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Case Report

Could the Yeargan Autologous Subchondral Nanoplasty[tm] and Mechanical Axis Deviation Protocol (NAMAD®) Halt Molecular Progression and Reverse the Clinical Symptoms of Knee Osteoarthritis? Clinical and Scientific Concepts with Case Presentation Including T2 Wetmap Cartigram® sequencing

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Abstract

Osteoarthritis causes a heavy disease burden globally and treatments are continually evolving. We introduced an autologous cell therapy protocol in 2006 that has continued to demonstrate promise clinically and on advanced imaging studies. In this report, we detail applicable scientific concepts, our surgical technique and present a case report for illustration.

Keywords: Osteoarthritis; Subchondral Bone; Nanoplastytm and Mechanical Axis Deviation Protocol (NAMAD®)

Arthritis is a disease of the subchondral bone primarily, not the articular cartilage [1,2]. With gravitational and musculoskeletal force vector directed load into the concave side of the joint, a mechanotransduction-mediated immunomodulatory signaling transduction mechanism leads to pathological, catabolic consequences that cause the predictable, progressive, organic destruction of the joint we call osteoarthritis [3,4]. Beginning with subchondral stiffening, a predictable pattern of arthritis progression follows from the concave side of the synovial joint to the convex side of the synovial joint [5]. During this maladaptive loading, soft structures in the joint, namely the proteoglycan extracellular cartilage matrix, are destroyed mechanically and enzymatically, ultimately resulting in cartilage dessication and autoinflammatory joint destruction [6] (Illustrations 1 and 2). Understanding the molecular stages of advancing arthritis promises to open doors to novel treatment pathways for clinically symptomatic osteoarthritis [7].

Osteoarthritis is a leading cause of disability worldwide and will continue to increase as the population grows and ages [8]. Arthritis costs over 80 billion with 65 billion in direct costs. In the setting of OA, reduced levels of physical activity, comorbid conditions and adverse effects of medications lead to a 55% increase in all cause mortality. OA increases the risk of developing heart disease by 50% and there is growing concern that without novel treatment algorithms, additional human suffering will certainly emerge and bring catastrophic cost consequences [9].

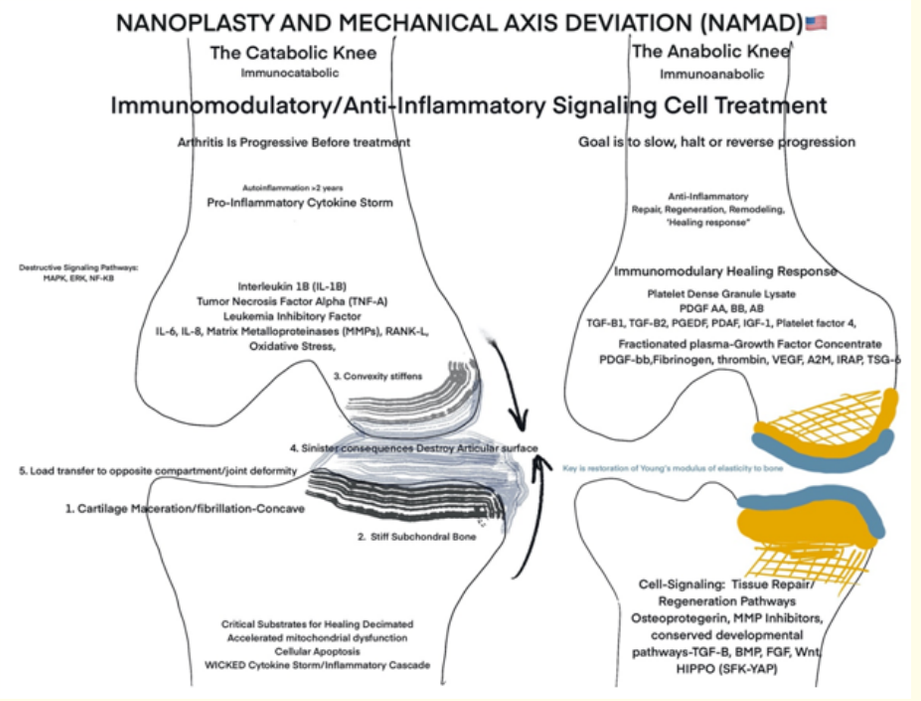


Illustration 1

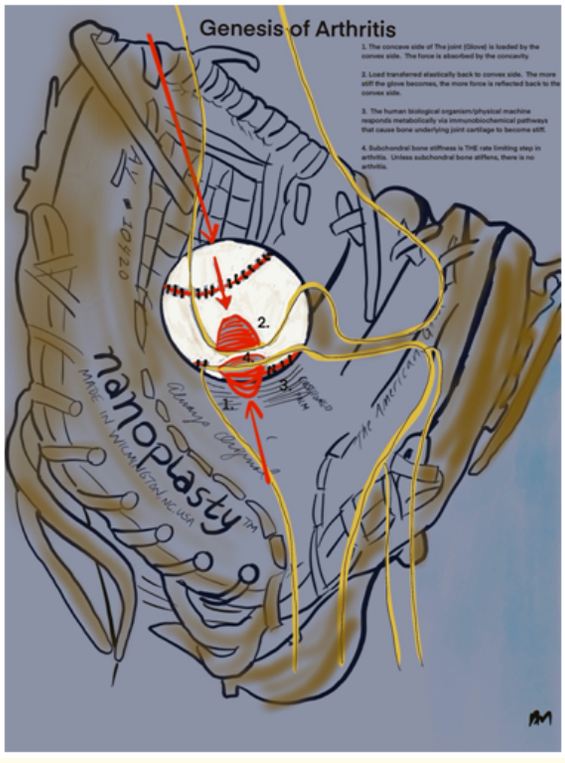


Illustration 2

Bone marrow concentrates for knee arthritis have received much attention over the last decade as a viable treatment for osteoarthritic knee pain and disability. In spite of the availability of these bone marrow concentrates, there has yet to be a gold standard for treatment suggested. We first introduced our signaling cell procedure to orthopedic surgery in 2006 [10]. The procedure has undergone multiple iterations since that time. In this article, we introduce our seventh-generation technique for signaling cell treatment in the setting of osteoarthritis of the knee and discuss the role of tumor necrosis factor stimulated gene six protein in our signaling cell product.

Herein, we describe the successful management of a patient with unicompartmental right knee osteoarthritis originally scheduled for total knee arthroplasty, who elected to undergo our clinical algorithm for microcore[tm] Nanoplasty[tm] and Mechanical Axis Deviation (NAMAD®). We discuss treatment concepts and a clinical algorithm including physical therapy and modalities like low intensity pulsed ultrasound (LIPUS) that can lead to success in the management of these patients in our hands. The algorithm is scientifically sound and the technique is reproducible and simple to perform in an office setting by any orthopedic surgeon. Patient selection is critical to achieving excellent clinical results and should be carefully metered by the indicating surgeon. Orthopedic immunobiologic procedures, while potentially efficacious, remain experimental and only cleared for safety by the FDA. Patients must be made to understand the facts behind the treatment and understand the risks, benefits and alternatives to all available treatments in order to provide true informed consent for any procedure.

Globally, direct out of pocket costs to patients for regenerative procedures to patient have been staggering and aside from marrow-based procedures have not demonstrated valuable clinical efficacy in a value-based setting. The chance in this setting for pseudoscience is great and cautious progress must continue to be made until we understand the limitations of these treatment strategies. Expectations for platelet rich plasma (PRP) have fallen short. Platelet rich plasma continues to struggle desperately for any indication, although some studies have suggested a possible role in the short-term management of arthritic pain. Extra-osseous bone marrow concentrate procedures may last less than two years depending on the cell product and treating healthcare provider, because they do not address the genesis of the arthritis, the non-compliant and stiff subchondral bone [11]. Intraosseous procedures like the subchondral nanoplasty[tm] promise to deliver structural and functional biologic alterations that may lead to long term relief from symptoms as bony subchondral remodeling follows interventions at the nanoscale and macroscale inherent to the Nanoplasty[tm].

Case Report

The patient is a 60-year-old female with symptomatic, unicompartmental varus gonarthrosis of the right knee. The patient initially presented in May 2018 with complaints of medial-sided knee pain severely limiting recreational and vocational pursuits and was felt appropriate for the procedure approximately eight weeks after presentation, having achieved their pre-habilitation goals. The patient was seen and evaluated by two other orthopedic surgeons who recommended total knee arthroplasty as the only treatment option. The patient presented to our clinic for alternative treatment strategies including orthopedic surgical immunobiologics and also for an explanation of pathophysiology of disease. She had also visited two pain medicine clinics proclaiming to offer regenerative medicine treatments who offered her wharton's jelly or umbilical cord cells respectively, with a list price just under $8500 for one joint injection. Neither of these other treatment applications are supported by any real literature and useful application is scientifically limited and of uncertain, if any, clinical efficacy. There may be short term relief from immunomodulatory effects from these treatments, although their cost is not justified in our opinion [12,13].

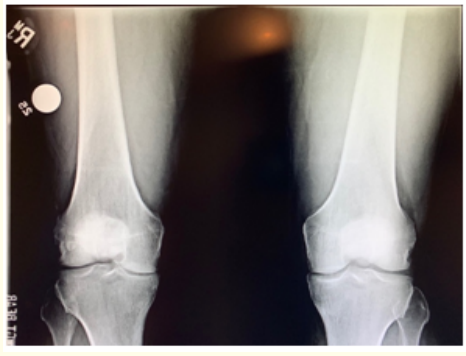
The patient's history was significant for remote prior partial medial meniscectomy and use of meloxicam (Mobic®) daily for years with occasional need for opioid medication they were using several times weekly for activity. (Following the procedure, the patient has not required any analgesics, oral or otherwise). The patient had failed multimodality conservative measures including physical therapy, topical and systemic non-steroidal anti-inflammatory medications (NSAIDs), corticosteroid (CS) and hyaluronic acid (HA) injections for over a three-year time period without adequate relief. The patient had a past medical history including controlled hypertension and gastroesophageal reflux disease optimized medically. The patient reported no allergies. Upon initial physical examination, the patient was noted to lack full terminal

range of motion equal to the contralateral, symptom-free, varus left knee. Pre-habilitation including manual stretching and strengthening of core and lower extremity was initiated immediately. Patient are referred to a physical therapist gait expert where formal on-site, custom lateral heel wedge orthotics are fashioned immediately. Achieving a full, active extension without demonstrable contracture after stretching out the posteromedial capsuloligamentous structures of the knee is mandatory in all patients who want to be considered for the procedure. No difference in side-to-side strength was detectable once the patient had completed the pre-habilitation phase. The importance of achieving full, terminal range of motion is critical to achieving an adequate clinical result with this technique and cannot be over-emphasized. Core, flexor and extensor strength should be optimized and balanced prior to proceeding with the algorithm. Failure to achieve a full, concentric range of motion prior to proceeding with signaling cell transplant therapy is not recommended because the malreduction at impact results in joint edge loading that equates to third body wear forces physically that prompt immunomodulated biochemical enzymatic joint destruction through a mechanotransduction mechanism.

The patient complained of pain in the anteromedial aspect of the ipsilateral right knee at the joint line and a small effusion was noted. The left knee examination was normal. Lumbosacral and hip evaluation were normal including hip version. The patient had two finger-breadths of varus in the pre-procedural setting without a varus thrust. Some static correction of the varus deformity of the right knee was able to be clinically demonstrated, indicating ligamentous compliance and suggesting tolerance for unloader brace wear. We use the Ossur® Rebound Cartilage unloader device (Ossur, Rekjavik, Iceland). Motor evaluation was normal and there were no gross neurovascular deficits distally. No asymmetry was detected. Foot and ankle examination were normal without hindfoot varus or valgus or pronosupination abnormalities. Clinical images are depicted in figure 1.

Plain films of the lumbosacral spine including flexion and extension views, hip and pelvis were normal. No phleboliths indicating prior VTED or primary lesions were noted. There was normal mineralization, no sacroiliac joint arthrosis or lumbosacral spondylosis or facet arthropathy. Radiographs of the knee, including long-standing films for alignment revealed medial compartment joint disease with joint space narrowing, tibial and femoral osteophytes and subchondral sclerosis of the concave and the convex sides of the medial joint. There was preservation of the lateral tibiofemoral and patellofemoral joints. Normal patellofemoral articulation. Radiographs are shown in figure 2.

Figure 1: Clinical presentation.



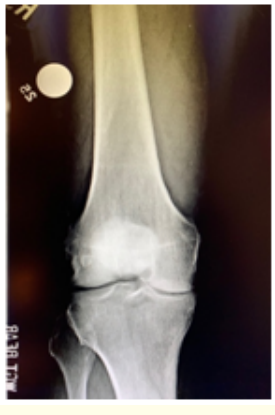


Figure 2A and 2B: Radiographs.

Pre-procedural magnetic resonance imaging is standard in all of our patients who are considered potential candidates for regenerative cartilage procedures. A T2 wetmap Cartigram® (General Electric Health®, Chicago, IL) was obtained and findings on imaging sequences including the Terracon® and Cartigram® views are shown in figure 3. Preoperatively, the T2 images were used to approximate trajectory and to further visualize the area of dense microstructure (Figure 4).

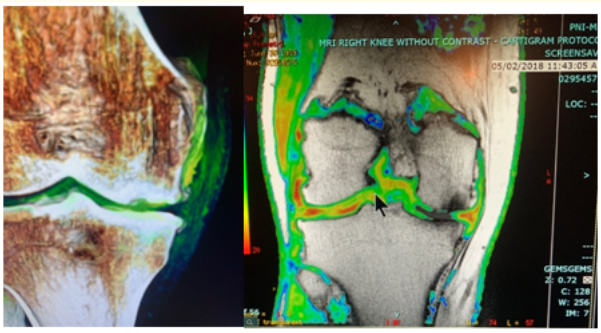


Figure 3A and 3B

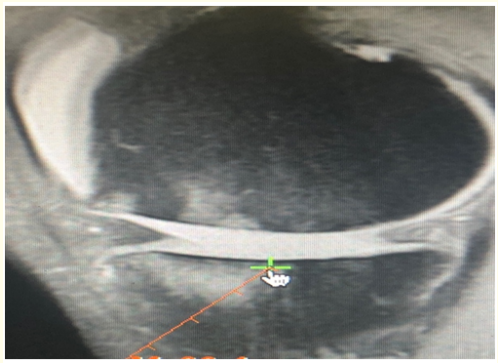


Figure 4: Pre-operative planning on T2 MRI of right knee.

Pre-procedural laboratory studies included serum chemistries and complete blood count with iron, calcium, magnesium and phosphorus levels. All were found to be within the normal range. Serum interleukin 6 was normal.

The patient was deemed appropriate for the intervention based on her ability to consent to the experimental procedure with a full understanding of all risks, benefits and alternatives to orthopedic surgical immunobiologic treatment, including no treatment. The patient's youth, remaining articular cartilage, absence of exclusionary alignment issues with demonstrable ligamentous compliance, ability and desire to comply with all treatment recommendations, excellent fitness and reasonable expectations made her a candidate for the procedure. It was felt that the patient could adequately benefit from the clinical NAMAD® program as follows.

The patient received pre-operative assurance from her primary physician that she was appropriate to tolerate the office procedure. The patient was admitted to the clinic. One hour prior to arrival, the patient self-dosed an oral sedative-hypnotic and a dose of antibiotic. The patient performed Chlorhexidine 3% scrub at home the evening before and the AM of the procedure at the harvest and target sites. Procedure briefing was accomplished before proceeding.

We positively identified the anterior ipsilateral gluteal pillar as the harvest site and the right knee joint as the primary target surgical site. Indelible marker was used to mark the targets with the MDs initials. The patient was fit for an Ossur Rebound unloader prior to the intervention. The patient has the unloader today for application post procedure. The patient's vitals were taken and found to be stable and within normal range, consistent with the prior clinical visit metrics. Once the patient was deemed appropriate to proceed for preparation, they were transported to the procedural suite via wheelchair and helped onto the procedure table into a seated position.

A 'time-out' assessment was called and the op site was confirmed by the attendant RN and MD visually by indelible marker. Patient confirmed NKDA. The patient was then carefully placed into the supine position for the marrow aspiration procedure. Full sterile isolation barriers were used during the procedure following the prep. In each setting, DuraPrep® sponges were used to paint the intended harvest and target sites followed by application of sterile sticky drapes and maintenance of sterile precautions. The gluteal pillar of the left hemi-pelvis was marked four fingerbreadths back (7 cm) from the ASIS at the thickest part of the iliac crest. Carefully, 10 - 15 mL of local anesthetic containing Lidocaine 1% plain mixed

1:1 with Marcaine 0.25%. Epinephrine was used to infiltrate the skin, subcutaneous tissue and periosteum about the right anterior iliac crest at the level of the gluteal pillar extraction. We let the local anesthetic take full effect so that it could be obviously demonstrated before proceeding. Patient stated VAS pain 3-4 for aspiration, coincident with mean of 3 typically in our experience.

The appropriate entry site was identified and marked, coinciding with the thickest portion of the anterior crest at the gluteal pillar. The Jamshidi was aimed towards the femoral neck. Using a 260 gram surgical mallet, the Jamshidi was gently and carefully advanced approximately 2.5 cm into the core of the pillar. The obturator was removed revealing the expected slow, but immediate egress of bone marrow.

12 mL of marrow plasma was extracted first for Arthrocare® thrombinator processing to allow for extraction of autologous thrombin for scaffold activation upon interosseous cell transplantation.

Next, six 10 mL syringes were used to aspirate bone marrow in sequential fashion with care taken to reposition the needle tip with rotation and/or advancement after each 9 - 10 mL aspiration to ensure the most efficient mesenchymal cell capture from the marrow.

Following completion of the bone marrow aspiration the Jamshidi was removed uneventfully. Pressure was held for 3 minutes followed by application of a sterile pressure dressing with 2% Bactroban ointment over a flexible fabric band-aid. The wound was checked prior to discharge of patient from the clinic and noted to be dry. The syringes were sequentially handed off as drawn to the RN assistant who immediately injected them through the clot/particulate filter into the sterile Celling Biosciences® ART® II Plus processor in preparation for centrifugation. Once all of the marrow had been transferred to the processing unit, it was counterweighted to 258g. The centrifuge was then loaded and set at a revolution speed of 3200 rpm for 14 minutes duration. Upon completion of centrifugation there were three distinct layers noted in the processor window including a robust buffy coat of nucleated cells. The plasma fraction was actively transferred through the processor's built-in A2M nanofilter to capture the growth factor concentrate into a total of 5.0 mL. This was mixed with the autologous thrombin and $CaCl_3$ in order to establish pliable ECM cellular scaffold for injection that would gel interosseously at the time of cell transplantation. The nucleated cellular injectate from the bone marrow fraction was aspirated from the ART II plus processor into a volume of 5.0 mL. Total volume for injection was 5.0 mL BMC and 5.0 mL GFC.

Next, the mini C-arm was draped sterile in preparation for the subchondral nanoplasty as the patient was prepped and draped in standard fashion. Initially, attention was turned towards the subchondral component of the nanoplasty. The bony anatomy was palpated and marked using an indelible marker. The insertion of the pes footprint serving as the starting point with trajectory directed towards the central depression of the medial compartment and confirmed in orthogonal planes. The angle was set at approximately 40 - 45º relative to a vertical line based off of the medial malleolus to approach the most affected area of the native load cylinder. We identified the ideal starting point and trajectory to converge on the most sclerotic subchondral zone which was manually fine-tuned in surgical fashion. Care was taken to avoid joint penetration and to cross the physeal scar during the approach (Figure 5). Avoidance of the joint cavity was confirmed during the intra-articular component of the procedure where only clear, yellow synovial fluid was observed without particulate.

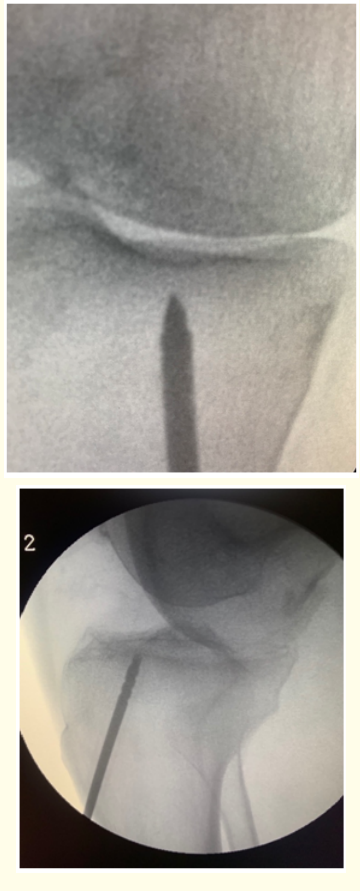


Figure 5: Advancement of the Jamshidi needle in the osteoarthritic knee. AP and Lateral views.

A 3 mm stab incision was made and a 260 gram surgical mallet was used to advanced a fresh Jamshidi® so that the distal tip was parked in the subchondral bone beneath the subchondral plate on image intensification. Once the position of the Jamshidi was confirmed in multiple planes, 15 mL bone marrow aspirate was aspirated and passed off the table. Following dilution and nucleocount, the cell tally was below the detection limit of the Nucleocounter 250 device, < 5 k/mL TNC.

Next the BMC/GFC/Thrombin injectate was very slowly injected interosseously, which the patient tolerated well. We have found this to be consistently the most uncomfortable part of the procedure for the patient. Once the injection was accomplished, the Jamshidi obturator was replaced and the injectate allowed to sit 2 - 3 minutes while the thrombin took full effect. Once the interosseous injection had been accomplished and with the Jamshidi indwelling, aspiration of the knee was accomplished. Aspiration of clear synovial fluid from the joint during the next step is confirmatory of extra-articular and appropriate Jamshidi introduction outside of the synovial folds of the knee joint.

14 mL of clear, straw colored synovial fluid without particulate was aspirated from the knee using an 18 ga needle. There was no evidence of hemarthrosis. Injection of the remaining 8.0 mL cellular/scaffold concentrate was then easily accomplished through the same right lateral para-patellar approach without difficulty using the indwelling 18 ga needle, which was removed promptly after scaffold injection. The injection site was cleaned with chlorhexidine 3%, dried, followed by application of Bactroban 2% ointment and a sterile flexible strip, which is standard for all of our puncture sites. A sterile compressive wrap was then applied. Following the knee joint injection, the joint was placed through a full ROM several times including patellofemoral translation. Motion was excellent and the injection was successful. The Ossur® Rebound® unloader was then applied and adjusted. The patient tolerated the procedure extremely well and there were no complications.

A final set of vitals were taken, found to stable and within normal limits. No ice or any anti-inflammatory measures are to be used to preserve natural healing. Follow up in 21days. ADLs with ambulation using Ossur Unloader Brace only.

SCi Nanoplasty-1.0 BMC/1.0 GFC/1.0 autologous thrombin.

Articular Injection-4.0 BMC/4.0 GFC.

In the setting of severe posteromedial structure contracture, we consider pie crusting versus Tenex-Health TX-2® to release tight medial structures including deep MCL where necessary.

Unloader Brace and bilateral custom lateral heel wedge orthotics. No impact activity. The patient will call me immediately with any questions or concerns. Pt has my mobile number, home number and email contacts and was personally contacted on the night of the procedure to ensure an excellent outcome.

We now provide a handheld personal low intensity pulsed ultrasound (LIPUS) device to all patients with instructions on appropriate use in the post-procedural setting.

The patient's total nucleated cell count was obtained immediately following the concentrated cell matrix procedure. Samples were preserved in heparin for enzyme linked immunosorbent assay assessment including bone marrow aspirate (BMA), bone marrow concentrate (BMC), platelet poor plasma (PPP) and growth factor concentrate (GFC) (Figure 6).

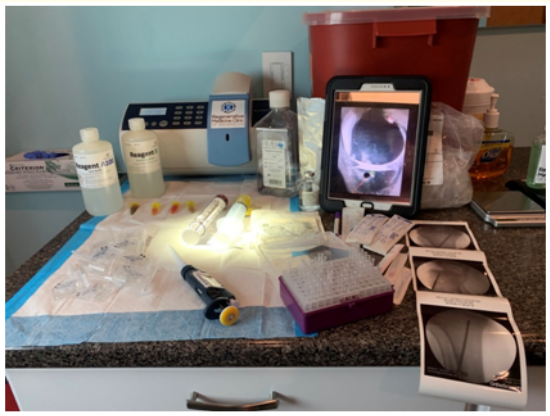


Figure 6: Laboratory analysis including total nucleated cell count and viability is done immediately following the immunobiologic procedure.

Post procedure

Post procedure the patient was allowed normal WBAT for two weeks while she continued leg extension exercises and core fitness. Unloader brace wear was at all times while gravity dependent, avoiding stairs. Gait and balance were the primary focus for the first two weeks. The patient was seen at two weeks and pain relief was approximately 50%. The patient was allowed to progress on our physical therapy algorithm specific to this procedure which demands achievement of full range of motion before progressing to strengthening. At six weeks the patient was seen progressing well and was allowed unloader brace wear with activity only and limited impact. At twelve weeks, the patient remained symptom free and able to enjoy recreational and vocational pursuits unhindered.

The patient is approaching three years follow up with no return of clinical symptoms and has returned to playing doubles tennis and pickleball without limitations. The patient is able to enjoy all of their desired recreational and vocational pursuits and indicated they would have the procedure again and that they felt the cost justified.

We perform serial MR Cartigram® Imaging at one-year intervals with the results shown in figure 7A and 7B. At one year, there has been interval healing of the subchondral bone on the convex side of the joint and healing on the concave side of the joint where arthritis was originally generated.

Low intensity pulsed ultrasound (LIPUS)

We now provide a handheld personal low intensity pulsed ultrasound (LIPUS) device to all patients with instructions on appropriate use in the post-procedural setting. All living organisms are subject to external physical forces in their environment. The conversion of these physical forces into biochemical signals and integration of these signals into a functional response is termed mechanotransduction. On a cellular level, a mechanical stimulus generates a biochemical signal, which in turn can bring about a number of intracellular processes. These include activation of complex signalling pathways, upregulation or downregulation of gene expression, and alteration of protein synthesis, resulting in adjustment of the intracellular and extracellular environment in response to the initial mechanical stimulus. This mechanosensitive feedback modulates cellular functions as diverse as migration, proliferation, differentiation, and apoptosis, and is crucial for organ development and homeostasis [14].

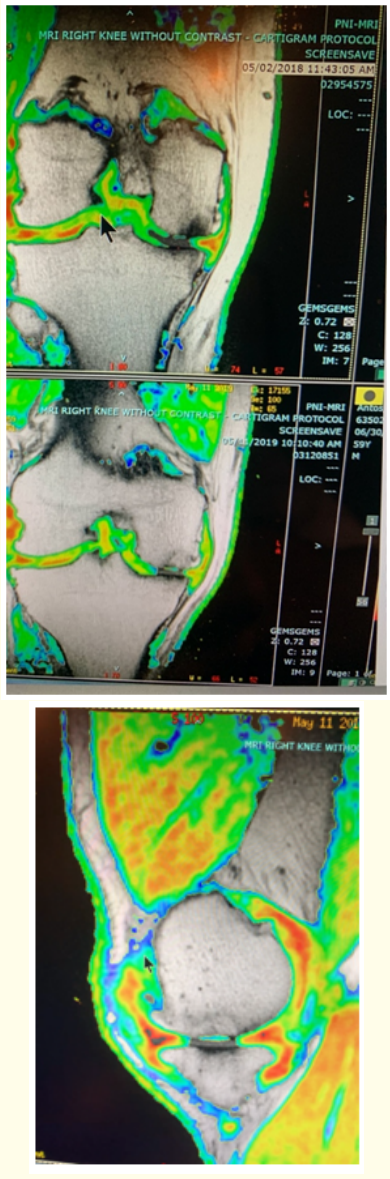


Figure 7A and 7B: T2 wetmap MRI demonstrating changes at one-year post procedure. The subchondral bone is healing and the arthritis is no longer progressing. New tissue is evident. (GE Cartigram®, GE Health®, Chicago, IL).

Low-intensity pulsed ultrasound (LIPUS) has been commercially available since its 1994 Food and Drug Administration (FDA) approval as an adjuvant therapy in the healing of primary fractures

[15]. It exerts a micromechanical stress over its target site and has been shown *in vitro* to increase the incorporation of calcium ions in cultures of cartilage and bone cells while stimulating gene expression implicated in the healing process [16]. *In vivo* work by Naruse., *et al.* implicates COX-2 as the central protagonist for mediating LIPUS-induced osteogenesis [17]. Application of LIPUS on bone marrow stromal cells elevated levels of IGF-I, OCN, and bone sialoprotein mRNA, which were in turn eliminated by application of a COX-2 inhibitor These findings have been substantiated by Tang., *et al*. who demonstrated increased expression of COX-2 in osteoblasts via activation of integrins and subsequently kinase pathways following application of ultrasound [18].

The technology is now widely used in clinical practice, despite the exact biological mechanism of function remaining unknown. Low-intensity pulsed ultrasound was prescribed by 21% of Canadian trauma surgeons in the management of acute tibial fractures in 2008, and LIPUS technologies are available to be prescribed on the NHS in the UK.

A number of preclinical and clinical studies have assessed the effects of this technology on fracture healing [19]. However, its use remains controversial. A 2017 systematic review of 17 sham controlled high-quality randomized trials assessed several outcomes such as functional recovery, number of subsequent operations, and time to radiological healing. This review also assessed each included study for risk of bias and reliability. The review concluded that high-quality randomized trials showed no effect on pain reduction, time to full weight bearing, or adverse effects related to the device. Furthermore, when higher credence was given to trials at low risk of bias, there was moderate- to high-quality evidence that LIPUS failed to accelerate radiological healing. LIPUS promises a relatively low-cost, non-invasive technology to assist in fracture healing and orthopedic surgical immunobiologic regenerative medicine options [20]. Unfortunately, despite the presence of many trials in the field, a definitive answer in support of its use remains elusive.

It is evident from review of the literature that the application of molecular-level mechanical forces has a clear osteogenic effect on both *in vitro* and *in vivo* cells. Macroscopically, the clinical evidence is less convincing. Current mechanotransductive technologies have failed to prove their utility despite tantalizing *in vitro* evidence and plausible biochemical mechanisms, leaving patients with the deleterious effects of fracture nonunion. A global consensus regarding the optimal way to treat nonunion remains undecided, but stimulating de novo bone formation is likely to be pivotal in the development of an effective therapy.

Given how far the understanding of the physiological mechanisms underpinning mechanotransduction has progressed, together with the osteogenic properties that numerous *in vitro* and *in vivo* mechanotransduction studies have demonstrated, it is hopeful that future research will identify effective novel targets for de novo bone formation utilizing mechanotransduction.

Total nucleated cell count

The patient's total nucleated cell count was obtained immediately following the concentrated cell matrix procedure. Samples were preserved in heparin for enzyme linked immunosorbent assay assessment including bone marrow aspirate (BMA), bone marrow concentrate (BMC), platelet poor plasma (PPP) and growth factor concentrate (GFC) (Figure 6). Total nucleated cell count was 3.22×10^8 with 98% viability.

The patient no longer had a requirement for NSAID or other analgesic therapy at final follow up.

Discussion and Conclusion

In animal models of orthopedic surgery including the human model, arthritis is a progressive disease that requires stiffening of the subchondral bone beneath the cartilage before inception.

In our experience, arthritis progression is predictable when sought out on MR Cartigram studies and advances in definite fashion: Impact from the convex side of the joint into the convex acts through a nanomolecular immunomodoulatory, mechanotransduction mechanism that is integrin and cadherin based. Ultimately, the material integrity of the chondral matrix is superseded by overload during impact activity. Once the load is passed through to the subchondral bone, an osteoclastic resorption front is established that soon leads to increased intraosseous pressure as new bone is laid down. Once intraosseous pressures exceed capillary perfusion pressures (30 mmHg), perfusion deficits lead to additional increases in Young's Modulus of elasticity and the material properties of

the previously elastic subchondral bone become compromised. Performing microcore decompression relieves intraosseous pressure and heralds the onset of immunomodulatory activity. Confused into believing the injury is acute, rather than chronic and not worthy of ATP expenditures, the immunology of the bone responds in favor of an anabolic response that leads to bone remodeling and restoration of native mechanical properties. Restoration of the material properties of native bone and joint mechanics may lead to an anabolic response in the articular cartilage with new cell differentiation, patterning and migration [21].

In the appropriate clinical setting of varus, unicompartmental knee osteoarthritis, the microcore decompression nanoplasty and mechanical axis deviation protocol (NAMAD®) we describe appears to stimulate subchondral bone remodeling and restore an anabolic environment to surrounding articular cartilage. Nanoplastic remodeling restores native material properties like Young's modulus of elasticity to the subchondral bone. Spatiotemporally based immonumodulatory signaling from mesenchymal stem cell concentrates may stimulate transition to an anabolic environment both interosseously and in the knee joint. We suspect that coring the stiff subchondral bone with aspiration and injection of the bone marrow concentrate product prompts a new osteoclastic resorption front that is followed by regional remodeling while the mechanical axis is renewed with a combination of physical therapy, knee unloader braces and custom lateral heel wedge orthotics. Maintenance of this new mechanical axis may lead to long-lasting clinical relief from symptoms, as is suggested by the restoration of proteoglycan signaling on Cartigram® (General Electric Healthcare, Chicago, IL) T2 wetmapping software enhanced sequences as demonstrated. We believe that the observed restoration of proteoglycan signaling on T2 wetmap cartigram sequences, may indicate a reversal of progressive osteoarthritis and have not observed progression of disease in any of our patients treated with the clinical NAMAD® algorithm. Using molecular techniques in combination with focus on the mechanical axis can lead to what appears to be enhanced anabolic signaling that can result in resolution of osteoarthritis symptoms and may lead to the reversal of molecular and structural disease.

We have extensive experience with the NAMAD® clinical procedure in hundreds of patients over the last 14 years and the procedure is not for everyone. Patient selection determines the success of the procedure. The procedure requires full range of motion, normal neurological function and a relatively uninvolved medial or lateral weight bearing compartment in the knee. Varus or valgus alignment should be somewhat correctable with orthotic and brace wear and manual therapy may be indicated with pre-procedural rehabilitation. Expectation/result mismatch may be encountered if patients are not appropriately evaluated and counseled regarding treatment capabilities that differ in each case. Orthopedic surgeons should be cautious in appropriate patient selection for these techniques until further study can fully delineate the potential of the procedure to halt or reverse the progression of osteoarthritis. In particular, we believe extreme caution should be used in any product containing genetic material that is not autologously sourced. Both Wharton's Jelly and umbilical cord blood products have begun to appear clinically in spite of a clear lack of evidence for their application. Neither of these other treatment applications are supported by any scientific clinical literature and making useful application potentially dangerous and of uncertain clinical efficacy. Some basic research has suggested there may be short term relief from the immunomodulatory effects from these treatments, although their cost is not justified in our opinion [12,13].

Bibliography

1. Barr AJ., *et al*. "A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis". *Arthritis Research and Therapy* 17.1 (2015):228.

2. Li G., *et al*. "Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes". *Arthritis Research and Therapy* 15.6 (2013): 223.

3. Jutila AA., *et al*. "Candidate mediators of chondrocyte mechanotransduction via targeted and untargeted metabolomic measurements". *Archives of Biochemistry and Biophysics* 545 (2014): 116-123.

4. Teichtahl AJ., *et al*. "Wolff's law in action: a mechanism for early knee osteoarthritis". *Arthritis Research and Therapy* 17.1 (2015): 207.

5. Hardcastle SA., *et al*. "Individuals with high bone mass have an increased prevalence of radiographic knee osteoarthritis". *Bone* 71 (2015): 171-179.

6. Zignego DL., *et al*. "Mechanotransduction in primary human osteoarthritic chondrocytes is mediated by metabolism of energy, lipids, and amino acids". *Journal of Biomechanics* 48.16 (2015): 4253-4261.

7. Fülöp T Jr., *et al*. "Ageing, autoimmunity and arthritis: Perturbations of TCR signal transduction pathways with ageing - a biochemical paradigm for the ageing immune system". *Archives of Biochemistry and Biophysics* 5.6 (2003): 290-302.

8. Allen KD and Golightly YM. "State of the evidence". *Current Opinion in Rheumatology* 27.3 (2015):276-283.

9. Osteoarthritis Prevention and Management in Primary Care.

10. https://www.researchgate.net/profile/Austin_Yeargan_Iii2

11. Pickarski M., *et al*. "Changes in articular cartilage and subchondral bone in the rat anterior cruciate ligament transection and meniscectomized models of osteoarthritis". *BMC Musculoskeletal Disorders* 12 (2011): 197.

12. L Wang., *et al*. "Human umbilical cord mesenchymal stem cell therapy for patients with active rheumatoid arthritis: safety and efficacy". *Stem Cells and Development* 22 (2013): 3192-3202.

13. Vieira Paladino F., *et al*. "The Immunomodulatory Potential of Wharton's Jelly Mesenchymal Stem/Stromal Cells". *Stem Cells International* (2019): 3548917.

14. Jaalouk DE and Lammerding J. "Mechanotransduction gone awry". *Nature Reviews Molecular Cell Biology* 10.1 (2009): 63-73.

15. Victoria G., *et al*. "Bone stimulation for fracture healing: what's all the fuss?" *The Indian Journal of Orthopaedics* 43.2 (2009): 117-120.

16. Claes L and Willie B. "The enhancement of bone regeneration by ultrasound". *Progress in Biophysics and Molecular Biology* 93.1-3 (2007): 384-398.

17. Naruse K., *et al*. "Anabolic response of mouse bone-marrow-derived stromal cell clone ST2 cells to low-intensity pulsed ultrasound". *Biochemical and Biophysical Research Communications* 268.1 (2000): 216-220.

18. Stewart S., *et al*. "Mecchanotransduction in osteogenesis". *Bone and Joint Research* 9.1 (2020): 1-14.

19. Azuma Y., *et al*. "Low-intensity pulsed ultrasound accelerates rat femoral fracture healing by acting on the various cellular reactions in the fracture callus". *The Journal of Bone and Mineral Research* 16.4 (2001): 671-680.

20. Higgins A., *et al*. "EXOGEN ultrasound bone healing system for long bone fractures with non-union or delayed healing: a NICE medical technology guidance". *Applied Health Economics and Health Policy* 12.5 (2014): 477-484.

21. B Nakken., *et al*. "Biomarkers for rheumatoid arthritis: from molecular processes to diagnostic applications-current concepts and future perspectives". *Immunology Letters* 189 (2017): 13-18.