Clinical Rationale and Rehabilitation Guidelines for Post Biologic Therapy

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KEYWORDS

• Orthobiologics • Tissue healing • Tissue loading • Rehabilitation

INTRODUCTION

Orthobiologic therapies such as platelet-rich plasma (PRP) have been increasingly studied as a treatment for several musculoskeletal and orthopedic injuries Involving tendons, ligaments, muscles, the intervertebral disk, and synovial joints. In the United States, PRP was first used in 1987 to control wound healing after cardiac surgery.[1] Over the last decade, there has been a significant increase in the utilization of orthobiologic therapies and cell-based therapies by orthopedic, musculoskeletal, and sports medicine physicians. Despite promising clinical results and the widespread use of PRP to treat musculoskeletal and orthopedic injuries, its use remains controversial due to the heterogeneity in study designs, lack of reporting standardization, and evidence of publication bias.[2,3]

ORTHOBIOLOGIC FORMULATIONS

PRP is the supinate fraction processed from autologous peripheral whole blood that has a platelet concentration above the normal baseline.

There are substantial differences in the content of platelet concentrations produced by the various automated and manual PRP recovery systems. PRP is produced by either single spin or double spin density gradient centrifugation producing platelet concentrations ranging from 1.7 to 12× baseline. There are substantial differences in the content of platelet concentrations produced by the various automated and

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manual PRP recovery systems. The most common methods of PRP production use of either a plasma-based system or a buffy coat system, which produce either a leukocyte-poor PRP (LP-PRP) or a leukocyte-rich PRP (LR-PRP), respectively. Regardless of the system used, all systems must release growth factors from platelets. However, they all differ in platelet, white blood cells, red blood cells, and plasma concentrations.

Today, there has been a significant amount of literature published on the effects of PRP. We currently know that PRP has an analgesic effect by diminishing inflammation, it can augment the proliferation of tenocytes, osteoblasts, and myocytes and can augment the secretion of hyaluronic acid by synovial joints, and when used in combination with hyaluronic acid creating a synergistic effect. Finally, PRP through its paracrine effect can augments stem cell migration.

TISSUE HEALING

The healing process is defined as a complex and dynamic biologic progression that results in the restoration of anatomic structure and function. Tissue healing is a process characterized by a predictable cascade of biological tissue responses triggered by the injury itself. Physiologic healing progresses through four overlapping stages: stage 1, Hemostasis, stage 2, the acute inflammatory phase; stage 3, the proliferative or repair phase; and stage 4, the remodeling phase (**Fig. 1**).

Hemostasis, stage 1, is the first and shortest phase of the healing cascade occurring within seconds to minutes, and this is the process of forming a blood clot to stop bleeding. Platelets are vital to hemostasis, also functioning as the physiologic trigger to activate acute inflammation and program tissue repair.[4]

The *inflammatory phase*, stage 2, begins immediately following the injury and continues for 48 to 72 h. Platelets are stimulated to provide hemostasis by forming a clot. Platelets in the clot then degranulate and secrete several growth factors, hemostatic factors, and cytokines from alpha granules that are necessary for the early stages of the clotting cascade. Histamine and serotonin are released from the dense granules and function to increase capillary permeability, activate macrophages, and allow inflammatory cells greater access to the injury site[5,6] The inflammatory phase can last up to 72 h and is characterized by localized pain, swelling, erythema, and increased local tissue temperature.

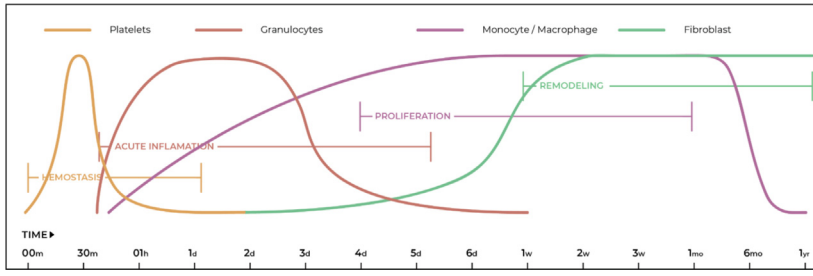

Fig. 1. Healing Cascade. The four stages of the healing cascade consisting of four partially overlapping stages- hemostasis, acute inflammation, proliferation, and remodeling. The particular cell type activity within each phase is crucial for the progression and successful execution of the healing cascade leading to tissue repair. (*Adapted from* Parrish WR, Roides B. Physiology of Blood Components in Wound Healing: an Appreciation of Cellular Co-Operativity in Platelet Rich Plasma Action. J Exec Sports Orthop.4(2):1–14. DOI:10.15226/2374-6904/4/2/00156.)

The *proliferative phase* (stage 3) begins with the activation of fibroblasts by growth factors and inflammatory mediators released during the acute inflammatory phase.[7] The proliferative phase is defined by cell proliferation, neovascularization, and matrix synthesis in addition to other metabolic processes that aid and remodeling and organization of the healing tissue.[8] During the ensuing 48 h to 6 weeks, anatomic structures begin to be restored, whereas tissue generation occurs. Fibroblasts begin to synthesize scar tissue and capillary neoformation begins to reestablish nutrients to the injured tissue. Stage 3 ends with the beginning of wound contracture.

The *remodeling phase,* stage 4, is the longest phase of the healing cascade, beginning several weeks after the initial injury and may last months to over a year depending on the severity of the initial injury.[7] Fibroblasts are responsible for remodeling, replacing the type 3 collagen matrix with the stronger type 1 collagen matrix. Fibroblasts either die through apoptosis or differentiate into myofibroblasts that align to the direction of force within the tissue. Failure to properly transition from the proliferation phase may lead to excessive or hypertrophic scarring.[7]

As with orthobiologic therapy such as PRP, there is great variability in reporting post-orthobiologic rehabilitation in return to activities. Several articles have proposed a standardized rehabilitation program following treatment with PRP.[9–11]

Townshend and colleagues,[2] performed a systematic review of post-procedure protocols following PRP injections for tendinopathy. They discovered significant variability in reporting periods of relative rest, weight-bearing restrictions, rehabilitation exercises, full return to play, and the use of nonsteroidal anti-inflammatory drug (NSAID) medications pre- and post-treatment.

THERAPY GUIDELINES FOR REHABILITATION

Prehabilitation or prehab is a concept that is not foreign to physical therapy. Prehabilitation was first mentioned in the literature in 1946.[12] The authors reported how a period of training for warfare, physical therapy, and strength training for the whole body, improved the physical and mental well-being of army recruits during the Second World War. Recently, prehabilitation has been mentioned in various orthopedic conditions and settings—ACL injury, joint replacements, regenerative cartilage surgery, and running.[13–18]

The intent of prehabilitation is to prepare a patient for optimal recovery from some type of procedure. The focus of this time period is on the restoration of osteokinematic and arthrokinematic mobility, soft-tissue extensibility, muscle flexibility, strength, balance, and proprioception. It also gives the clinician an opportunity to focus on improvement on other areas of the body that the patient would benefit from.

Emphasis is given to determine the reason for the injury-what, how, and why. In the case of ligament injuries, before biologic treatment, dynamic imaging/ultrasound is performed to establish baseline measurements of ligament morphology and joint stability. Baseline metrics include stressed and non-stressed ligament tensioning in comparison to the contralateral joint. These measurements are repeated at key time periods post-injection per Podesta and colleagues.[20] These metrics are then used to confirm tissue healing and joint stability for the purpose of rehabilitation progression.

A key component to prehabilitation with respect to biologics is patient education regarding the overall phases, time frames, and expectations for recovery from biologic treatment[19] (**Box 1**).

Rehabilitation progression following PRP injection is based on several individual factors—the combinations of time since injection, physiologic healing mechanism,

Box 1
Pre–Post Injection Treatment Instructions

Before PRP Treatment:
1. Stop all nonsteroidal anti-inflammatory medications NSAIDs 2 to 3 weeks before the procedure.
2. Prehab-gain general understanding of the healing process, time frames, use of heat to facilitate vascularization and local metabolism, and set patients up for best outcome.
3. Use of functional outcome tools such as the Kerlan–Jobe Orthopedic Score (KJOCS), Shoulder Pain and Disability Index (SPADI), Lower Extremity Functional Scale, Patellofemoral Index (SCOR), etc., are commonly used to establish the patient's baseline subjective functional status.
4. Establish baseline with imaging (dynamic MSK ultrasound, fluoroscopy, MRI)

Post-PRP Treatment:
1. Apply a thermal heat agent for 15 min four times per day when awake for 2 weeks.
2. Acetaminophen for pain as needed.
3. Increased pain and inflammation are expected in the treated tissue after the procedure.
4. Range-of-motion exercises as tolerated after the procedure.
5. Continue to use any braces, splints or crutches as recommended by your physician after the treatment.
6. Dynamic MSK ultrasound at 6 to 7 weeks to determine tissue continuity, integrity, and joint stability to safely progress later phase rehabilitation and higher-level functional activities.

patient's health and age, severity of injury, tissue integrity, response to physical therapy treatment dosage, as well as adherence to appropriate home programs. Characteristics of optimal loading include controlled and directed force to the selective tissue; early loading through functional ranges; an appropriate blend of compressive, tensile, and shear loading; variability in magnitude, direction, duration, and intensity; includes neural overload; needs to be dynamic and reflect demands of that tissue; and is functionally appropriate. Optimal loading is tissue and adaptation specific. It improves the mechanical properties of tissue and creates better fiber alignment and less disorganized matrix formation. The goal of rehabilitation following PRP injections is to progressively and therapeutically place appropriate amounts of physical stress and optimally load through and along the injured tissue to help facilitate healing.[20]

Loading is tissue-specific (**Table 1**). For instance, ligament, muscle, and tendon soft-tissues require linear loading due to fiber alignment. However, articular cartilage requires controlled and progressive compressive loading due to osteochondral matrix physiology. It responds optimally to progressive compression or shear, which creates a 'pumping effect' that provides joint cell nutrition, molecule transport, and joint lubrication. Successful functional outcomes for cartilage repair necessitate the correct quantity of loading. For example,:

- *Insufficient loading*: leads to adverse effects, delays healing, thinning and softening articular cartilage, decreases matrix content, chondrocytes, and yields less lubrication (immobilization)
- *Moderate loading*: *essential for cartilage health* and aides repair (low impact, bike, and swim)
- *Excessive loading*: detrimental to cartilage (high impact, Plyometrics)

General guidelines, expectations, and treatment interventions following orthobiologic injections are based on loading and tissue healing cascade and repair principles. A clinical framework that includes criteria-based progressions, goals within the healing phases, and clinical rationales for progression following orthobiologic injections are suggested in **Table 2**.[20]

Table 1
Tissue-specific loading and healing timeline

Tissue:	Healing Capacity Vascularity	Force to Facilitate Healing	Tissue Healing Time	Loading Protection
Muscle	Good, abundant	*Contractile Loading* Isometric- > Concentric- > Eccentric muscle	6–8 wk	ROM parameters, SubMax Isometrics- > Max Isometrics- > Concentrics- > Eccentrics- > Ballistic progressions
Tendon	Fair, less	*Contractile Loading* Isometric- > Concentric- > Eccentric	8–12 wk	ROM parameters, SubMax Isometrics- > Max Isometrics- > Concentrics- > Eccentrics- > Ballistic progressions
Ligament	Less, Diminished	*Tension* Controlled fiber Tension in line of stress	7–14 wk	Bracing with protected ROM parameters
Cartilage Labrum Intervertebral Disc	Limited/absent	*Cyclical Compression, Decompression & Shear* Imbibing pumping effect; controlled	6–12 wk	Bracing, Unloading, progressing weight bearing, Aquatics, Stationary Bike, weight bearing loading and controlled torsional stress
Subchondral Bone/Bone		Controlled Weight Bearing	6–12 wk	Weight Bearing Status, Unloading

Controlled physical stress to the tissue (muscle, tendon, ligament, and bone) is imparted throughout the rehabilitation duration to facilitate repair and may include tension, torsion, compression, and shear.[20] The stress or loading is imparted via manual therapy techniques, dosed medical exercise therapy progressions, as well as functional strengthening and return to play phase exercises. There is limited evidence in the literature defining specific protocols following PRP injection and limited documentation regarding tissue healing time frames following PRP injection.[10,11,21,22] There is no absolute progression or transition between phases and there can be variability between patients pending each individual case.

The goal following orthobiologic injection is to promote adequate tissue healing such that the tissue is able to once again maximally withstand the physiologic stresses and forces placed upon it with daily functional demands or sporting activities.[20] Collagen fibers run in parallel alignment that affords the tissue to withstand tensile forces and unilateral stress placed upon it.[23] The following information is based on the authors' clinical experience treating patients who have undergone orthobiologic injections with PRP and bone marrow-derived progenitor cells to ligament, tendon, muscle, intra-articular joints, and subchondral bone since 2006.

Phase I–II (Hemostasis/Inflammatory)

Time: 0 to 7 days.

Goals:

- Allow the PRP to absorb the injected tissue.
- Avoid cross-link disruption.
- Facilitate integrity of cross-link formation.

Phase One consists of early mobilization, gentle self-stretching, and protected or unloaded weight-bearing functional activities to prevent the deleterious effects of immobilization and to promote tissue healing.[20] Owing to the elevated inflammatory response, the patient commonly feels an increase in pain for the next 1 to 3 days following the injection. Following PRP injection the majority of the growth factors are released within the first hour of injection but continued release occurs up until about 7 days following injection.[24,25] Thus, the home program for the first 7 days following PRP injection is aimed at avoiding disruption of this physiologic mechanism and includes: rest, gentle active motion, submaximal isometric holds in all pain-free planes and ranges to help fiber alignment, pain medications such as over-the-counter analgesics avoiding NSAIDs, to control symptoms. Use of a heating agent at home following biologics injection is recommended. Thermotherapy increases tissue temperature, blood flow, and metabolism (providing a closer physiologic environment). Increased blood flow facilitates tissue healing by supplying protein, nutrients, and oxygen at the site of injury. A 1°C increase in tissue temperature is associated with a 10% to 15% increase in local tissue metabolism.[25] This increase in metabolism aids the healing process by increasing both catabolic and anabolic reactions needed to degrade and remove metabolic by-products of tissue damage and provides the milieu for tissue repair.[26]

Phase II (Inflammatory/Early Proliferation Phase)

Time: 8 to 21 days.

Goals:

- Avoid disruption of collagen cross-link bridging and formation.
- Initiate early motion.

Table 2
Criteria-based progressions and clinical rationale for rehab phases

Rehabilitation Phase	Criteria to Progress to this Phase	Anticipated Impairments and Functional Limitations	Intervention	Goal	Rationale
Phase I-II Hemostasis/ Inflammatory Phase Post Injection (0–7 d)	• Post Injection with no signs of infection	• Day 1–2: painful in the tissue/joint • Day 3–6: Diminishing pain and improving significantly • Day 7: Minimal pain, improved quality of ROM	*Restrictions:* ***Avoid all varus, valgus, A-P & rotational loads & ligament stressing, or and any loaded contractile activities or exercises*** ***Maintain any limited weight bearing precautions*** • Tissue/joint specific protected bracing & weight bearing • No exercise except for rehab program • UE injections - no lifting > body wt. • Tylenol for pain • Heat pack for 15 min, 4x/day for 1–2 wk. • Avoid ice over treatment site • Shower ok 24 h after procedure	• Protect tissue • Allow biologic to absorb • Daily activity as tolerated within provided brace • Avoid excess loading or stress to treated area • Improve tissue vascularity and joint synovialization via gentle movement of extremity to improve • Avoid tissue overload or exercise unless approved by doctor	• Minimizes stress on injection site • Cross link initiation and homeostasis occurring as biologic activating to preparing for cross bridging

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Table 2 (*continued*)

Rehabilitation Phase	Criteria to Progress to this Phase	Anticipated Impairments and Functional Limitations	Intervention	Goal	Rationale
			• No submersion in water, bath, pool, hot tub or ocean for 1 wk. *PT Progression: (Home Based)* • Progress PROM to AROM, to point of initial resistance, within brace restraints, and only within physician ROM restraints • Gentle sub maximum Isometrics (lower to mid-range sub maximal holds) twice a daily		
Phase II Inflammatory/Early Proliferation Phase (8–21 d)	• No signs of infection *2-4-wk delay/slower progression with ligament injections due to decreased vascularization	• Pain • Limited ROM ○ pain with light UCL stress tests and ADL's ○ Limited UE strength	*Restrictions:* ***Avoid all varus, valgus, A-P & rotational loads & ligament stressing, or and any loaded contractile activities or exercises*** ***Maintain any limited weight*	• Facilitate collagen deposition • Avoid homeostasis • Avoid disruption of collagen crosslink • Maintain any restricted weight bearing status • Continue Phase 1 Rehabilitation recommendations	• Minimizes stress on injection site • Allow the PRP to absorb at the location • Prepare for cross bridging • Tissue is not yet ready for excessive weight bearing, compression, shearing, tensile, and contractile loads

	*bearing precautions**** • Tissue/joint specific protected bracing & weight bearing • No exercise except for rehab program • No concentric contractions or exercises to affected tissue except for unloaded ADLs and/or ambulation • For UE procedures, no lifting more than a dinner plate. *PT Progression: (Home Based)* • Gradually progress AROM to point of initial resistance ○ Obtain > 90% full ROM by end of week 2 ○ AAROM to point of resistance or pain • Continue Phase 1 exercises, (gentle submax. isometrics) • Gradually progress to full weight bearing with protective brace if applicable	• Consult physician regarding cross-training and return to exercise options • Improve tissue vascularity and joint synovialization by initiating upper body exercise if you had lower body procedure or LB exercise for UB	

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Table 2
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Rehabilitation Phase	Criteria to Progress to this Phase	Anticipated Impairments and Functional Limitations	Intervention	Goal	Rationale
			• Continue Heat pack as in Phase I		
Phase III Proliferative Phase (3–6 wk)	• Full pain-free ROM • Able to tolerate full weight bearing (dependent on treated tissue)	• Limited UE/LE strength and cardiovascular endurance • Limited tissue tolerance to weight bearing, compression, shearing, tensile, and contractile loads or functional activities • Pain (diminishing) • Limited tolerance with heavier lifting, pushing, pulling functional activities	*Restrictions:* ***Avoid all valgus loads or ligament stressing activities/ exercises x 7 wk*** ***Avoid all compressive torsional loads for articular cartilage tissue x 5–6 wk*** • Continue use of assisted devices as instructed by physician procedures • No over stressing of tissue through exercise or impact activity • Initiate high repetition low load therapeutic concentric exercises for muscle/tendon • Initiate unloaded cyclical high volume compression-	• Protect tissue • Facilitate collagen deposition • Avoid disruption of collagen cross-link and facilitate parallel fiber alignment • Minimize deconditioning • Communication among physician, physical therapist & patient is essential during this key transitional phase	• Pain threshold significantly reduced • Collagen synthesis occurring, aligning in the longitudinal axis Nominal tables that are really just one-column lists are best represented as boxes, so Table 1 and 4 has been converted to Box 1 and 2, and subsequent tables have been renumbered sequentially. Please verify. • Cross bridging occurring and matrix integrity improving • Tissue beginning to withstand tensile forces and loads • Use modalities to facilitation collagen

		decompression exercises for cartilage/ joint • Improve tissue vascularity and joint synovialization by initiating upper body cardiovascular exercise if you had lower body procedure or LB exercise for UB • No exercises except for supervised rehab program • (3–6 wk) *PT Progression Overview:* • Pain should not increase > 2 points on 10-point VAS • Modalities for collagen synthesis & pain control: • Moist heat, nonthermal ultrasound, cold laser, Russian stim, ES, Shock Wave Therapy (ESWT) Manual Therapy Techniques • Gentle Soft-tissue Mobilization along	formation & remodeling • Soft-tissue mobilization techniques have mechanical, physiologic, histologic, and neurologic effects on the tissue which facilitate the healing mechanism and fiber alignment • Progress toward light ligamentous loading by end of phase III • Tissue tensile strength should be strong enough to initiate stress loading exercises • BFR enables strengthening using a light load and a relatively low volume of work • Cardiovascular training to improve endurance & tissue repair

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Table 2
(*continued*)

Rehabilitation Phase	Criteria to Progress to this Phase	Anticipated Impairments and Functional Limitations	Intervention	Goal	Rationale
			the line of tissue fibers • Joint Mobilizations to maintain arthrokinematics Therapeutic Exercises: • AROM to point of initial resistance sub maximum to max isometrics • Emphasize proper postural alignment, distal joint position Adjust exercise progression based on severity of injury • Gradual progression of early to mid-phase weight bearing activities (aquatics, unloaded treadmill, elliptical) • Initiate low resistance, high repetition, concentric, open chain exercise		

			• Initiate Blood Flow Restriction (BFR) exercises • Initiation and progression of eccentric exercises as concentric strength increases Neuromuscular Re-education: • PNF and rhythmic stabilization exercises • Proprioceptive training • Use of taping techniques as indicated for facilitation/inhibition		
Phase IV Remodeling Phase (6–15 wk)	Overlap of timelines is based on the patient's condition and severity of injury • Pain-free ligament provocation tests • Improving to no pain with resisted contractile tests	• Limited UE/LE strength • Limited ligament & tendon tensile strength during early phase IV • Diminished but improving weightbearing or joint compressive exercise loading tolerance • Limited joint proprioception • Altered timing and mechanics with sports	*Diagnostic imaging:* • Diagnostic Ultrasound (~6–8 wk) to determine extent of healing and exercise progression and return to activity or sports status *PT Progression: (Physical Therapy)* *Modalities*: • Continue as needed *Manual Therapy;* • Continue Deep transverse friction mobilization/massage	• Restore normal tissue integrity & fiber alignment • Maximize tissue vascularity and joint synovialization • Increase tissue tensile strength • Improve joint proprioception • Improve force production, tissue elasticity and ability to withstand tensile stretching	• Increased tissue integrity & strength of repaired tissue • Improved ability to produce force, withstand tensile stretching, absorb shock, and increased tissue elasticity • Reassess Functional Index Score and dynamic imaging to correlate with objective exam findings to determine soft-tissue and

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Table 2
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Rehabilitation Phase	Criteria to Progress to this Phase	Anticipated Impairments and Functional Limitations	Intervention	Goal	Rationale
	• Pain-free joint stability with stress testing • Show tissue integrity & joint stability with dynamic imaging • Subjective Functional Index Tool indicates patient is ready to progress through Phase IV to return to play status • Functional Testing performed to determine return to activity	specific & functional activities	to increase tissue vascularization and break up tissue adhesions *Therapeutic Exercise:* • Progress exercise and functional mobility integrating UE/LE CKC exercises as appropriate • Progress eccentric exercise • Progressive plyometric loading from <body weight to full body weight-bilateral to single • Progress to ballistic, explosive training • Sport specific training ○ ≦ 50% effort up to week 8 ○ ≦ Below 75% effort up to week 10 ○ ≦ Below 90% effort up to week 12	*Critical Decision-Making Period-determine if tissue has sufficiently healed via dynamic imaging or if a second injection and/or surgical intervention is warranted* • Prepare for return to activity, sports	subchondral bone healing, joint stability and pace of current exercise progression can continue, or if a second injection and/or surgical intervention is warranted

- Initiate Interval Sport Programs (Throwing, running, on field drills) pending results of Diagnostic US
- Return to sports 10–15 wk depending on the sport/activity

Neuromuscular Reeducation:

- Light concentric resistance pulley or tubing patterns with controlled speed emphasis
- Light Resistance PNF exercises performed manually using distal hand placements and initiating joint specific motions and adding pulleys or tubing/bands
- Progress proprioception exercises to unstable surfaces

Week 6–7 Critical Decision-Making Period

**Dynamic imaging (MSK ultrasound) is used to confirm ligament healing,

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Table 2
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Rehabilitation Phase	Criteria to Progress to this Phase	Anticipated Impairments and Functional Limitations	Intervention	Goal	Rationale
			joint stability, and load progression. • Initiate ligament and joint loading when healing and joint stability are determined, exercise progression is initiated. • Initiate eccentric tendon loading If sufficient healing and stability has not occurred at 6–7 wk, a second injection vs surgical stabilization may be warranted *Week 8–10*: Progress to fast twitch and dynamic exercises • Increase speed, resistance, and functional strengthening • Add kinetic chain functional and sport specific loading progressions		

**Pending repeated US imaging findings progress to return to play phase 4

Week 10–12:

Reassess Objective Exam results, Functional Testing, and Subjective Functional Tool Scores to determine return to higher level activity and/or sport-specific play

- Begin interval Return to Sport program. Start interval throwing, batting, tennis serves, volleyball hitting programs pending repeat US imaging findings,

Weeks 12–16:

Progress from 75-90+ % in controlled setting. Gradual return to sport at 12–15 wk

- Initiate high repetition no resistance loading exercises.
- Obtain 90% full range of motion.

Phase Two consists of continued gentle active motion and increased activity at home. The patient should obtain 90% of full ROM by the end of week 2.[20] Light soft-tissue mobilizations should commence toward the end of week 3 to the injected tissue and surrounding fascia at this time. However, to avoid disruption of collagen cross-link bridging and formation, deeper soft-tissue techniques (transverse friction, etc.) are not implemented until the sixth week following injection.[20] Gentle early motion of the local joints facilitates the physiologic tissue healing response following PRP injection that proceeds through the inflammatory, reparative, and remodeling phases. Furthermore, early motion and self-stretching prevents joint adhesions, increases muscle contraction, muscle fiber size, and tension, as well as increases resting levels of glycogen and protein synthesis. Mechanical stimulation (ie,: motion and controlled external loading) is a prerequisite for platelet effect in the early post-injection phase. Platelets influence the early stages of tissue repair, and this allows mechanical stimulation to further drive the reparative phase healing.[27]

Submaximal-maximal effort isometrics performed three times per day are also initiated in attempts to create light tension in the direction of the tendon fibers. However, any tensioning forces to injected ligament tissue are avoided at this time (valgus elbow stress to ulnar collateral ligament [UCL]) and until 7 weeks post-injection. Intermittent rest and care with resuming work and normal daily functional activities are also encouraged at home to help control post-injection symptoms and early inflammatory elevation.

Progressive full arc motion in the first two phases prevents ligament atrophy and increases ligament linear tissue stress and stiffness-particularly at a bone-ligament junction. Ligament stressing exercises or functional activities as well as excessive muscle or tendon tension is avoided during this phase. There may be a 2- to 4-week delay with ligament healing due to decreased tissue vascularization **Table 3**.[20] Exercises that exert tension on the UCL (Valgus stress) are not begun until later phase 3.

Early motion restoration aids connective tissue lubrication between collagen cross-links, increases collagen mass, decreases abnormal collagen cross-links, and prevents adhesion development. Following PRP injections, articular cartilage responds to early motion, intermittent compression, and decompression loading with improved metabolic activity and increased health of the cartilage matrix. Muscle, tendon, ligament, and bone tissue all respond favorably to motion. Restoring full range of motion during the first 10 to 14 days following PRP injection is advocated.[20]

Modalities used in the first two phases of PRP rehabilitation can include ultrasound, laser, and electrical stimulation. The use of modalities during this phase is aimed to further stimulate tissue healing and increase local perfusion and oxygen delivery to the site. Nonthermal ultrasound is commonly used to facilitate tissue repair and regeneration in damaged tissue. There is research that supports the use of therapeutic ultrasound to increase boney and muscle tissue regeneration.[28–30] However, most

Table 3
Tissue vascularization

Tissue Vascularization			
Ligament	Tendon	Bone	Muscle
Less			More

studies that support the use of nonthermal ultrasound and laser to aid tissue healing are based on animal studies. It is still unclear if using a pulsed nonthermal ultrasound is more effective than a low-intensity continuous protocol in terms of proliferation and tissue healing. The use of laser treatment in patients with lateral epicondylosis was found to lower subjective overall pain levels with reports of 90% to 100% relief in more than 45% of the patients who were treated with laser.[31] In addition, studies have found the use of low-energy laser improves tensile strength and stiffness in repairing medial collateral ligament in rats at 3 and 6 weeks after injury.[32] When rehabilitating after tendon PRP, to help increase endorphin release and minimize tissue response to loading and manual mobilizations, the authors have found positive results using Russian electrical stimulation with the following parameters: 2500 Hz frequency, 50 pps, 10/10 s duty cycle, 2 s ramp time for 10 to 12 min.

Progressive loading with shoulder, elbow, and wrist exercises during phases 2 to 4 is a critical component of the post-PRP injection treatment plan. The first two phases include use of concentric low-load higher repetition exercise dosage—three sets of 20 to 25 repetitions is recommended. Once the patient reaches three sets of 25 repetitions the weight is increased by 1 pound and progresses from there. Proper postural alignment, proximal and distal joint positioning, and control throughout the range, etc. are emphasized. This submaximal intensity using higher repetition progression improves tissue vascularization, helps align collagen cross-links, promotes tissue healing, and enables the tissue to start adapting to controlled amounts of stress.[20] Endurance training versus strengthening has been used in the early phases with success following PRP injections. Submaximal loading exercises reduce homeostasis and tissue breakdown and symptom exacerbation during the first 2 to 4 weeks. Studies have shown that resistance exercise is more effective in inducing acute muscle anabolism than high-load low volume or work matched resistance exercise modes (isometrics).[33]

Phase III (Proliferative/Reparative Phase)

Time: 3 to 6 weeks.

Goals:

- Adjust exercise progression based on type of tissue and severity of injury
- Use of modalities to aide tissue proliferation (recommend pulsed US, laser, electrical stimulation, extracorporeal shockwave therapy [ESWT], blood flow restriction [BFR] therapy)
- Begin high repetition loading and concentric
- Begin functional activities
- *Avoid Ligament stress for 7 weeks with activities of daily living and exercise*
- **Progress to Eccentrics week 4 to 6**

Pain levels have typically lessened by the third week. Collagen synthesis is occurring and aligning in the longitudinal axis. At this point, the tissue is beginning to withstand tensile forces and loads. However, it is important to adjust exercise progression based on the type of tissue and the severity of injury (ligament healing and proliferation take longer).[20] BFR has been shown to increase loading and training capacity for those who are not ready or may not tolerate heavier training loads and is often initiated in week 3 following orthobiologic injection. Specifically, BFR has been shown to produce increased muscle mass, strength, as well as cross-sectional patellar and Achilles tendon stiffness at comparable levels to conventional high-load resistance training.[34] The ability to provide the skeletal muscle with a sufficient exercise stimulus using a light load and a relatively low volume of work is helpful for muscle, tendon, ligament, and joint that is important in the earlier post-injection phase of healing.[35]

Soft-tissue mobilizations and progressive loading via resisted exercise are key components of the post-injection reparative and remodeling phases[20]. The primary pathologic mechanism that leads to tendinopathy includes chronic microscopic tearing in hypovascular tendon tissue. These repetitive tears heal by scar formation versus the normal tendon-healing pathways of vascularization and inflammation mechanisms.[36] Thus, during the reparative and remodeling phase of muscle and tendon tissue, the use of soft-tissue mobilizations techniques (ASTYM, deep transverse friction mobilization, Active Release, Graston Technique) in conjunction with appropriate exercise progressions is an important component of the healing process to help minimize this scar formation and promote anatomic tissue fiber healing in line of stress.[20] These techniques, however, should be used with caution to avoid tissue alignment disruption and once in the remodeling phase after 6 to 8 weeks post-injection.

Deep transverse tissue mobilization (DTFM) and friction massage had been implored with positive results. As described by Cyriax, DTFM is an aggressive form of soft-tissue mobilization in which localized pressure or distractive manipulation of tissues is directed tangentially across the longitudinally oriented collagen component of the injured tissue. To promote normal resolution of the collagen tissue, the tissue to be treated should be in a moderate stretch position (not painful).[37] Deep Transverse Friction mobilizations and other soft-tissue manipulation techniques have mechanical, physiologic, histologic, and neurologic effects on the tissue which facilitate the healing mechanism of PRP injections (**Box 2**). Reaction to DTFM may include rapid desensitization, latent post-treatment soreness, and moderate tissue bruising covering the area of tissue contact is acceptable.[38]

The use of extracorporeal shockwave therapy is effective in reducing pain and improving function.[39–41] The proposed mechanisms of ESWT involve inducing suppression of inflammatory reactions and oxidative stress and eliciting neovascularization in degenerative tissues.[42] The use of ESWT combined with PRP injection are beneficial on pain reduction and recovery of physical activity of patients with insertional Achilles tendinopathy and can relieve the pain synergistically for KOA.[43,44]

Eccentric loading is initiated early in the reparative and remodeling phases at approximately weeks 5 to 6 for muscle belly and 6 to 8 for tendon pending individual patient status. Owing to its positive effect on improving tissue integrity, strength, and improved function, eccentric loading is the other important component of the post-PRP injection rehabilitation.[20] Eccentric contractions function to decelerate a limb, provide shock absorption, and generate forces 14% to 50% greater than a maximal concentric contraction does.[45] This increased force generation improves musculotendinous integrity by inducing muscle hypertrophy and increased tensile strength or by lengthening the musculotendinous unit.[46]

Unlike concentric phase 1 to 2 exercises, eccentric loading has been shown to aid in stable angiogenesis in early tendon injury.[47] Daily eccentric loading was found to not have any detrimental effect on tendon vascularity or microcirculation.[47] A systematic review of tendinopathy found that eccentric exercises had the most clinical efficacy in regenerating function.[48] Other studies have found that eccentric exercise progressions are an effective treatment for chronic tendinosis.[49,50] Eccentric tendon loading exercise progressions are thus implemented into the post-injection rehabilitation by week 4 to 5 pending individual patient response.[20]

There is no clear consensus on the best non-operative treatment for muscle injuries beyond immediate rest and anti-inflammatory medications or modalities.[29] In chronic tendinosis injuries, rest has been found to be a less effective treatment efficacy.[48,51] In turn, eccentric exercise and loading have been shown in many studies to be beneficial in treating patients with tendinosis.[46,47] The optimal dosage and frequency of

Box 2
Effects of deep transverse tissue mobilization

Mechanical
- Distortion and elongation of collagen fibers
- Increased interstitial mobility

Physiologic
- Localized hyperemia
- Stimulate white blood cell invasion and healing production
- Destruction of substance P

Histologic
- Prevents scar formation and haphazard collagen orientation
- Stimulate collagen orientation along lines of stress via "Piezzo-electric effect"

Neurologic
- Initial nociceptor stimulation
- Mechanoreceptor stimulation
- Pain inhibition via "Central Biasing Mechanism"

eccentric loading for treating chronic tendinosis have not yet been established.[52] However, the literature indicates that to optimize treatment PRP injection should be combined with the mechanical stimulus of the tissue in order to promote optimal post-injection tissue healing and repair.[20]

Phase IV (Remodeling Phase)

Time: 6 to 12 weeks.

Goals:

- Eccentric loading, plyometric training return to sport/activity (pending individual sport and post-injection status variable from patient to patient)
- Continue tissue remodeling facilitation with deep transverse friction and soft-tissue mobilizations
- *Diagnostic ultrasound (~ 6 to 7 weeks) may be repeated to determine the extent of healing
- Resume full functional or sporting activity for 10 to 12 weeks pending progress with the post-injection program

The injected tissue commonly shows increased tensile strength during the remodeling phase.[20] Tissue remodeling facilitation is continued in phase four with the use of deep transverse friction and soft-tissue mobilizations. Depending on the response to the eccentric strengthening progression, the patient progresses to speed and coordination drills, plyometrics, ballistics, and more explosive sport-specific phase 4 exercises.

At this point, connective tissue has improved tensile strength as its fiber orientation is better aligned and suited to withstand more demanding tensile stress.[53] The functional strengthening, plyometrics, ballistics, neuromuscular power, and coordination exercises are performed at more intense levels to enable the patient to meet the demands of his or her sport or job activity. Typically, selective tissue tension tests (ligament stress tests, resisted muscle-tendon tests in a lengthened position, weight-bearing, and compression tests for bone) are non-provocative. Use of follow-up functional tools to ascertain patient readiness to resume higher level exercises, and return to sport or work is recommended. Studies regarding the efficacy of using scores on

Table 4
Estimated average tissue healing response time

Tissue Recovery Time			
>4–8 wk.	>6–8 wk.	>10–12 wk.	>11–15 wk.
Joints	Muscle belly	Ligaments[a]	Tendons

[a] Ligament healing may be delayed 2 to 4 wk; avoid varus/valgus.

subjective functional tools or questionnaires to help determine when a patient is ready to safely resume a particular activity or sport given a certain subjective score have not yet been published.

There are no clearly defined or objective means of determining when an athlete is able to safely return to play or when a patient is able to return to a functional activity (job duty). A grading system has been used to describe tendinopathy.[54] However, the use of a detailed clinical examination together with the repeat ultrasound imaging findings, as well as the patient's subjective assertions and functional index score as to whether the patient is ready to resume certain activities or sports are all used to assist the physician, therapist, and athletic trainer in determining when the patient is ready to resume the desired activity. Interval running programs, on-field agility progressions, and interval throwing programs are initiated in phase 4. Although there are several notable documented cases in which an athlete has returned to play at an earlier time period following PRP injection, most patients have been able to resume full functional or sporting activity by 10 to 12 weeks (**Table 4**).[20]

SUMMARY

The use of orthobiologic modalities such as PRP in orthopedics and sports medicine to deliver high concentrations of naturally occurring biologically active growth factors and proteins to the site of injury is very promising and continues to evolve. Early protection and tissue-specific progressive loading are critical components to successful outcomes following orthobiologic intervention. Each tissue heals and responds differently. Ligament, tendon, muscle, and articular cartilage each have unique healing properties that require tissue-specific loading. The authors have found using a criteria-based loading and exercise progression guided by dynamic imaging when appropriate to further advance the goal-oriented rehabilitation program. Each patient and injured tissue are unique and require specificintervention and rehabilitation.

DISCLOSURE

L. Podesta, MD, Editor, Biologic Orthopedic Journal E. Honbo, PT, DPT, OCS, Cert. DN, The Authors have nothing to disclose. R. Mattfeld, PT, DPT, OCS, ATC, The Authors have nothing to disclose.

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