polyethylene inserts in total knee arthroplasty: A systematic review

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Introduction: Modern total knee arthroplasty (TKA) systems use a variety of locking mechanisms to secure the polyethylene insert to the tibial tray. The most common locking mechanisms include peripheral rim locking and dovetail or tongue-in-groove locking mechanisms. Peripheral rim models have a circumferential raised locking mechanism around the tibial tray, whereas dovetail models have grooves in the tibial tray with corresponding areas in the polyethylene insert. The purpose of this review is to provide an update on the evidence regarding the effect of tibial tray locking mechanisms on backside polyethylene wear.

Methods: A Pubmed/MEDLINE query was performed utilizing keywords pertinent to backside wear rates of tibial tray locking mechanisms in TKA. Twelve articles met inclusion criteria and were used in this review.

Results: Backside wear on crosslinked, ultra-high molecular weight polyethylene inserts was most commonly assessed by scanning electron microscopy and the Hood score. These were used on retrieved polyethylene inserts or on a force-displacement-controlled knee simulator in one study. Data showed that peripheral fit locking mechanisms had slightly decreased backside wear rates when compared to dovetail locking mechanisms. However, one study found that peripheral rim locking with nonpolished trays had the highest amount of backside wear of the locking mechanisms studied. Dovetail mechanism implants showed more abrasive wear than other types. Nonpolished tibial trays had more backside wear than polished trays across all locking mechanism types. These results were found to be similar in both posterior stabilized and cruciate retaining designs.

Conclusions: Peripheral rim locking mechanisms show a slight decrease in the amount of backside wear compared with dovetail locking mechanisms. Additionally, polished trays show a decreased amount of backside wear when compared to nonpolished.

Biography

Safa Fassihi is a US-based physician pursuing a career in orthopedic total joint arthroplasty. His research focuses on newer arthroplasty techniques and how they affect patient outcomes. In this specific analysis, he collaborated with a US board-certified orthopedic surgeon who performs a high volume of both simultaneous and staged bilateral total knee arthroplasty.

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High number of negative radiographs for suspected tibial shaft fracture adds expense and increases patient throughput time in the emergency department

Safa Fassihi
George Washington University Hospital, USA

Purpose: The diagnosis of tibial shaft fractures (OTA 42A-C) is commonly made by emergency department (ED) providers prior to orthopedic consultation. Due to the subcutaneous anatomy of the tibia, a comprehensive history and physical examination are often sufficient for fracture diagnosis, with radiographs serving as a secondary aid. A high rate of negative X-Rays increases cost and inefficiency in the ED. This study aims to define the rate at which tibial radiographs are negative for suspected fracture.

Methods: At a Level I trauma center, a prospective database was retrospectively evaluated for ED radiographs taken from 2014 to 2016. Only radiographs obtained for suspected fracture of the tibial diaphysis were included. From this, the rate of negative diagnostic studies and the associated costs, ED throughput time, resource utilization, and radiation exposure were calculated.

Results: During the study period, 734 tibia radiographs were performed for diagnosis of tibial shaft fracture without suspected adjacent articular pathology. Of these, 565 (76.9%) were negative for tibial shaft fracture. Patient charges were increased by these radiographs through both higher radiology charges ($598 per tibia radiographic series) and higher professional charges. The mean time to obtain a tibia X-ray series in the ED was 57 minutes (SD: 47 minutes; Median: 47 minutes). The radiation exposure from a tibia radiographic series was 15 millirems.

Conclusion: At this institution, a large proportion of the radiographs obtained for suspected tibial shaft fracture are negative. The resources and time spent acquiring these radiographs places higher demands on physicians and staff while increasing charges and radiation exposure to patients. In addition, these negative radiographs add throughput time in the ED, thereby potentially contributing to ED overcrowding. The authors propose a systematic approach to maximize the diagnostic efficiency of tibia radiographs and subsequently improve resource allocation in the ED.

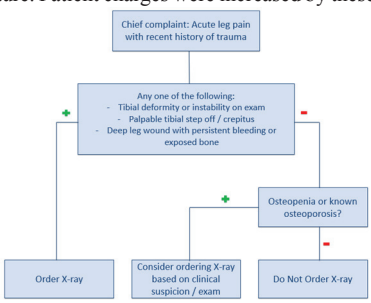

Figure 6: Suggested algorithm for ordering tibia X-rays

Biography

Safa Fassihi is a US-based physician pursuing a career in orthopedic total joint arthroplasty. His research focuses not only on total joint arthroplasty but also on improving the procedural and financial efficiency of the healthcare system. This specific analysis was based upon his experience at a level 1 trauma center, in which he recognized that there was significant emergency department overcrowding on a regular basis, so he sought to minimize any factors that may be contributing to this problem. He noticed that tibia X-rays were frequently ordered for suspected tibial shaft fracture and were negative most of the time. He collaborated with a US board-certified orthopedic traumatologist to identify the extent of this problem and offer a potential solution.

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Accepted Abstracts

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Immune-phenotyping IRF5 genetic risk and therapeutic strategies to target IRF5 hyper-activation in SLE

Betsy J Barnes
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Statement of the Problem: The transcription factor interferon regulatory factor 5 (IRF5) is a central mediator of innate and adaptive immunity. Genetic variations within IRF5 associate with risk of systemic lupus erythematosus (SLE), amongst other autoimmune diseases, and mice lacking Irf5 are protected from lupus onset and severity, but how IRF5 functions in the context of SLE disease progression remains unclear. The purpose of this study is to determine how IRF5 genetic risk contributes to SLE disease onset and severity, and whether targeting IRF5 with select inhibitors will alleviate disease severity and mortality.

Methodology & Theoretical Orientation: Studies were performed in blood from genotyped healthy donors, SLE patients and the NZB/W F1 model of spontaneous murine lupus.

Findings: Using the NZB/W F1 model of spontaneous murine lupus, we show that murine Irf5 is already hyper-activated before clinical onset in a cell type-specific manner. In healthy donors carrying IRF5 genetic risk, we detect IRF5 hyper-activation in the myeloid compartment that drives an SLE immune phenotype. In SLE patients, IRF5 hyper-activation correlates with SLEDAI and dsDNA titers. To test whether IRF5 hyper-activation is a targetable function, we developed novel inhibitors that are cell permeable, non-toxic and selectively bind to the inactive IRF5 monomer. Treatment of NZB/W F1 mice with inhibitor attenuated lupus pathology by reducing serum ANA and dsDNA titers and reducing the number of circulating plasma cells and age- or autoimmune-associated B cells (ABCs), which alleviated kidney pathology and improved overall survival. In ex vivo human studies, the inhibitor blocked SLE serum induced IRF5 activation in healthy immune cells and reversed basal IRF5 hyper-activation in SLE immune cells.

Conclusion & Significance: This study provides the first *in vivo* pre-clinical support for treating SLE patients with an IRF5 inhibitor.

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Radial diffusivity role in classification of patients with antiphospholipid syndrome and "normal" radiological exams

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Statement of the Problem: Antiphospholipid syndrome is defined as an autoimmune disease which is associated to thrombosis with common impact on MRI. However non-thrombolitic APS patients usually present "normal" routine MRI examinations. So, there is an interest to find a way to diagnostic them. Methodology & Theoretical Orientation: Diffusion-Tensor MRI (DT-MRI) was performed on 30 women with recurrent pregnancy loss (15 controls [C]; 15 antiphospholipid patients [APS] with high blood titre of Lupus Anticoagulant or Anti-b2- Glicoprotein-I antibodies). Assessed with Radial Diffusivity (RD), preceding study has demonstrated microstructural brain disruption in APS patients. Here, RD values were extracted within the significant clusters, in which voxels were considered attributes to perform Hoeffding tree classification. This is an incremental decision-tree learning model that assumes the distribution of data don't change over time. Thus, small samples may be enough for optimal splitting threshold.

Findings: A total of 5225 attributes were found significant to produce 96.67% of accuracy (29 instances). Kappa statistics was 0.93, mean absolute error was 0.03 and the relative absolute error was 6.59%. All, but one control, subjects were correctly classified, resulting sensitivity of 1 and specificity of 0.93.

Conclusion & Significance: Radial Diffusivity index is an efficient attribute to classify patients with Antiphospholipid syndrome by means of Hoeffding tree algorithms. Moreover, RD values can be used as markers to follow the progression of the disease.

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Inflammatory back pain in psoriatic arthritis is significantly more responsive to corticosteroids compared to back pain in ankylosing spondylitis: A prospective, open-labelled, controlled pilot study

Muhammad Baig
Galway University Hospital, Ireland

Background: The efficacy of corticosteroids in patients with psoriatic arthritis (PsA) and inflammatory back pain has not been studied to date. In this controlled trial, we aimed to investigate the comparative performance of corticosteroids in patients with active axial-PsA (AxPsA) versus those with active ankylosing spondylitis (AS).

Methods: Patients with AxPsA and AS (naïve to biologic therapies), who not only had clinically active disease, but also had bone marrow oedema on magnetic resonance imaging of the sacroiliac joints, were recruited. Clinically active disease was defined as inflammatory back pain (fulfilling Assessment of Spondyloarthritis International Society (ASAS) expert criteria), with spinal pain score (numerical rating scale 0-10) ≥4 and Bath AS Disease Activity Index (BASDAI) score ≥4 despite taking nonsteroidal anti-inflammatory drugs. Moreover, we recruited a control group of patients with non-inflammatory lower back pain. All patients received a single, intra-muscular dose of depot corticosteroid injection (triamcinolone acetonide 80 mg) at baseline. The intra-muscular corticosteroid option was used to overcome any drug compliance issues. Clinical outcome assessments were made at the following time points: baseline, week 2, and week 4. The primary efficacy end point was mean change in Ankylosing Spondylitis Disease Activity Score (ASDAS) at week 2. Key secondary outcomes were mean change in the BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Quality of Life (ASQoL) at weeks 2 and 4.

Table 2

Primary and secondary outcome measure responses at week 2 and week 4 of corticosteroid treatment

Parameter	Axial psoriatic arthritis	Ankylosing spondylitis	Control	*P* value, AxPsA vs. AS
Mean difference from baseline to week 2				
ASDAS	1.43 ± 0.39	1.03 ± 0.30	0.81 ± 0.26	0.004
VAS	2.46 ± 0.91	1.66 ± 1.1	1.0 ± 0.94	0.003
ASQoL	3.80 ± 1.82	2.4 ± 1.72	0.7 ± 0.67	<0.001
BASFI	2.38 ± 0.68	0.95 ± 0.91	0.44 ± 0.41	<0.001
BASDAI	1.93 ± 0.56	1.13 ± 0.33	0.84 ± 0.24	<0.001
Mean difference from baseline to week 4				
ASDAS	1.09 ± 0.32	0.77 ± 0.27	0.73 ± 0.24	0.007
VAS	2.00 ± 0.92	1.33 ± 0.72	1.30 ± 0.82	0.054
ASQoL	3.53 ± 1.35	2.26 ± 1.53	0.70 ± 0.67	<0.001
BASFI	1.76 ± 0.82	0.78 ± 0.63	0.48 ± 0.24	<0.001
BASDAI	1.57 ± 0.49	0.85 ± 0.45	0.62 ± 0.23	<0.001

Results: In total, 40 patients were recruited (15 with AxPsA, 15 with AS, and 10 controls). At week 2 following corticosteroid treatment, patients with AxPsA had significantly greater improvement in the mean ASDAS compared to patients with AS (1.43 ± 0.39 vs. 1.03 ± 0.30, p = 0.004), and also when compared to controls (p <0.001). At week-4, similar significant trend of ASDAS improvement was seen among AxPsA patients compared to AS patients (1.09 ± 0.32 vs. 0.77 ± 0.27, p = 0.007) and controls (p < 0.001). Similarly, the mean BASDAI, visual analogue scale spinal pain score, ASQoL and BASFI improved significantly among patients with AxPsA compared to patients with AS and controls at week 2 (p <0.05), with this trend also largely maintained at week 4.

Conclusions: Axial inflammation in patients with PsA responds significantly better to corticosteroids than in patients with AS. This furthers the argument and adds to the growing evidence that AxPsA and AS are distinct entities.

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Establishment and cryopreservation of human mesenchymal stem cells from wharton's jelly of umbilical cord

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Introduction: Stem cells are special human cells that have the ability to develop into many different cell types and also have the ability to repair damaged tissues. Mesenchymal stem cells (MSCs) are currently considered as 'Medicinal Signaling Cells' and a promising resource in regard to cell-based regenerative therapy. Umbilical cord is a human term perinatal tissue which is easily attainable, and a promising source of stem cells with no associated ethical concerns.

Material and Method: Wharton's jelly (WJ) is the gelatinous matrix that surrounds and provides protection to the umbilical cord blood vessels. Being more primitive, MSCs from human umbilical cord exhibit greater proliferative capacity and immunosuppressive ability. Thus as compared to adult stem cells it gives them a therapeutic advantage.

Conclusion: Being a primitive stromal cell population, WJ-MSCs offer the advantage of faster proliferation rate and reduced immunogenicity as compared to adult tissue derived MSCs. Hence, successful isolation of robustly proliferating healthy MSCs from WJ of human umbilical cord, which retain all the basic MSC properties, assumes importance.

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Yes-associated protein (YAP) is a target for invasive breast carcinoma

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Yes-associated protein (YAP) is an oncoprotein encoded by YAP1 gene. Hippo pathway activation results in sequestration of YAP in the cytoplasm and degradation. Whereas, when the Hippo pathway is deactivated, YAP is translocated into the nucleus and promotes transcription of downstream genes stimulating growth and inhibiting apoptosis. Numerous studies showed that overexpression of YAP induces epithelial-mesenchymal transition, inhibits apoptosis and increases cancer stem cells number *in-vitro*. Levels of YAP were found to be elevated in many human cancers and related to poorly differentiated tumors. Therefore, YAP has emerged as a prime target for developing anti-cancer drugs. This study aims to investigate the immunohistochemical expression of YAP in breast cancer tissue compared to benign tumors and normal breast tissue. The nuclear expression of YAP was evaluated in six cases of benign fibroadenomas, 6 cases of in- situ ductal carcinomas, 6 cases of normal breast tissue samples as well as 60 cases of invasive breast carcinoma, 57 ductal (IDC) and 3 lobular (ILC). Staining was analyzed and blindly scored. Nuclear staining of more than 20% of the nuclei was considered positive. Cytoplasmic staining was scored according to its intensity as (+1 mild, +2 moderate, +3 strong). The results were then correlated with grade, stage and hormone receptor positivity in each of those tissues. All cases of normal, benign and in-situ carcinomas depicted no nuclear YAP expression. YAP expression in these cases was mostly cytoplasmic and varied in expression between mild, moderate or strong. On the other hand, 60% of invasive breast carcinomas cases showed positive nuclear staining suggesting that YAP is active in these tumors and could have possible carcinogenic role. Our data showed that YAP is highly active in breast adenocarcinoma and suggest that further studies are required to investigate the exact pathway responsible for YAP activation and its involvement in carcinogenesis.

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Response to immunomodulator treatment as diagnostic criterion of cirrhosis due to autoimmune hepatitis

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Autoimmune hepatitis is a progressive inflammatory disease that directly attacks the hepatocytes, in the long term and without timely treatment leads to cirrhosis. Worldwide, it is estimated between 11.6-35.9 cases/100,000 inhabitants, therefore, in medical practice it is low considered in the diagnosis of chronic hepatitis; because the simplified diagnostic criteria for this disease are complex, since they focus on expensive diagnostic means and in low and middle income countries, access is difficult, the opportunity for diagnosis and treatment is also important Consider the sensitivity of these. In addition, it is important to consider the sensitivity of these diagnostic means. Some cases are atypical, in which clinical improvement with immunomodulatory treatment is highlighted as a diagnostic criterion of the classic criteria of 1999 to establish the diagnosis of autoimmune hepatitis due to the high sensitivity of the response to treatment evidenced at 48 hours. Therefore, it is important to consider the start of immunomodulatory treatment against autoimmune hepatitis once the main causes of chronic liver disease have been ruled out, despite not fulfilling the diagnostic criteria, as this prevented progression of the disease, a fatal outcome and mortality in the patient. The absence of immunosuppressive therapy between diagnostic criteria is a limitation for diagnosis and treatment.

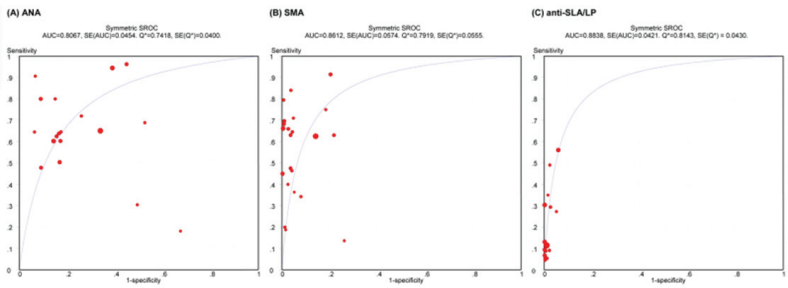

Figure 3. SROC curves for ANA, SMA and anti-SLA/LP. Each solid circle represents each study in the meta-analysis. The size of each study is indicated by the size of the solid circle. SROC = summary receiver operative curve, ANA = antinuclear antibodies, SMA = smooth muscle antibodies, anti-SLA/LP = antibodies to a soluble liver antigen/liver pancreas, AUC = area under the curve, SE = standard error, Q* = Cochran Q.
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