Fractional and Deep-Tissue Heating Dual-Laser System Combined with Biologics: A Novel Device-based Therapy for Musculoskeletal Tissue Pathologies of the Joint

Michael A. Scarpone, D.O.
Medical Director of Trinity Sports Medicine, Assistant Professor of Orthopedic Medicine, Drexel University School of Medicine, Allegheny General Hospital Campus

Summary of Device and Suggested Therapeutic Approach for Treatment of Joint Disease

Background

Musculoskeletal (MSK) disorders are debilitating and painful conditions that profoundly impair health, particularly in older adults. These disorders often have three interrelated pathologies: 1) loss of skeletal muscle mass, 2) tendinopathy, and 3) osteoarthritis (OA). There are currently no comprehensive treatment protocols for pain reduction that holistically address these joint pathologies which involve bone, tendon, ligament, muscle, and cartilage.

The restorative musculoskeletal therapies fall into three broad categories.

1. Injected Autologous Biologics:
Platelet-rich plasma (PRP) and Bone Marrow Concentrate (BMC) therapies have made considerable progress over the last decade, demonstrating a reduction in pain, improved daily activity, and the promotion of repair in bones, tendons, and ligaments, while slowing the rate of cartilage degradation in osteoarthritis.[1-3] As with cell therapy in oncology, these autologous therapies are dose-dependent with higher doses correlating with better results.[4]

2. Deep Tissue Heating and Photobiomodulation:
Deep tissue heating, as well as Photobiomodulation (PBM) employing extracorporeal illumination with near-infrared (NIR) light, has been utilized as a therapy for joint and muscle pain for decades. Recently, clinicians have begun extending this light therapy into biologic-based treatment regimens comprising illumination of autologous tissue or biologics to facilitate preconditioning before injection. Additionally, it has been used as extracorporeal illumination after a fractional coagulative procedure as part of a regimen of multiple visits, typically spanning several months.[5-7]

3. Fractional Coagulation of Cartilage:
A laser-based treatment of cartilaginous tissue, like the fractional, non-ablative skin rejuvenation protocols first developed over twenty years ago and widely used today in dermatolog[8,9], has been developed. Contrary to earlier approaches with laser systems that used contiguous or large area irradiation[10], preliminary data reported in this work suggest that non-ablative, i.e., coagulative **fractional** techniques are a promising treatment for joint cartilage growth and restoration, leading to improved mobility and reduced pain.

Purpose

A new device and an associated treatment protocol have been developed that can be used in conjunction with injected biologics to target the disease pathologies and enhance symptomatic outcomes.

Results from studies addressing pain and impaired mobility associated with musculoskeletal pathologies are reviewed in this paper. Also reviewed is the latest information on three musculoskeletal restorative therapies, based on which a comprehensive treatment protocol for an in-office treatment procedure with a new device is presented.

New Device

Regenalase™ is a system with a 1550 nm laser and a 980 nm laser that recently received FDA clearance. The 1550 nm laser is cleared for coagulating soft tissue including the meniscus cartilage. The 980 nm laser is cleared for elevating tissue temperature to treat medical conditions, including temporary relief of pain, muscle spasms, and increased local circulation. The 1550 nm laser is designed specifically for coagulating musculoskeletal soft tissue and meniscus cartilage. The cartilage is accessed using a cannula that serves as a conduit for the optical fiber, under NanoScope (a needle arthroscopy system by Arthrex) or ultrasound guidance. Local anesthesia is used. Coagulation is obtained with irradiation from the 1550 nm laser delivered via a fiber through an 18-gauge cannula with the tip of the fiber placed in contact with the cartilage. The Regenalase™ system's 980 nm diode laser light is applied externally as a follow-up procedure.

Literature Review

A review of various studies in the literature and clinical trials with Regenalase™ has led to the development of a combination therapy protocol suitable for an office setting. The studies included a) fractional coagulative treatment for cartilage restoration, b) pain reduction using PBM with NIR deep tissue heating for musculoskeletal pain relief, c) injected biologics including Platelet-Rich Plasma and Bone Marrow Concentrate, and d) photobiomodulation to pre-condition biologics. In addition, a fractional laser protocol for musculoskeletal pathologies also based on clinical studies with Regenalase™ will be discussed.

Conclusion

A combination therapy comprising multiple treatments for joint restoration and preservation combines 1) biologics pre-conditioned with near-infrared light, 2) a fractional fiber laser delivered through an 18-gauge cannula, and 3) photobiomodulation therapy. This unique multi-pronged approach allows tissue to be treated from the "inside out and outside in" in a sequence that optimizes the synergy of each therapy's unique capability.

Additionally, non-ablative (coagulative) fractional laser therapy for Laser Disc Reconstruction (LDR) has shown promise in addressing discogenic pain syndrome by improving mobility and reducing pain associated with degenerative disk disease (DDD).

DEVICE DESCRIPTION AND THERAPEUTIC APPROACH FOR TREATMENT OF JOINT DISEASE

Introduction – A multifaceted problem demands a multifaceted therapy

Joint tissue atrophy associated with aging is the greatest non-modifiable risk factor for morbidity. Epidemiological studies show that from the second to the eighth decade of life, whole-body and appendicular lean mass decline by approximately 20% in men and 30% in women[11]. Osteoarthritis and tendinopathies are often associated with pain resulting in diminished daily activity that, in turn, reduces quality of life and accelerates skeletal muscle and tendon atrophy. An important step in reversing this negative feedback cycle is to address pain that reduces activity. With appropriate physical therapy and proper nutrition, it is possible to restore muscle, ligament and tendon strength. This leads to increased daily activity, thereby creating a positive feedback cycle that delays the progression of age-related debilitating pathologies.

Osteoarthritis: Osteoarthritis is a leading cause of pain and disability worldwide and affects the entire joint organ comprised of synovium, cartilage, subchondral bone, vascular network, tendons, ligaments, and muscle. The initial phases consist of pain and inflammation caused by mechanical trauma and/or metabolic changes that lead to joint destabilization and anatomical abnormalities involving cartilage and subchondral bone. Elderly patients presenting with edema in the subchondral bone of the femur's trochlear groove opposite chondromalacia are at significantly greater risk of progression to Total Knee Arthroplasty (TKA) within two years post-diagnosis[12,13]. Ligament laxity and muscle atrophy (especially related to quadriceps) contribute to the progression of osteoarthritis. Additionally, the synovium can be a source of multiple pro-inflammatory mediators, resulting in increased catabolic products in the synovial fluid, which decreases the concentrations of cartilage-protecting factors while increasing the production of cartilage-degrading factors.

Tendinopathies: Tendinopathy is a musculoskeletal disorder characterized by tendon pain during activity or upon palpation, swelling, and loss of function. Chronic tendinopathy resulting from an excess of immune inflammatory cells was a common misconception. Instead, histopathological investigation of pathologic tendons revealed that collagen degeneration and a paucity of infiltrating cells to repair the tissue, particularly collagen, together with inflammation, are the main causes of chronic tendinopathy.[10-11, 14] Exacerbating this condition is the inherently limited vascularity, which is crucial for healing.

Regenerative Therapies – A Total Joint Approach

Any joint treatment plan should address all the pathologic tissues to maximize the likelihood of a successful regenerative intervention. Three therapies are listed below, that when taken together synergistically, accomplish this objective.

Biologics: PRP and Bone Marrow Aspirate Dose Response

PRP has become a cornerstone of regenerative medicine. Several authoritative journal articles have demonstrated that ultrasound-guided PRP injections are effective in treating soft tissue including muscle, ligament, tendon, synovium, and cartilage.[15] This is consistent with a total joint approach that is especially advised when a patient presents with multiple pathologies contributing to the symptoms. Furthermore, a consistent theme in the literature suggests that contrary to low-dose PRP, high-dose PRP is effective across all MSK ailments. For example, a recent study found that the PRP dose for an intra-articular injection in patients with knee OA must contain at least 10 billion platelets to provide relief versus a control of hyaluronic acid (HA) or saline.[16]

Critical to successful regenerative healing is local proliferation of immature stem cells and complementary cells with upregulated growth factors. This observation is consistent with bone marrow rescue therapy in oncology, where the stem cell content of the graft is the driver of clinical success. Hernigou, *et al.* demonstrated in non-union, KOA, and osteonecrosis models that clinical improvement was linked to the stem cell content of the graft as measured by Colony-Forming Unit-Fibroblast (CFU-f).[17] This correlation between the CFU-f content of the biologic and clinical outcome has been repeated by other groups[18] as well. Hernigou, *et al.* aspirated between 200 and 400 mL of aspirate that was processed to reduce the cellular fraction volume to between 15 and 40 mL. Each mL of aspirate after processing typically contained between 2000 and 5500 Cfu-f.

Photobiomodulation (PBM)

The light used in PBM encompasses visible to near-infrared (NIR) low-level light, which alters and improves cellular function by facilitating the electron transport chain in ATP production.[19] Nitric oxide (NO) acts as a signaling molecule to regulate oxygen consumption based on cellular needs, ensuring that ATP production matches the metabolic needs.[20] When mitochondria are at rest, NO occupies the site on cytochrome c oxidase (Complex IV) used by oxygen to create ATP. When cytochrome c oxidase is exposed to 810 or 980 nm red light, albeit via different mechanisms, this bound nitric oxide is released and replaced by oxygen, increasing ATP production.[21-23] The release of NO results in elevated levels of extracellular NO that cause vasodilation (Fig. 1).

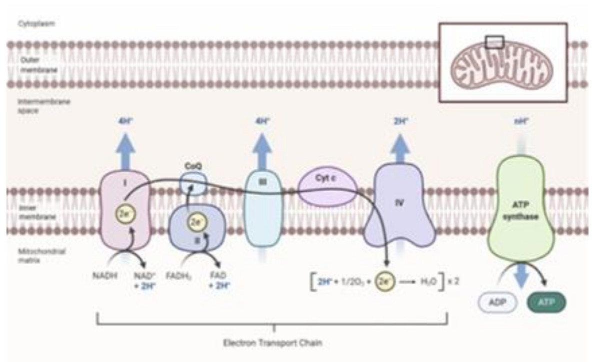


Figure 1. Electron transport in cytochrome c oxidase (Complex IV). During Complex IV electron transport process, the molecule NO binds to the heme a3-Cu_B binuclear center - the active site where oxygen is normally reduced to water creating the proton gradient essential for ATP production.

Before proceeding to the final therapeutic category, fractional laser treatment, it is essential to understand the interactions between laser light and tissue. Light may be treated as a wave or as a stream of packets of electromagnetic energy, known as photons. The energy of a photon is inversely proportional to its wavelength. A red photon has a wavelength greater than that of a blue photon and so has proportionately less energy. Quantum mechanics teaches that an atoms or molecule's electronic energy levels are multiple, discrete and unique. All the electrons fill up the lowest levels (ground state) but when an incident photon's wavelength equals the amount of energy needed to raise the outermost electron to the next higher energy level, an electronic transition results with absorption of the photon (Fig 2).

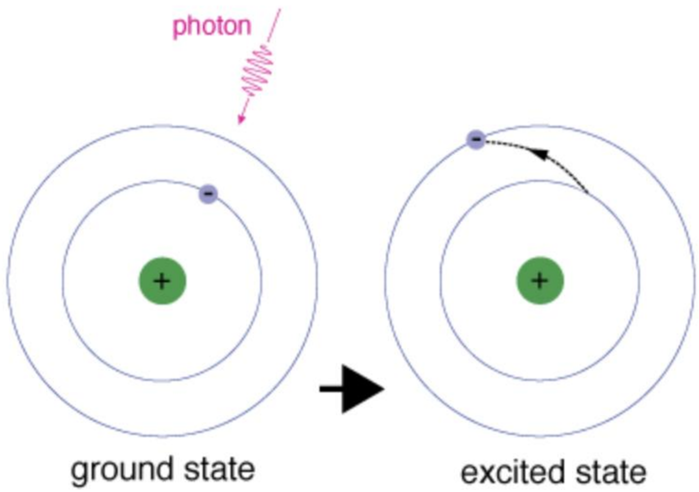


Figure 2. Shown are the first two energy levels of a hydrogen atom as an example to illustrate the absorption of a photon resulting in an electronic transition. When a photon with an appropriate wavelength (equivalently, appropriate energy) is absorbed, the electron transitions to the next highest energy level. The photon energy equals the difference in energy of the first two levels.

There are many applications where the absorbed photon energy by a biomolecule can affect a biomechanical or biochemical function. For example, conformational change in proteins, photoisomerization of molecules in the retina, and mitochondrial electron transport in cells can obtain the required energy, at least in part, from absorption of an appropriate wavelength photon by a chromophore. For example, the release of carbon monoxide from carboxyhemoglobin is facilitated by a conformational change initiated by the absorption of blue to green color photons. Another example is photoisomerization, in which visible photons absorbed by chromophores in the rods and cones of the eye initiate electrochemical, neural signals to the brain. We cannot see photons outside the visible spectrum, for example, gamma or X-rays, because the differences in the molecular electronic energy levels of the chromophores in the retina do not sufficiently match those wavelengths of light. Finally, the electrons in the molecule cytochrome c oxidase will absorb significantly only photons within a specific wavelength range (800 nm – 850 nm), which increases mitochondrial metabolism and ATP production by enhancing the photodissociation of NO bound to the heme or copper centers. In general, photons in the UV and visible regions of the electromagnetic spectrum cause electronic transitions in biomolecules.

Certain photon wavelengths absorbed by a chromophore can result in excitation of the molecule's vibrational states, a photothermal process, and a rise in local temperature. These wavelengths in the near-IR (NIR) or mid-IR (MIR) region of the electromagnetic spectrum are longer than those in the visible region. For example, light with a 980 nm wavelength is absorbed by water and converted into thermal energy. This process also increases ATP production, but the mechanism is not fully understood.[22]

Coagulative Fractional Lasers and PBM – Mechanisms of Action

When light energy is incident on tissue, except for the light reflected back, most is eventually absorbed within the tissue because there are many native chromophores that absorb a broad range of wavelengths. Water is an important chromophore throughout tissue that absorbs 980 nm light and very strongly absorbs 1550 nm light. As discussed earlier, light at these wavelengths excites the water molecule's vibrational states, thereby converting the laser energy to thermal energy. A properly chosen laser wavelength and energy dose will raise the water in the tissue to a desired therapeutic temperature precisely and only within the laser beam's path. For example, the 980 nm wavelength, unlike the 660 nm wavelength, is not as highly absorbed by tissue's other chromophores (e.g., hemoglobin) and a sufficient amount can reach deeper tissues. This makes 980 nm light ideal for applications of both PBM and deep heating of MSK tissue.

For highly absorbed 1550 nm light, the controlled denaturation of proteins, such as collagen, can be easily realized, and this is the primary mechanism in non-ablative fractional therapy. In a fractional laser treatment, the laser beam creates a spatially precise regular pattern of very small, microscopic channels of denatured or coagulated tissue (fractions of a millimeter in diameter and less than a millimeter in depth) that comprise less than a few percent of the total tissue volume. Each coagulated zone is surrounded by otherwise healthy tissue that promotes a fast-healing response, resulting in replacement by new tissue over an area larger than the microscopic size of the denatured zones. Early clinical study results suggest that a similar technique, adapted for MSK tissue, is promising for cartilage restoration. Histological analysis from animal studies has shown that this fractional coagulative treatment can generate hyaline-like cartilage in chondromalacia.[24] The multiple mechanisms of action for laser-treated cartilage are further elucidated in another white paper.[25]

Laser Parameters

A laser may be fired continuously (continuous wave or CW) or may be pulsed. There are four important laser device parameters that affect the temperature rise in tissue: (1) The laser average and pulse power are the average number of photons (multiplied by the photon energy) emitted per unit time over an extended period (many pulses if not CW) and the number of photons. (multiplied by the photon energy) emitted per unit time during a laser pulse (Joules/sec = Watts). (2) The pulse width is the duration of the output power that determines the amount of energy (= power x pulse width) delivered per pulse. (3) The laser wavelength(s) that may be chosen to match as closely as possible an absorption peak of a target chromophore. (4) The diameter of the laser beam illuminating the target determines the irradiance or intensity (power per unit illuminated area, W/cm^2). For a given output power, the beam can be focused tightly on a smaller area, causing a higher intensity and temperature rise.

Extra-corporeal PBM

(1) Pre-conditioned Biologics

A PRP device filled with an autologous sample lends itself to near-infrared range (NIR) Photobiomodulation (PBM) treatment prior to transplantation. For example, ex vivo exposure of whole blood to NIR light in the range of 700 –1000 nm dramatically improves platelet function and reduces markers of the M1 phenotype in activated macrophages. Treatment with PBM of older hDFs (human-derived fibroblasts) was found to enhance their migration ability, resulting in rejuvenation levels comparable to those of young hDFs. For example, in *in vivo* experiments, the treatment of old hDFs demonstrated a superior skin wound healing effect, surpassing that of young hDFs. PBM treatment of older cells induces rejuvenation, leading to increased therapeutic efficacy compared to untreated cells.[26] The 980 nm wavelength has been demonstrated to be a key component of effective PBM therapy in several studies.[21-23]

(2) Extra-corporeal PBM with light alone

Extra-corporeal PBM with NIR light is best used as an adjunctive therapy in a multimodal approach. Typically, a series of visits are scheduled over several weeks. With over 400 clinical trials (RCTs) and more than 4,000 laboratory studies published using deep tissue laser therapy, this adjunctive therapy is becoming a standard for treating soft tissue and joint maladies. The benefits of the 980 nm laser light include pain relief, lower inflammation, improved circulation, and enhanced muscle function. Clinical applications include osteoarthritis, acute or chronic tendinopathies, fibromyalgia, neck and back pain, and various types of sports injuries including sprains and strains.

Risk Return Analysis in Regenerative Medicine

In summary, the standard of care in regenerative medicine is to source autologous biologics and concentrate thereof for transplant to the damaged tissue. Research has clearly indicated that higher doses are needed to achieve more consistent success. The risks of this extended procedure include infection, anemia, and unintended trauma that increase with the volume of tissue harvested. However, the minimum dose thresholds may be favorably affected by the addition of an adjunctive therapy, such as laser-based fractional treatment, and should be a subject for future studies.

Clinical Studies

Cartilage restoration in Knee Osteoarthritis (KOA)

Two case series studies were conducted in the Dominican Republic and the United States (New York, NY), and a third study was conducted at two locations in the United States: Steubenville, Ohio, and Denver, Colorado. These studies investigated the laser treatment of knee cartilage. The Dominican Republic and New York studies confirmed 1) that the procedure is well tolerated in an office setting under local anesthesia, 2) that the recommended clinical guidelines are sufficiently detailed to be reproducible but flexible enough to address the complete cross-section of patient population, and 3) that combining biologics with the Regenalase Fractional fiber laser protocol did not cause any unforeseen side effects. The studies in Ohio and Colorado also included measuring functional improvement (via wall squats) and changes in pain. However, the follow-up period of the study in the United States significantly overlapped the COVID-19 pandemic restrictions which significantly reduced direct patient follow-up visits.

Case Series, New York, NY
Eighteen (18) patients were treated at a single center in NYC for KOA in an IRB (Western IRB) approved study. All patients received an MRI prior to any therapy to confirm the KOA diagnosis. Each patient first had a bone marrow aspirate of approximately 8 mL taken from the iliac crest. During the Regenalase procedure, laser energy was delivered via an optical fiber through an 18-gauge cannula, with ultrasound used to confirm the fiber tip placement. Post Regenalase treatment, bone marrow aspirate was injected into the arthritic joint through the same introducer cannula. Due to the COVID–19 pandemic, no post-procedure follow-ups were conducted, except for monitoring for adverse events. No adverse incidents related to the procedure were reported.

Case Series, Dominican Republic
Eleven (11) patients were treated in the Dominican Republic, with a patient satisfaction survey conducted six months post-treatment. Patients were asked to rate their satisfaction with the procedure, primarily based on pain relief, using a scale of 0 to 10, with 10 being the highest rating. Ten patients had painful KOA, and one patient had a painful meniscal tear. Nine patients, including the patient with a meniscal tear, were treated with a combination of PRP and Regenalase. Two patients with KOA were treated with a combination of adipose tissue and Regenalase. Each patient had the fiber laser delivered over an 18-gauge introducer cannula using a nano-scope camera to confirm the fiber placement. Each patient in the PRP group received three PRP treatments, the first occurring 30 days post-Regenalase treatment, and the subsequent two spaced 30 days apart. The two patients with KOA who received an adipose tissue graft had the graft injected into the joint after the Regenalase procedure was completed. The graft tissue was delivered through the same introducer cannula. After six months, all 11 patients reported a satisfaction level of 9 or 10 with no adverse events related to the procedure.

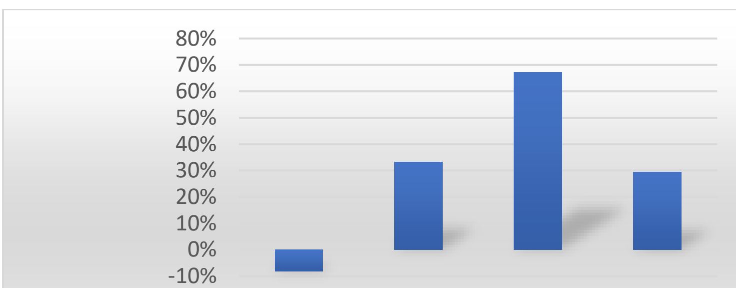
Case Series, Steubenville*, Ohio*
Thirty-two (32) patients with diagnosis of painful KOA were treated. Patients with bilateral KOA were randomized to have only one knee treated. All patients initially had an MRI to confirm the diagnosis. Patients were randomized into three groups: 1) laser only 2) laser and bone marrow 3) sham. All patients were placed under conscious sedation in one of the groups as to which they were blinded. In the cases of bilateral knee OA, the patients were blinded as to which knee was sham. For the Regenalase procedure, each patient had the fiber laser delivered through an 18-gauge cannula, with ultrasound used to confirm the fiber tip placement. The fiber was also placed inside the joint via a cannula for the sham procedure, but the laser was not fired. The primary outcomes were pain score, Knee Injury and Osteoarthritis Outcome Score, Junior (KOOS jr score) and wall squats at both 6 months and 12 months follow-ups post Treatment. These patients were also treated during the height of the COVID–19 pandemic. As a result, 15 participants were lost to follow-up during the first six months, and 24 were lost to follow-up during the 12-month period.

Case Series Ohio & Colorado

Nine (9) patients were treated under conscious sedation for painful KOA all of which presented with subchondral bone edema confirmed via MRIs prior to therapy. Patients with bilateral KOA had both knees treated. Each patient first had a bone marrow aspirate of approximately 8 mL taken from the iliac crest. For delivery of the marrow into the subchondral bone, a C-arm was used to guide the injection. For the Regenalase procedure, each patient had the fiber laser delivered over an 18-gauge cannula using ultrasound or a C-arm to confirm the fiber tip placement. The primary outcomes were pain score, KOOS jr score and wall squats at both 6 months and 12 months. These patients were treated during the height of the COVID–19 pandemic. As such, all nine patients were lost to follow-up during the 12-month follow-up period.

Outcome Measure 1 - Wall Squats

A significant overall improvement in the number of wall squats was reported for patients from each treatment group. All patients in the laser-only and laser plus Inter-Osseous groups reported improvement, and 86% of patients in the laser + bone marrow group showed improvement. Compared to the Control group, only 50% of the patient's showed improvement. The results are shown in graphical format in Figure 3.



	control (n=2)	Laser + bma (n=7)	Laser (n=4)	IO plus laser (n=3)
Percent change	-8%	33%	67%	29%

Figure 3. Mean percent improvement from baseline in wall squats by group at 6 months. Glossary: bma: Bone Marrow Aspirate injected intra-articular: IO – Sub chondral Intra-osseous injection of BMA & intra-articular BMA injection

A significant overall improvement in the number of wall squats was also reported at 12 months as shown in Figure 4, with each patient showing continued improvement from the six-month results.

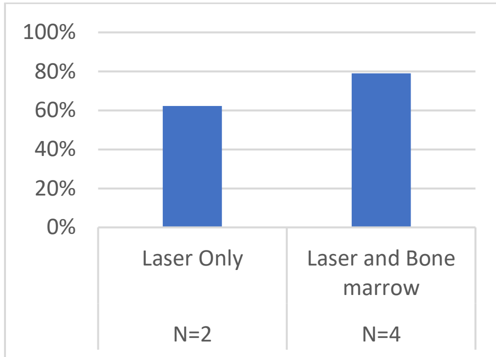


Figure 4. Mean percent improvement from baseline in wall squats for laser only and laser plus Bone Marrow Aspirate (BMA) groups at 12 months.

Outcome Measure 2 - Pain

Each treatment group reported a significant overall improvement in best (least amount of pain) and worst pain as shown in Figure 5. Individually, all patients in the laser + bone marrow and IO groups reported improvements in both scores. In the laser-only group, 80% of patients reported improvement in worst pain, and 60% reported improvement in best pain. In the control group, only a modest improvement was reported in both scores.

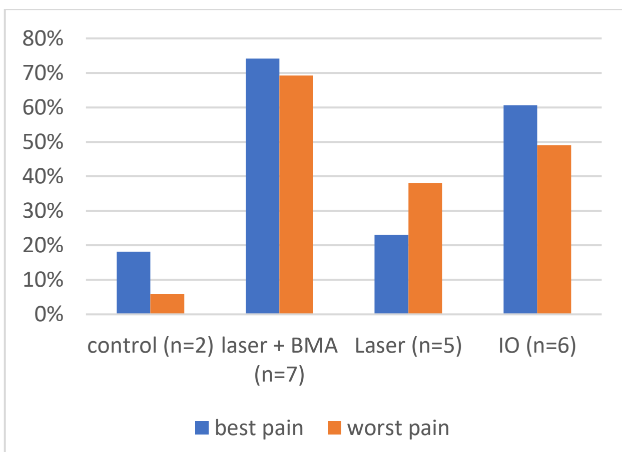


Figure 5. Reported mean percent improvement of best and worst pain by group at 6 months post treatment.

Each treatment group reported a significant overall improvement in both best and worst pain over the 12-month period. Individually, all patients in the laser group improved between 6 and 12 months. However, in the laser and bone marrow group, one patient reported an increase in pain during the second six-month interval. Interestingly, this patient showed the greatest improvement in functional wall squat test score at 12 months.

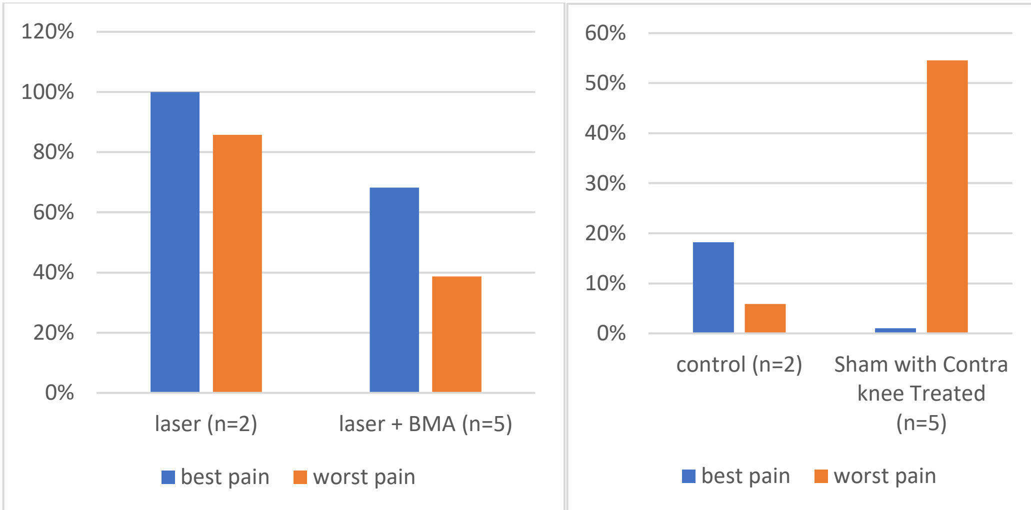


Figure 6. Twelve mos. (left) and 12 mos. (right): Control versus Contra-lateral Knee Treated

As shown in Figure 6, a significant improvement in pain symptoms was observed in the contralateral knee for patients in the treatment group compared to the control group, which received no intervention. This improvement is logical, as relieving symptoms in the treated knee would reduce the load placed on the opposite knee.

For the three patients in the treatment group with bilateral KOA, the contralateral knee showed a 100% improvement in best pain and an 86% improvement in worst pain.

Laser Reconstruction of Lumbar Intervertebral Discs

A specific protocol utilizing a pulsed, 1550 nm laser has been employed to treat thousands of patients with spine disc conditions, with a 10-year follow-up and no reported adverse side effects associated with the treatment [Provide reference, if available]. Animal studies and histology taken several years after the therapy from deceased patients (unrelated causes of death) show the presence of hyaline cartilage in the area of treatment.

Fifty subjects with discogenic pain syndrome of lumbar intervertebral discs (3 or 4 degrees on the Pfirrmann scale via MRI) presenting with positive discography and chronic pain (VAS $\geq$ 4) for at least 6 months participated in a 12-month study to evaluate the Laser Disc Reconstruction (LDR) procedure. Participants were equally divided into a control and an LDR group with statistically equivalent scores for age, VAS pain and Pfirrmann scales. LDR was performed whereby three or four zones of the disc are exposed to a series of pulses from the 1550 nm laser delivered over a 400 µm core diameter fiber via an 18 ga needle. VAS pain scores and quality of life assessment, Social Functioning (Short Form SF-36 Health Survey) and Owestry Disability Index (ODI) were measured at 1, 3, 6, and 12 months post-treatment.

Favorable and statistically significant improvement in VAS, SF-36 and reduction of Pfirrmann scores were seen in the LRD group versus baseline at 12 months. A statistically significant reduction in ODI at all time points was also observed in the LRD group as opposed to the Control group, which exhibited no significant change. See Figures 7 and 8.

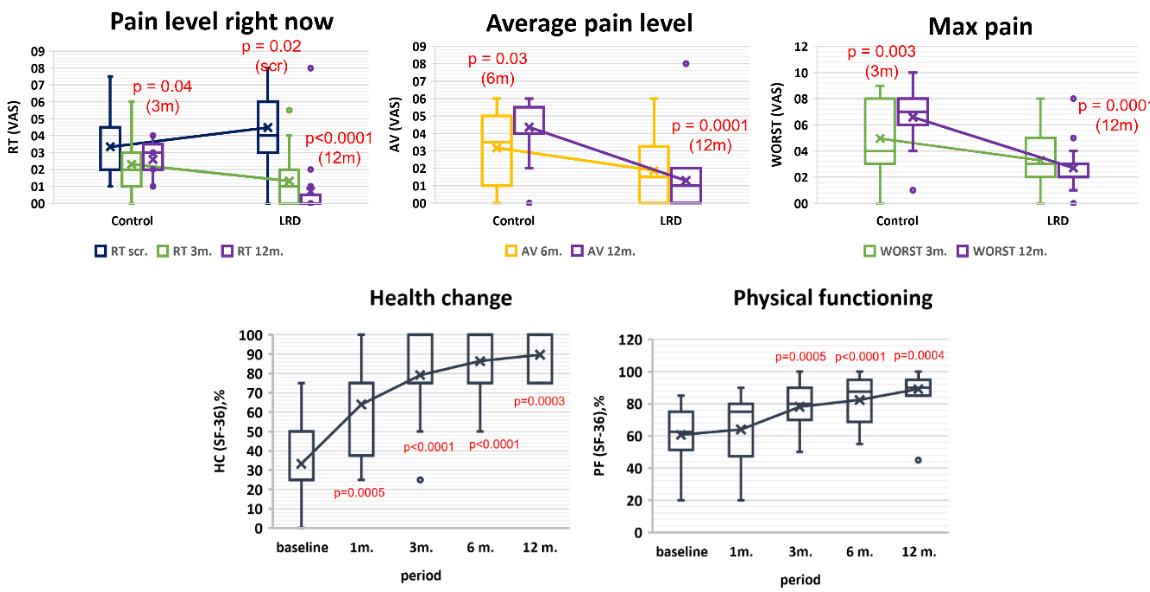


Figure 7. Top Panel. VAS pain scores for control and LRD groups at 3, 6, and 12 months.
Bottom Panel. SF-36 Health change and Physical Functioning at baseline, 1, 3, 6, and 12 mos.

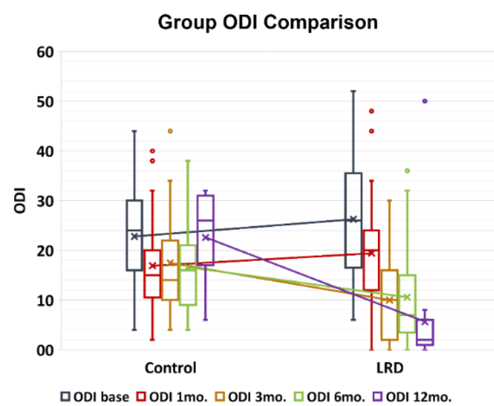


Figure 8. Comparison by group of ODI at baseline, 1, 3, 6, and 12 months

Discussion

We recommend a multimodal preservation strategy for KOA, incorporating fractional laser and PBM therapies as a promising adjunct to autologous biologics. Fractional protocols in both the spine and joints have been documented that may stimulate the formation of new hyaline cartilage.[24,27,28] No therapy is currently available that provides this key component in joint preservation.

We also recommend a deep tissue PBM protocol, administered over several visits, following the biologic and fractional laser therapy visit. The NIR deep tissue laser treatment helps manage pain and inflammation, promoting healing through increased vascularization. This therapy is a non-surgical, viable option to NSAIDs. Clinical applications for deep tissue lasers include osteoarthritis, acute or chronic tendinopathies, fibromyalgia, neck and back pain, and any type of traumatic sports injury, including sprains and strains. Further, numerous studies have documented that autologous samples can be enhanced by pre-conditioning with exposure to NIR PBM laser light, leading to better clinical outcomes. A clear blood bag with a large surface area is well-suited for sample pre-conditioning with the Regenalase system. This step offers potential benefits at no additional cost or risk, except for an extra 15 minutes of preparation time. We recommend pre-conditioning all samples prior to transplantation.

Conclusion

The management of the interrelated pathologies of 1) a loss of skeletal muscle mass, 2) tendinopathies, and 3) osteoarthritis requires new tools and approaches for treatment addressing the entire joint. Patients will benefit most when their healthcare providers offer a multimodal approach that combines different types of therapies in a synchronized manner. To this end, a treatment for KOA via a single-portal, arthroscopic, outpatient or in-office procedure is proposed combining injectable biologics with fractional and PBM laser treatment. This approach has promising efficacy with limited risks (excellent benefit to risk ratio) and warrants further investigation to optimize the treatment parameters and synergies.

References

1. G. Crowley JL, Soti V. Platelet-Rich Plasma Therapy: An Effective Approach for Managing Knee Osteoarthritis. Cureus. Dec 19;15(12), 2023.
2. H. Lana, J.F., Purita, J., Jeyaraman, M., de Souza, B.F., Rodrigues, B.L., Huber, S.C., Caliari, C., Santos, G.S., da Fonseca, L.F., Dallo, I., Navani, A., De Andrade, M.A.P., & Everts, P.A. Innovative Approaches in Knee Osteoarthritis Treatment: A Comprehensive Review of Bone Marrow-Derived Products. *Biomedicines*, *12*(12), 2812, 2014.
3. I. Balusani P Jr, Shrivastava S, Pundkar A, Kale P. Navigating the Therapeutic Landscape: A Comprehensive Review of Platelet-Rich Plasma and Bone Marrow Aspirate Concentrate in Knee Osteoarthritis. Cureus. Feb 23;16(2), 2024.
4. Dose–response correlation for CAR-T cells: a systematic review of clinical studies; Journal for Immunotherapy of Cancer; Anand Rotte, Metthew J Frigault, Ayub Ansari, Brad Gliner, Christopher Heery and Bijal Shah; December 2022.
5. Baroni BM, Leal Junior EC, De Marchi T, Lopes AL, Salvador M, and Vaz MA. 2010a. Low level laser therapy before eccentric exercise reduces muscle damage markers in humans. *Eur J Appl Physiol* 110: 789–96, 2010.
6. Baroni BM, Leal Junior EC, Geremia JM, Diefenthaeler F, and Vaz MA. 2010b. Effect of light-emitting diodes therapy (LEDT) on knee extensor muscle fatigue. *Photomed Laser Surg* 28: 653–8, 2010.
7. Chang S, Carpena NT, Kang BJ, Lee MY. Effects of Photobiomodulation on Stem Cells Important for Regenerative Medicine. Medical Lasers 9:134-141, 2020.
8. “Advancements in Laser Technologies for Skin Rejuvenation: A Comprehensive Review", published in the *Journal of Cosmetic Dermatology* in 2024.
9. “Review of Fractional Nonablative Lasers for the Treatment of Dermatologic Conditions in Darker Skin Phototypes", published in *Dermatologic Surgery* in May 2024.
10. Manfred Bernard, Matthias Grothues-Spork, Peter Hertel, Yadollah Moazami-Goudarzi, “Reactions of meniscal tissue after arthroscopic laser application: An in vivo study using five different laser systems”, Arthroscopy: The Journal of Arthroscopic & Related Surgery, Volume 12, Issue 4, 1996, Pages 441-451,
11. Minetto MA, Giannini A, McConnell R, Busso C, Torre G, Massazza G. Common Musculoskeletal Disorders in the Elderly: The Star Triad. J Clin Med. 2020 Apr 23;9(4):1216.
12. Ochi J, Nozaki T, Nimura A, Yamaguchi T, Kitamura N. Subchondral insufficiency fracture of the knee: review of current concepts and radiological differential diagnoses. Jpn J Radiol. May;40(5):443-457, 2022.
13. Villari E, Digennaro V, Panciera A, Ferri R, Benvenuti L, Cesare F. Bone marrow edema of the knee: a narrative review. Arch Orthop Trauma Surg. May;144(5):2305-2316, 2024.
14. Chang S, Carpena NT, Kang BJ, Lee MY. Effects of Photobiomodulation on Stem Cells Important for Regenerative Medicine. Medical Lasers 9:134-141, 2020.
15. Nie LY, Zhao K, Ruan J, Xue J. Effectiveness of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Meta-analysis of Randomized Controlled Clinical Trials. Orthop J Sports Med. 2021 Mar 2;9(3)
16. Bansal, H., Leon, J., Pont, J.L. *et al.* Platelet-rich plasma (PRP) in osteoarthritis (OA) knee: Correct dose critical for long term clinical efficacy. *Sci Rep* **11**, 3971 (2021).
17. Hernigou P, Bouthors C, Bastard C, Flouzat Lachaniette CH, Rouard H, Dubory A. Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomized study. Int Orthop. 2021 Feb;45(2)

18. Bieri et al. Phase I and registry of autologous bone marrow concentrate evaluated in PDE5 inhibitor refractory erectile dysfunction. Journal of Translational Medicine 2020
19. Farzad Salehpour, Javad Mahmoudi, Farzin Kamari, Saeed Sadigh-Eteghad, Seyed H Rasta, Michael Hamblin, Brain Photobiomodulation Therapy: a Narrative Review, Molecular Neurobiology, 55(1) August 2018.
20. Gregory Pappas, Melissa L. Wilkinson, and Andrew J. Gow, Nitric Oxide Regulation of Cellular Metabolism, Nitric Oxide, Vol 131, pp8-18, Feb. 2022.
21. Andrea Amaroli, Claudio Pasquale, Angelina Zekiy, Anatoliy Utyuzh, Stefano Benedicenti, Antonio Signore, and Silvia Ravera, Photobiomodulation and Oxidative Stress: 980nm Diode Laser Light Regulates Mitochondrial Activity and Reactive Oxygen Species Production, Hindawi Oxidative Medicine and Cellular Longevity Volume 2021, Article ID 6626286, 11 pages, 2021.
22. Wang Y, Huang YY, Wang Y, Lyu P, Hamblin MR. Photobiomodulation of human adipose-derived stem cells using 810nm and 980nm lasers operates via different mechanisms of action. Biochim Biophys Acta Gen Subj. Feb;1861(2):441-449, 2017.
23. Dimitrios Agas, Reem Hanna, Stefano Benedicenti, Nicola De Angelis, Maria Giovanna Sabbieti and Andrea Amaroli, Photobiomodulation by Near-Infrared 980-nm Wavelengths Regulates Pre-Osteoblast Proliferation and Viability through the PI3K/Akt/Bcl-2 Pathway, *Int. J. Mol. Sci.* 2021, *22*(14), 7586; 11 May 2021.
24. Sobol E, Shekhter A, Guller A,. Baum O, Baskov A, Laser-induced regeneration of cartilage, *Journal of Biomedical Optics*, 16: 080902- 090909, 2011.
25. “Laser Treatment of Cartilage – Mechanisms of Action”, IPG Medical White paper.
26. Eroglu, B., Genova, E., Zhang, Q. *et al.* Photobiomodulation has rejuvenating effects on aged bone marrow mesenchymal stem cells. *Sci Rep* **11**, 13067, 2021.
27. Baskov, A., Borshchenko, I. A., Baskov, V., Shekhter, A., & Sobol, E. (2022). Laser Reconstruction of Spinal Discs Experiments and Clinic. *Applied Sciences*, *12*(2), 675.
28. Baskov, A. V., Borshchenko, I. A., Shekhter, A. B., Baskov, V. A., Guller, A. E., & Sobol, E. N. (2015). Long term clinical results in laser reconstruction of spine discs. *Journal of spine*, *4*(1).