PRP

Platelet Rich Plasma

A New Paradigm of

Regenerative Medicine

Dariusz J. Nasiek, MD, DABA, DABPM, DABIPP

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Foreword

"The doctor of the future will give no medicine, but will interest his patients in the care of the human frame with diet and the prevention of disease." Thomas A. Edison.

The treatment of the conditions that are described in this book exemplifies the use of our own body to exact a cure. Scientists and physicians have found that the use of the bodies' blood platelets in treatment can not only repair damage caused by injury, but can also regenerate the damaged tissue.

Platelets have been implicated in the formation of clots in vital organs by impeding the blood flow and by clotting. However, more recent studies have shown that platelets also attract stem cells, which play an essential role in regeneration and repair.

This book offers more information on treatment with PRP (Platelet Rich Plasma) as a therapy for tissue damage and injury. It also offers a glimpse into the future of utilizing stem cell therapy.

Congratulations to the author for bringing this information to our attention.

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Dedication

This book is dedicated to my dear parents
Stefania and Ludwik Nasiek
for the enormous emphasis
they placed upon my education,
and for their contribution towards it.

I would also like to acknowledge all the teachers and mentors
who have guided me through my life.

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THIS BOOK IS INTENDED FOR INFORMATIONAL PURPOSES ONLY.

It is not the purpose of this book to give medical advice.

The information contained herein is not a substitute for a thorough examination and consultation by a physician.

ISBN 978-0-9885190-0-8

Composed and produced by Master Printing USA, Inc.

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Introduction

If you have ever struggled through a long-term rehabilitation from a nagging physical injury, you are not alone.

You may have even learned a few lessons yourself from your own experience and research during the healing process. You might know that the classical approach in Orthopedic Medicine and Surgery relies largely on stabilizers such as ACE bandages, slings, casts, plates, and screws which are used to immobilize broken bones, hurt joints, and painful tendons.

This phase of healing is a period of inactivity during which your body slowly repairs the damage. Over time, with some consistent rehabilitation, the body regains its efficiency and returns to its former flexibility.

For most people, the arduous and painstaking process of rehabilitation is the only option available.

Recently though, professional athletes like Tiger Woods, suffering from a sore knee, and Chris Canty, defensive tackle for the New York Giants hampered with a hamstring injury, have discovered a noninvasive process called Platelet Rich Plasma therapy. This process put them back on their feet faster and got them back in the game sooner.

The news is now out.

Platelet Rich Plasma delivers a potent one-two-punch:

1. It is more effective than the traditional approach.
2. It regenerates damaged and irreparable tissues or organs.

It is more effective as it uses platelets and relies upon growth factors derived from cells responsible for repair and regeneration.

The regeneration is done by stem cells.

Although stem cell therapy has been controversial in the past, for many years platelets and growth factors have been used to effectively speed up the healing process.

This book will do more than just educate you about the process and benefits of platelet therapy.

It will explain in plain language why Platelet Rich Plasma in conjunction with physical therapy put active individuals and athletes back on their feet faster and got them back in the game sooner.

It will also discuss other noninvasive pain management options that have benefited patients, including the revolutionary stem cell therapy.

Most importantly, you will gain a clinical perspective on the efficiency of Platelet Rich Plasma from an expert in the field of pain management, as well as a greater understanding about why and when Platelet Rich Plasma Injections are the best option.

Avoiding Surgery

If you have ever had to decide whether having surgery in order to eliminate a nagging long-term physical injury is your best option, it is likely that this was a difficult decision for you to make.

To opt for the surgery or not is a tough choice. Especially, when there is no clear cut indication for having a surgical procedure and when the surgery is not immediately considered a life saving solution.

If you were patient of mine, we would discuss why I believe that any nonurgent or nonemergency surgery should be avoided in lieu of a minimally invasive therapy.

It is better to carefully observe how your injury has developed. This observation could result in a noninvasive solution. Sometimes, the injury might even heal naturally.

My rationale for this approach is simple.

First of all, each surgical procedure carries inherent risks, even though the risk is low, it should be avoided if possible.

Secondly, surgery is an irreversible process and it should be avoided at all costs if nonsurgical or minimally invasive options exist.

And finally, it is wise to incorporate lifestyle modifications before arriving at the point of no return.

PART I

A BASIC UNDERSTANDING

Chapter 1

Platelet Anatomy and Physiology

Blood components

Blood contains a liquid component and cells.

The liquid component is called plasma. It is made mostly of water and acts as a transport medium for cells. Plasma contains fibrinogen, a protein that acts like a net at a wound site where it catches platelets to form a blood clot.

Red blood cells (RBC) that transport oxygen account for 93% of all blood cells. White blood cells (WBC) that fight infection, kill germs and carry off dead blood cells make up 1% of the total blood volume while platelets make up the remaining 6% (1).

Platelets are responsible for hemostasis, but also play a pivotal role in healing because they are rich in growth factors and cytokines.

Growth factors derived from activated platelets play a role in the construction of new connective tissue, revascularization, bone mineralization and they have anti-inflammatory and antibacterial properties (7) (8).

Platelets

Platelets are the smallest component of blood cells. They are derived from fragmentation of mother cells - megakaryocytes – formed in the bone marrow. Platelets are small cell fragments measuring 23 microns. They are considered cell fragments because they do not have a nucleus containing DNA and are unable to multiply (1). However, they contain organelles and structures such as microtubules and are able to produce chemical products in the form of granulesin platelets. Because of these organelles, platelets synthesize and release large amounts of biologically active proteins that promote tissue regeneration (6).

There are three types of granules: alpha, delta, and lambda.

Alpha granules, the most important of the three, are formed during the original megakaryocytes maturation. The granules measure 200-500 nm in diameter. Alpha granules contain platelet factor 4,

transforming growth factor-β1, platelet-derived growth factor, fibronectin, B-thromboglobulin, vWF, fibrinogen, and coagulation factors V and XIII. Each platelet has approximately 50-80 alpha granules. They contain bioactive proteins and play a role in hemostasis and tissue healing. Activated platelets excrete the contents of these granules into their canalicular systems and into the surrounding blood vessels.

Delta granules, also known as dense granules, contain ADP or ATP, calcium, and serotonin.

Lambda granules, like lysosomes, contain hydrolytic enzymes.

The average lifespan of a platelet is 5 to 9 days. Platelets are a natural source of growth factors. They circulate in the blood and are involved in hemostasis, leading to the formation of blood clots and tissue repair leading to tissue regeneration.

Platelets release a multitude of growth factors including platelet-derived growth factor (PDGF), a potent chemotactic agent, and transforming growth factor (TGF) beta, which stimulates the deposition of extracellular matrix. Both of these growth factors have been shown to play a significant role in the repair and regeneration of connective tissue like muscles, tendons and ligaments.

Other healing-associated growth factors produced by platelets include: basic fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF), platelet-derived epidermal growth factor (PDGF), and vascular endothelial growth factor (VEGF).

Thus far, over 1100 types of proteins inside the platelets have been identified by researchers.

The most common platelet proteins include:

1. Platelet-derived growth factor - PDGF
2. Transforming growth factor - TGF
3. Platelet-derived epidermal growth factor - PDEGF
4. Vascular endothelial growth factor - VEGF
5. Insulin-like growth factor - IGF

6. Basic fibroblast growth factor - bFGF
7. Epidermal growth factor - EGF
8. Cytokines
9. Chemokines

Local application of these factors in increased concentrations through Platelet-rich plasma (PRP) has been used as an adjunct to wound healing over the past several decades.

PRP also has antibacterial effects (8). Platelets and leucocytes can release a variety of small antibacterial peptides upon contact with pathogens via a nonoxidative mechanism. Another advantage of those peptides is that they promote potent microbial killing activities with very little toxicity to normal cells. PRP helps with the antimicrobial activities of immune system defenses that help protect against infection.

Finally, PRP enhances the gene expression of:

1. Cellular matrix proteins
2. Collagen production
3. Tenocyte proliferation
4. Mitogenic activity - the ability to increase the division and production of new cells. Many growth factors found in platelets are also involved in the homeostasis of articular cartilage. They have been studied in vitro and have been shown to assist in cartilage repair (9).

There is constant reference to healing, regeneration, rebuilding throughout the book. From beginning to end the book leaves no doubt that the regeneration process is the physiological basis for tissue repair and the foundation of the new paradigm of regenerative medicine.

Important facts about platelets

- Platelets are produced in the bone marrow, from fragmentation of megakaryocytes - large mother cells.
- The physiological range for platelet concentration is 150-400 $\times 10^9$ per liter. By comparison platelet-rich plasma (PRP) for medical use contains at least 2- 5 times that number.

- Approximately 10^{11} platelets are produced each day by an average healthy adult.
- The lifespan of circulating platelets is 5 to 9 days.
- Platelet production is regulated by a hormone produced by the liver and kidneys called thrombopoietin.
- Each mother cell, megakaryocyte, produces between 5,000 and 10,000 platelets.
- Reserve platelets are stored in the spleen, and are released when needed by sympathetically-induced splenic contraction.
- Old platelets are destroyed by phagocytosis in the spleen and in the liver.

Platelet function

The main function of platelets is the maintenance of hemostasis. This is achieved primarily by the formation of thrombi, which occurs when the endothelium of blood vessels is damaged.

The second significant function of the platelets is to assist in the regeneration of damaged tissue through the delivery of growth factors and the attraction of stem cells to the injured area.

References

1. Campbell, Neil A. Biology (2008). (8th ed.).
2. Maton, Anthea; Jean Hopkins, Charles William McLaughlin, Susan Johnson, Maryanna Quon Warner, David LaHart, Jill D. Wright Human Biology and Health (1993).
3. O'Connell SM, Impeduglia T, Hessler K, Wang XJ, Carroll RJ, Dardik H Wound Repair Regen 2008, 16 (6): 74956.
4. Knighton DR, Ciresi K, Fiegel VD, Schumerth S, Butler E, Cerra F., Surg Gynecol Obstet 1999. 170 (1): 5660.
5. McAleer JP, Sharma S, Kaplan EM, Persich, Adv Skin Wound Care 2006, 19 (7): p 35463.
6. Marx RE, Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent. 2001 10(4): p.225-228.
7. Samson S, Gerhardt M, Mandelbaum B, Platelet rich plasma injection grafts for musclocutaneus injuries: a review. Curr Rev Musculoscelet Med (2008) 1 165-174.
8. Moojen DJ. et al. Antimicrobial activity of platelet-leukocyte gel against Staphylococcus aureus. J. Orthop. Res. 2008; 26(3): 404-410.
9. Kajikawa Y. et al. Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing. J. Cell Physiol. 2008; 215(3): 837-845.

Chapter 2

Understanding How Tissue Heals

It would be beneficial to understand how the tissue heals and what role platelets play in this process.

Healing is the restoration of damaged living tissue to normal or near normal function. It is the process by which the cells regenerate and repair to reduce the size of a damaged area. Healing incorporates both the removal (cleaning) and the replacement (rebuilding) of a dead tissue (1) (2) (3).

The replacement can happen in two ways:

1. *by regeneration:* the necrotic (dead) cells are replaced by new cells that form tissue similar to the original.
2. *by repair:* injured tissue is replaced with scar tissue.

Of course, the regeneration method is superior to that of a mere repair as it returns full function to the damaged tissue or organ.

Most organs will heal using a combination of both mechanisms. The body has a predictable response to tissue injury. The purpose of this response is to promote the best recovery and healing of the injured area. Until recently, medical interventions in this process were meant to provide an optimal environment for it to occur in. New regenerative medicine specialists aspire to steer the healing process into a speedy and full regeneration (2) (3).

Healing is a complex and dynamic process of restoring cellular structures and tissue layers.

The three phases of healing are:

1. Acute inflammatory phase
2. Repair phase
3. Remodeling phase

Although these categories overlap slightly, they can be further divided into five distinct phases:

1. The clotting phase
2. The inflammatory phase
3. The proliferative phase

4. The maturation phase
5. The remodeling phase

And while the process of tissue healing may be considered a series of separate events, in actuality the entire process occurs in tandem on different planes at the same time and is much more complex than it seems.

Within these broad phases is a complex and coordinated series of events that include chemotaxis, phagocytosis, neocollagenesis (formation of new collagen), collagen degradation, and collagen remodeling.

In addition, angiogenesis, epithelization, and the production of new glycosaminoglycans (GAGs) and proteoglycans are vital to the healing process (6). (The definitions of these anatomical and physiological terms can be found in the glossary of terms in the back of the book).

Clotting phase: The healing of a wound begins with clot formation to stop bleeding and to reduce infection by trapping foreign bacteria, viruses and fungi. This happens immediately after the injury. Clotting is followed by an invasion of neutrophils (white blood cells) beginning 3 to 24 hours after the wound has occurred, with mitosis (divisions and multiplications) beginning in epithelial cells after 24 to 48 hours. *Platelets are responsible for the clot formation.*

Inflammation phase: The inflammatory response is what causes pain, swelling, redness, and warmth around an injured area. This is the body's way of protecting itself. The swelling causes stabilization in the area. Because of the increased blood flow the area gets warmer, increased permeability occurs, and the tissue swells. In the inflammatory phase the blood delivers macrophages and other phagocytic cells that kill bacteria, debris, and damaged tissue (1) (2).

The blood also releases chemical factors such as growth factors that encourage fibroblasts, epithelial cells and endothelial cells to migrate to the area and divide to form new capillaries. *Platelets are responsible for delivering growth factors to the healing site.*

Proliferative phase: This phase occurs when the inflammation has subsided and your body begins to repair the injured area. In the proliferative phase, immature granulation tissue containing plump active fibroblasts is formed. Fibroblasts quickly produce abundant type III collagen, which heals the scar left by an open wound. While regenerating, granulation tissue moves from the border of the injury towards the center.

As granulation tissue matures, the fibroblasts produce much less collagen and become more spindly in appearance. They begin to produce the much stronger type I collagen. Some of the fibroblasts mature into myofibroblasts which contain the same type of actin (contracting protein) found in smooth muscle. This enables them to contract and reduce the size of the wound. Platelets are responsible for the initial delivery of growth factors to speed the process of proliferation and rebuilding of the damaged tissue (2) (3).

Maturation phase: During the maturation phase the unnecessary vessels formed in the granulation tissue are removed by apoptosis (programmed cell death), and type III collagen is largely replaced by type I collagen. In the beginning, the collagen is similar to sticky glue. It needs to be aligned in order to perform its function. The primary result of this phase is an improvement in the quality, orientation and tensile strength of the collagen. Collagen which was originally disorganized is now cross-linked and aligned along tension lines. This phase can last a year or longer. Ultimately, a scar made of collagen containing a small number of fibroblasts remains. *Rehabilitation and physical therapy play a major role in the maturation phase of tissue regeneration.*

Remodeling phase: Tissue remodeling lasts the longest, sometimes for years. During this phase tissue is remodeled as a result of old cells being replaced by new cells in response to stress, loading pressure and other numerous physiological and pathological factors. The final appearance and function depends on many factors. *Rehabilitation plays a major role in the maturation phase of tissue remodeling*.

The healing process may result in one of the following outcomes:

1. SCAR formation - nonfunctional tissue
2. Reparation of partially functional tissue
3. Formation of NORMAL TISSUE - fully functional tissue

Platelets are involved in many phases of tissue healing and are critical in the normal process of repair and regeneration (6). The addition of supranatural levels of platelets allows the process of regeneration to go faster and smoother with a final result of NORMAL TISSUE formation (5).

References

1. Grey Joseph E., Harding Keith G., ABC of Wound Healing (ABC Series). (2006)
2. Stocum, David L., Wound Repair, Regeneration and Artificial Tissues (Molecular Biology Intelligence Unit Series). (1995)
3. Heister, L, A. General System of Surgery in Three Parts; Containing the Doctrine and Management. (2012)
4. Einhorn TA, The science of fracture healing. J Orthop Trauma 2005, 19 (suppl.) 4-6.
5. Alsousou J. et al The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery. The Journal of Bone & Joint Surgery (Br), 2009, Vol.91-B, No.8. p. 987-995.
6. Nurden AT. et al. Platelets and wound healing. Frontiers in Bioscience. 2008; 13: 3532-3548.

PART II

CLINICAL APPLICATIONS

Chapter 3

Historic Overview

PRP and its various forms were originally used in clinical practice as an adjunct to surgery to assist in the healing of various tissues, especially to promote tissue healing in prosthetic surgery. PRP promotes the healing of the tissues around the implant and controls blood loss in prosthetic surgery (1).

Initially PRP was used in oral surgery (2). Subsequently, PRP has seen various orthopedic applications and has been used in surgery of the hip, shoulder, and in knee procedures (4). More recently PRP injections have been used for the management of muscle, tendon, and cartilage injuries, as well as in sports medicine and for pain management (3). The newest applications of PRP can be seen in the field of plastic surgery and cosmetic medicine where it is used to regenerate old skin, remove wrinkles and to avoid collagen volume loss (5).

Allogeneic fibrin glue, which is derived from the same organism, was originally introduced in 1970.

The first reference of PRP in clinical trials dates back to 1987 when after open heart surgery PRP was used to prevent the need for a homologous blood product transfusion.

In 1990, autologous fibrin gel or fibrin serum (also known as fibrin glue) was used in haemostatic and adhesive preparation.

In 2003, the first scientific support for the management of cartilage problems was described. Since then, the application of PRP has rapidly expanded throughout the medical world. This progress is described in multiple articles, reviews, and books that have been published touting its benefits.

The results are beneficial for three important reasons:

1. Relative ease of use
2. Low cost
3. Alternative to major surgical procedures. (This is particularly true for athletes with sports injuries who need to get back in the game quickly, but also for older patients when speed of recovery is important and surgery avoidance is a high priority.)

References

1. Bergoff W. et al. Platelet-rich plasma application during closure following total knee arthroplasty. Orthopedics. 2006: 29 (7) p. 590-598.
2. Garg AK. The use of platelet rich plasma to enhance the success of bone grafts around dental implants. Dent. Implantol. Update. 2000; 11(3): 17-21
3. Anitua E. et al. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials 2007; 28: p.4551-4560
4. Everts PA et al. Platelets gel and fibrin sealant reduce allogenic blood transfusions in total knee arthroplasty. Acta Anaesthesiologica Scand. 2006; 50 (5) p.593-599
5. Epply BL et al. Platelet rich plasma: a review of biology and applications in plastic surgery. Plast Reconstructive Surg. 2006; 118 (6) p.147-159

Chapter 4

Clinical Application of PRP Injections

Clinical application of PRP is growing as new studies are being published and new areas of treatments are being developed every year.

PRP in the treatment of tendon injuries

Chronic tendon disorders are quite common in athletes and in active people. Surrounding tissue such as synovium and peritendon tissue are also affected. Tendinopathy is characterized by swelling, pain, and loss of full range of motion.

PRP is a treatment option for the management of a chronic tendon injury. Positive effects on tendon healing have been established in animal and human studies. Mechanical testing indicates that there has been improvement in maturation of the tendon and cartilage when compared with controls. There has also been an increase in the formation of new bones and cartilage at the healing site.

Most of the studies involving PRP in humans are on the Achilles tendon, patellar tendon, wrist extensor and supraspinatus tendon. These studies indicate that there is evidence that PRP injections into the Achilles tendon facilitate early recovery from the procedure after surgery. There are also studies suggesting that the injections of PRP are beneficial in chronic patellar tendinopathy (1) (2) (3).

Platelet-derived growth factors show the important role of growth factors in repair of damaged ligaments and homeostasis. Platelets are involved during the early stage of medial collateral ligament and ACL healing and regeneration.

PRP in the treatment of cartilage injuries

PRP has been used as a treatment for the management of articular cartilage injuries of the knee, hip, and ankle. The most commonly reported method of clinical application consists of multiple intra-articular injections of PRP (3) (4) (5).

Favorable results in pain reduction and improved function have been reported. Intra-articular injections were compared to a common nonsurgical treatment such as hyaluronan injections, and

they demonstrated better pain control and improvement in the physical function.

It has been shown that several growth factors may improve cell regeneration. Regenerative effects of PRP have been documented both on patients and and in the laboratory. Studies report the use of PRP to augment ACL reconstruction. One study documented a 48% decrease in the amount of time it took to achieve a complete homogenous graft signal when measured by MRI. These reports suggest that the intra-articular injections have been successfully used to reduce pain and improve function (4) (5).

Platelet-derived growth factors also play an important role in meniscus homeostasis and repair. Platelets are involved during the early stage of meniscal regeneration and healing.

PRP in the treatment of muscle injuries

Muscle strains and sprains along with muscle contusions are very common in sports and general activities. In the general population, muscle strains can be extremely painful and may be responsible for the increase in the level of pain and absence from work or school.

Despite the advances in conservative measures like rehabilitation, the pain relief process can be long and the possibility of re-injury is high.

The management of muscle injuries through conservative measures includes the following:

1. Stretching and strengthening regimen
2. Gradual return to activity
3. Injections of local anesthetic and steroids into the muscles

None of these techniques guarantee a full recovery.

PRP has the ability to speed up the recovery process in muscle injuries rehabilitation (6).

Despite the limitations of PRP, scientific studies have measured the use of this noninvasive pain management protocol to facilitate the healing of injuries and help patients return to activities sooner. While only minor scientific support exists for the use of PRP in the management of muscle pain, its usage has increased.

References

1. Sanchez M. et al. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. Am. J. Sports Med. 2007; 35(2): 245-251.
2. Sanchez M. et al. Management of post-surgical Achilles tendon complications with a preparation rich in growth factors: a study of two cases. Injury EXTRA. 2009; 40:11-15.
3. De Vos RJ. Et al. Platelet-rich plasma injection for chronic Achilles tendon tendinopathy: a randomized controlled trial. JAMA. 2010; 303(2): 144-149.
4. Sanchez M et al. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. Clin. Exp. Rheumatol. 2008; 26(5): 910-913.
5. Kon E. et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. Knee Surg Sports Traumatol Arthroscop 2010; 18(4): 472-479.
6. Hammond JW. et al. Use of autologous platelet-rich plasma to treat muscle strain injuries. Am. J. Sports Med. 2009; 37(6): 1135-1142.

Chapter 5

Clinical Studies

Multiple medical studies have shown that PRP therapy can accelerate the healing of tissues and help with injuries such as tendonitis, ligament tears, osteoarthritis, and most recently facet arthropathies and disc degeneration (1).

Clinical studies in various areas are provided here to demonstrate the positive outcomes of PRP use. The following studies were carefully chosen to demonstrate different areas of application and reflect various study designs. They reflect a relatively young field that is expanding to include new applications and new areas which accompany the need for further research.

We'll start with seven clinical studies in vivo, done with a live body, followed by a final study in vitro, done on an animal, in a laboratory. While each of these are lengthy, formidable studies, you will find a brief commentary after each conclusion to help you understand its overall value.

Study 1

The American Journal of Sports Medicine 2010.
Positive effect of autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial-platelet-rich plasma versus corticosteroid injection with a one-year follow-up. Author: Joost C. Peerbooms

Background: Platelet-rich plasma (PRP) has shown to be a general stimulation for repair.

Purpose: To determine the effectiveness of PRP compared with corticosteroid injections in patients with chronic lateral epicondylitis.

Results: For the purpose of the study successful treatment was defined as more than 25% reduction of pain in the visual analog pain scale. The results showed that, according to the visual analog pain scale scores, 49% in the corticosteroid group and 73% of PRP group had successful outcome following the study.

Conclusion: Treatment of patients with chronic lateral epicondylitis with PRP injections reduces pain and significantly increases function exceeding the effects of corticosteroid injections.

Summary: PRP treatment has helped a majority of patients to reduce their pain and enjoy greater mobility as compared to the results of those patients receiving steroid injections. This improvement was sustained over time with no reported complications.

Study 2

International Journal of Sports Medicine 2010.
Treatment of Achilles tendinopathy with platelet-rich plasma.
Author: K. Gaweda

Background: Achilles tendinopathy commonly impedes the functioning of an active person, but condition improves when the treatment of PRP injections is being implemented.

Purpose: The aim of the study was to evaluate the effectiveness of Achilles tendinopathy treatment with autologous platelet-rich plasma (PRP).

Results: 14 prospectively selected patients were evaluated using the American Orthopedic Foot and Ankle Society (AOFAS) scale and Ultrasonography (US). During follow-up visits, a significant improvement was observed in the clinical and imaging results of all the patients. Only two of the patients complained of pain at the end of 18 month follow-up studies.

Conclusion: A significant improvement in functional evaluation scores with simultaneous lack of complications suggests a substantial value of PRP treatment. The study showed very high patient satisfaction and activity improvement; these results are encouraging.

Summary: PRP injections have helped patients with Achilles tendinopathy to function better, with fewer complications.

Study 3

Clinical and Experimental Rheumatology 2008.
Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee osteoarthritis (OA): A retrospective cohort study.
Author: M. Sanchez

Background: Platelets derived from blood, which form a preparation rich in growth factors (PRGF), have the potential to enhance the capability of cartilage to repair itself.

Purpose: The goal of this study was to explore whether the PRGF could be used for treatment of osteoarthritis of the knee.

Results: 30% of patients with osteoarthritis were treated with PRGF and another 30% were treated with hyaluronan as a control group. After five weeks, the observed success rate in improvement of pain perception was 33.4% in the PRGF group and 10% in the hyaluronan group. Intra-articular administration of PRGF, along with biocompatibility and nonimmunogenicity, is an attractive approach to osteoarthritis treatment. The autologous nature of this therapy is very relevant to osteoarthritis management since the disease affects primarily people over the age of 60, who are most prone to drug-toxicity.

Conclusion: There is a higher success rate when using PRGF for treatment of patients with osteoarthritis of the knee than when using hyaluronan.

Summary: PRP injections have helped to relieve osteoarthritic (OA) knee pain more effectively than hyaluronan (Synvics) injections.

Study 4

Knee Surgical Sports Traumatology and Arthroscopy 2010. *Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions.*
Author: Elizaveta Kon

Background: Platelet-rich plasma (PRP) is a natural concentrate of autologous blood growth factors experimented with in different fields of medicine in order to test its potential to enhance tissue regeneration.

Purpose: The aim of this study was to explore this novel approach to treat degenerative lesions of articular cartilage of the knee.

Results: 100 consecutive patients, affected by a chronic degenerative condition of the knee, were treated with PRP intra-articular injections. The patients were evaluated at 6 and 12 month intervals with an objective visual analog pain scale used for clinical evaluation. A statistically significant improvement of all cases was seen from the time of basal evaluation to the end of the therapy and then during the follow-up period 6-12 months later. 80% of patients were satisfied with the treatment results.

Conclusion: PRP injections have a clinical relevance in reducing inflammatory and degenerative articular processes and improving knee function and quality of life. The short-term results of the study were encouraging and indicated that treatment using autologous PRP intra-articular injection is safe and may be useful for the treatment of early degenerative pathology of the knee.

Summary: ***Following PRP injections patients enjoyed both short and long-term improvement in knee function and mobility. PRP is safe and may be an effective approach for treating early signs of aging in the knees.***

Study 5

Injury, International Journal Care of Injured 2009.
Platelet-Rich Plasma: New Clinical Application: a pilot study for treatment of jumper's knee.
Author: Elizaveta Kon

Background: PRP growth factors help to improve pain stemming from jumper's knee.

Purpose: The aim of the study was to explore this novel approach to treating chronic patellar tendonitis with PRP injections by gathering and assessing the number, timing, severity, duration, and resolution of related adverse events occurring among study participants before and after treatment. Another purpose was to analyze the results obtained to determine feasibility, safety, indications, and application of this method in further studies.

Results: 20 male athletes with a history of pain in the knee prepatellar region received PRP treatment and were evaluated at six month follow-up. No severe adverse events were observed, and statistically significant improvements in all scores were recorded in all patients.

Conclusion: The results suggest that this method, which aids the regeneration of tissue and which otherwise has low healing potential, may be safely used for the treatment of jumper's knee. Treatment with PRP injection in a regenerative area has the potential to reduce pain and allow the majority of patients to go back to full tendon-loading activity.

<u>Summary:</u> Following PRP injections, tissue regeneration in the knee was improved and there was an increased potential for pain relief.

Study 6

American Journal of Sports Medicine 2006. *Treatment of chronic elbow tendonitis with buffered platelet-rich plasma. Author: Allan Mishra*

Background: Elbow epicondylar tendonitis is a common problem that is usually resolved with nonoperative measurers. When these measures fail, however, patients are interested in an alternative nonsurgical intervention.

Purpose: The purpose of the study was to determine the effects of treatment of chronic severe elbow tendonitis with buffered platelet-rich plasma to reduce pain and increase function in patients who considered surgery.

Results: 140 patients with elbow epicondylitis were evaluated in this study. Eight weeks after the treatment with platelet-rich plasma patients noted 60% improvement in the visual analog pain scale scores versus 16% improvement in the control group. After six months, the patients treated with platelet-rich plasma noted 81% improvement in their visual analog pain scale. At the final follow-up, there was a 93% reduction in pain compared with the visual analog pain scale scores before the treatment.

Conclusion: Treatment of patients with chronic elbow tendonitis with buffered platelet plasma reduced pain significantly in this investigation. Platelet-rich plasma should be considered before surgical intervention. No PRP patients had worsened after treatment and there were no complications in the study.

Summary: PRP has been shown to be very effective in treating elbow tendonitis and is a viable alternative to surgery.

Study 7

Journal Tissue Engineering 2007. *Intervertebral disc (IVD) regeneration using platelet-rich plasma and biodegradable gelatin hydrogel microspheres.*
Author: Masateru Nagae

Background: Platelet-rich plasma has the potential to regenerate intervertebral discs.

Purpose: The purpose of the study was to determine the potential of growth factors to regenerate intervertebral discs and treat IVD degeneration. In addition, the therapeutic effect of the combined administration of PRP and biodegradable gelatin hydrogel microspheres on degenerated IVD was investigated in a vivo animal study.

Results: Histologically, notable progress in intervertebral disc degeneration was observed in the control and PRP group. In contrast, progress of IVD degeneration was remarkably suppressed over the 8-week period in the PRP group. Intense immunostaining, for proteoglycans in the nucleus pulposus (NP) and inner layer of annulus fibrosus (AF), was observed 8 weeks after administration of PRP-impregnated microspheres. Almost all microspheres were indistinct 8 weeks after the injection, and there were no apparent side effects in this study.

Conclusion: Results suggest that the combined administration of PRP and gelatin hydrogel microspheres into the intervertebral disc may be a promising therapeutic modality for inhibiting intervertebral disc degeneration inhibition.

Summary: PRP injection into an intervertebral disc helps to regenerate the disc with no side effects.

Study 8

American Journal of Sports Medicine 2008. *Platelet-rich plasma enhanced tendon repair. A cell culture study in vitro. Author: Marieke De Mos*

Background: Autologous platelet-rich plasma (PRP) application appears to improve tendon healing in traumatic tendon injuries, but basic knowledge of how PRP promotes tendon repair is needed.

Purpose: The intent of this study was to evaluate the effect of platelet-rich plasma, as well as endogenous growth factors produced by human tenocytes, on cell collagen production.

Results: Platelet number in PRP increased 2.55. Both PRCR and PPCR increased cell number and total collagen.

Conclusion: In human tenocyte cultures PRCR and PPCR stimulate cell proliferation and total collagen production. Autologous PRP application appears effective in the healing of chronic traumatic tendon injuries and tendinopathies. PRP clot releasate stimulates cell proliferation, collagen deposition, and enhances the gene expression of matrix degrading enzymes and endogenous growth factors produced by human tendon cells which may promote the return to normal function after traumatic injuries.

Summary: ***PRP injections stimulate cell growth and collagen production which help to improve the healing of tendons.***

With the growing number of successful clinical applications for PRP in medical literature comes the need for larger and better designed clinical trials to document the healing properties of PRP.

I chose the first seven human studies to help you gain an understanding of the effects of PRP on actual patients, while the final study was performed on animals in the laboratory.

Here is a brief summary of the above eight studies:

- PRP treatment has helped patients to reduce their pain and enjoy greater mobility as compared to the results of patients receiving steroid injections (study 1).

- PRP injections have helped patients with Achilles tendinopathy function better, with fewer complications (study 2).

- PRP injections have helped to relieve osteoarthritic knee pain more effectively than Synvisc injections (study 3).

- Patients enjoyed both short and long-term improvement in knee function and mobility after PRP injections (study 4).

- PRP is safe and may be an effective approach in treating early signs of aging in the knees (study 4).

- Tissue regeneration in the knee was improved and there was an increased potential for pain relief. This is another example of how PRP can accelerate healing (study 5).

- PRP has been shown to be very effective in treating elbow tendonitis and is a viable alternative to surgery (study 6).

- There were no side effects after treatment when PRP injections were combined with hydrogel to effectively treat intervertebral disc degeneration (study 7).

- PRP injections stimulate cell growth and collagen production which helps to improve the healing of tendons (study 8).

References

1. Alsousou J. et al. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. J. Bone Joint Surg. Br. 2009; 91(8): 987-996.
2. Marx RE: Platelet-rich plasma: Evidence to support its use. J. Oral Maxillofac. Surg. 2004;62:489-496.

Chapter 6

Clinical Application of PRP for Cervical and Lumbar Facet Arthropathy

In practice, physicians are using PRP to treat neck and lower back pain originating from painful cervical and lumbar facets. This condition is known as cervical and lumbar facet syndrome and also as facet arthropathy. Results when using PRP to treat this condition are very favorable (1).

Facet arthropathy is similar to other joint arthropathies where treatment with PRP has almost always been successful. The regenerative properties of PRP help to reduce pain and increase mobility following an injury. This treatment also works on healing in many degenerative conditions (2).

Traumatic neck and back pain is very often related to whiplash injuries with the following symptoms: nonradiating neck/back pain, becoming worse with extension or posterior tilt, tenderness in the projection of the facet joints, and positive facetogenic maneuvers. This type of acceleration/deceleration injury can occur as a result of a rear end accident or an abrupt stop of the car.

Confirmation of the diagnosis is identified by positive response to the medial branch block. Upon completion of the block (if the block is positive), the result will be that of temporary pain relief and increased range of motion.

More clinical trials are needed to document the increase of PRP in clinical applications and explain why the ligaments and muscles heal faster after PRP injections. Because there are no standardized protocols available regarding blood collection and PRP preparation, more needs to be done to standardize these areas. Physical Medicine and Rehabilitation protocols following PRP injections also need to be established to facilitate recovery after injections.

In our practice, every patient follows a structured physical therapy (PT) protocol. Following the PRP injection our PT protocol incorporates the following:

1. 24-48 hours of rest followed by a minimal amount of PT.
2. A more comprehensive PT protocol begins 72 hours after the initial injection.

3. The PT is done for 3-4 weeks followed by a medical evaluation.
4. Additional PRP injections are performed in 4 week intervals.

Ad 1. A relative rest period following the PRP injection is necessary to provide the opportunity for the platelets to work at the site of injury and to reduce the intensity of the pain where the actual injection was performed. Excessive movements may displace the PRP matrix from the point of injection.

Ad 2. Physical therapy (PT) protocol requires 2 to 3 visits per week and incorporates techniques that facilitate the maturation and remodeling phases of the healing phases as described in chapter 2.

Ad 3. & 4. Upon evaluation, the decision to continue PRP injections is based on the relief of symptoms and the ability to perform a full range of motion exercises.

Three PRP injections followed by physical therapy seems to be the optimal protocol in most cases with a high success rate of function recovery and the elimination of neck and back pain.

References

1. Nasiek, D. PRP helps to regenerate injured facets joints following MVA injury (study in progress).
2. Mei-Dan O. et al. Autologous platelet-rich plasma: a revolution in soft tissue sports injury management? The Physician and Sports Medicine, psm. (2010),12.p 1835.

Chapter 7

Comparing PRP Injections with Synvisc® Injections and Stem Cell Therapy

Injections of blood product in the form of PRP have been used successfully for many years throughout various medical and surgical fields.

Let's compare PRP injections with Synvisc® and stem cell injections.

Synvisc® injections vs. PRP injections

Previously developed injections such as Synvisc® were and are still used to treat osteoarthritis of the knee. They are successful in eliminating pain and improving function. Synvisc-One®, which is a natural hyaluronic acid derivative, is used for treatment of pain due to osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative nonpharmacological therapy such as physical therapy (PT), manipulation, and simple analgesics like acetaminophen. It can provide up to 6 months of osteoarthritic knee pain relief with just one injection (1). Synvisc® is made from a natural substance that lubricates and cushions the joint. The injections of the viscous products provide lubrication to the joint. The product has no biological activity itself and needs to be administered repeatedly in order to provide relief (1).

PRP injections, on the other hand, are biologically active and stimulate healing, repair, and tendon regeneration. More studies are necessary in order to uncover the full potential of their effects as they speed up the recovery and healing process (2).

Stem cell injections vs. PRP injections

New frontiers have been tested with new injections that target specific cells. Omnipotent stem cells can be utilized to regenerate specific tissues rather than to provide nonspecific healing properties. Direct stem cell injections are the latest process in development. Stem cells delivered from bone marrow aspiration and from fatty tissue aspiration present great biological healing potential. They can influence faster regeneration and promote the development of new tissues. Stem cells have the remarkable potential to develop into many different cell types in the body. They serve as an internal repair system, dividing without limit to replenish other cells. When a stem cell divides, each new cell has the potential either to remain

a stem cell or become another type of cell with a more specialized function, and under certain conditions it can be induced to become a tissue cell, organ cell or cell with specialized functions. Research on stem cells continues to advance knowledge of how healthy cells replace damaged cells.

PRP injections, like stem cells, are biologically active and stimulate healing, repair, and regeneration. PRP depends on growth factors to speed the recovery and the recruitment or facilitation of the stem cells from the vicinity and/or circulation. The PRP uses the attributes of the stem cells, but at a restricted level. More studies will help to uncover their full potential as they speed up the recovery and healing process through recruitment of the stem cells.

References

1. Manufactures insert from injectible Synvisc® and Synvisc-one® products.
2. Anitua E. et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. Rheumatology. 2007; 46(12): 1769-72.

Chapter 8

Rehabilitation and Physical Therapy

Rehabilitation and physical therapy are the most important contributing factors to insure complete restoration and recovery after PRP injections.

Traditionally the convalescence process included the following:

1. Eliminating or reducing activities
2. Adding passive types of therapy
3. Using nonsteroidal anti-inflammatory drugs like Aspirin, Motrin, and Aleve

I will explain why this is ***not*** the best and fastest road to recovery.

First, physical activity in any form speeds up recovery (1)(2).

Secondly, both active and passive therapy need to be incorporated (4).

Finally, while the anti-inflammatory medication may help in the short term, in the long term it will slow down the healing process and may lead to undesirable outcomes such as tendinopathy and chronic pain.

In our practice, we advise our patients to follow these important steps in physical therapy and rehabilitation following the PRP injections:

1. Rest for the first 24-48 hours after PRP procedure to prevent displacement of the newly-formed PRP mash at the injection site.

2. Implementation of advised and slow range-of-motion activities with the addition of physical therapy after the first 48 hours.

3. Resuming activities and a full physical therapy protocol after 72 hours.

4. Restriction on the use of steroidal and nonsteroidal anti-inflammatory medication for a period of 4 weeks.

5. Intake of Tylenol or weak painkillers to reduce pain and facilitate an exercise program.

Ad 1-4. The goal of physical therapy is to improve function, decrease pain, and increase strength.

Ad 5. The goal of medication is to create a pain-free physical therapy experience and to allow for continuation of normal activities.

Incorporating physical activity and a moderate exercise program in conjunction with physical therapy will immediately increase the water content and the blood flow in healthy tendons and in those tendons with tendinosis (1). An increase in water content and blood flow in the vicinity of the injury will speed up the recovery. Increased blood circulation brings more platelets and growth factors to the injured area which leads to a quicker recovery (1).

According to many experts, exercise may prevent or reduce the production of the chemical agents responsible for producing pain in tendinosis (2). These agents, associated with symptomatic tendinosis, include substance-P, Glutamate, Calcitonin, and other active peptides, amongst others. These neuropeptides may be responsible for tendinosis pain. However, patients who exercise have lower levels of these substances in their blood (2). The same is true following physical therapy.

As you may know, exercise stimulates the production of collagen synthesis, an enzyme responsible for stimulation of collagen production. This suggests that exercise may increase the size of a tendon because it increases the production of collagen type I (5). This may be of further benefit because fibroblasts, which help repair damaged areas of tendons, normally synthesize a greater proportion of type III collagen (type III collagen is not as strong and resembles scar tissue). As a result, physical therapy exercises may strengthen tendons and protect them from subsequent overuse (5).

Weight-bearing exercises have long been known to strengthen tendons by increasing blood flow, oxygen uptake, and metabolic rate (3)(4). They also prevent collagen degradation and improve collagen synthesis in healthy tendons. The same may be true for repairing injured tendons. Weight lifting may also strengthen degenerative tendons in the same way it does in healthy ones (4).

It is important to participate in physical activity to be able to depend on yourself and resume a normal life, but it should be done in a controlled rehabilitation setting from the onset of treatment. Otherwise, unsupervised physical and/or sports activity may actually cause or aggravate damage, tendinosis, etc. On the other hand, exercise under the supervision of a medical doctor and physical therapist will promote faster healing and optimize the regeneration process.

References

1. Alfredson H. et al., The chronic painful Achilles and patellar tendon: research on basic biology and treatment. Scandinavian Journal of Med. Science Sports. 2005; 15 p.252-259
2. Puffe T. et al., Mechanical factors influence the expression of endostatin an inhibitor of angiogenesis in tendons. Journal of Orthopedic Res. 2003; 21, p. 610- 616
3. Shalabi A. et al., Immediate Achilles tendon response after strength training evaluated by MRI. Medical Science Sports Exerc. 2004; 36, p. 1841-1846
4. Tipton CM. et al. The influence of physical activity on ligaments and tendons. Medical Science Sports. 1975; 7, p. 165-175
5. Maffulli N. et al. Tenocytes from ruptured and tendinopathic Achilles tendons produce greater quantities of type III collagen than from normal Achilles tendons: an in vitro model of human tendon healing. American Journal Sports Medicine. 2000; 28, p.499-505

Chapter 9

Seeing the PRP Process and Understanding the Techniques for the Application of the PRP

The following photographs will illustrate the technical aspects of the process from admission to discharge.

1. Arrival at the surgical center.

2. Admission protocol with a registered nurse at the surgical center.

3. Discussion with the surgeon, documenting and obtaining informed patient consent.

PREPARATION

The preparation of the PRP occurs in an operating room or preoperative area of the hospital, outpatient facility or physician's office. It begins with blood collection. A sterile technique is used when withdrawing and preparing PRP.

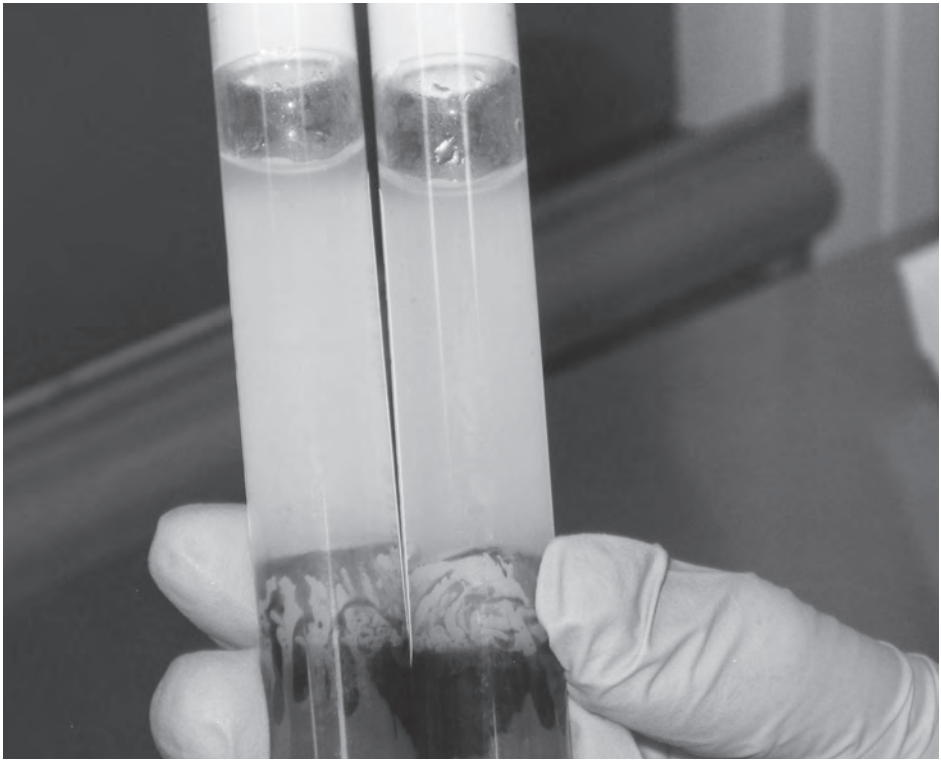
4. Blood drawing.

Blood drawing. Final stage.

5. Blood processing. Preparing for centrifugation.

Centrifugation.

Blood sample following centrifugation.



Transfer of PRP for activation.

Transfer of PRP to the sterile syringe for injection.

PREPARATION FOR INJECTION

A strict aseptic sterile technique is followed when preparing the surgical field for injection. The sterile technique and antibacterial properties of the PRP make an infection unlikely.

6. Positioning of the patient in the operating room on the operating room table.

7. Preparation of the surgical field.

VISUALIZATION

PRP is considered most effective when injected as close as possible to the site of the injured tissue. The process recommended to ensure the accuracy of needle placement includes two visualization techniques, ultrasound and fluoroscopy.

Ultrasonography allows the visualization of tissues with the use of ultrasonic waves. It works on the principle that sound is reflected at different speeds by tissues of different densities.

Ultrasonograpy does not use radiation and is a portable technology. Resolution and penetration depend upon wave frequency.

Fluoroscopy allows for the examination of internal structures of the body by means of a live continuous X-ray image. Some structures with high mineral bone content are opaque to conventional X-rays. Live fluoroscopy, with the use of contrast, provides live images of high resolution for examination of bones and joints during the time of procedure or surgery.

8. Identification of abnormality by means of ultrasound guidance.

Ultrasound machine.

8A. Identification of the pathology using C-arm (X-ray machine).

APPLICATION

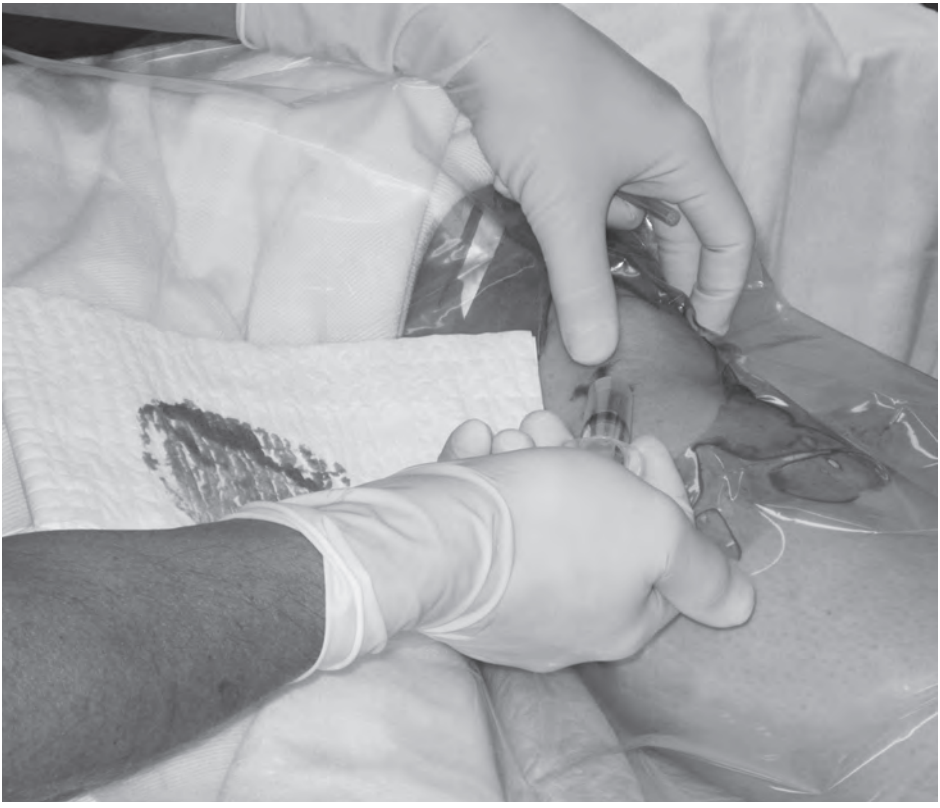
PRP can be used both percutaneously by means of a syringe injection or by direct placement during an open surgical procedure in the form of fluid injection, gel or gelatinous structure positioned directly into or on the surgical field.

PRP can be mixed with other biological materials such as bone grafts or ligament grafts and then injected into the tissue.

PRP can also be applied directly to the surface of the skin.

Most commonly the PRP is applied in a liquid form injected directly from a syringe under guidance of ultrasound and/or fluoroscopic visualization.

9. Injection of local anesthetic with or without sedation anesthesia.



ACTIVATION OF PRP BEFORE/DURING APPLICATION

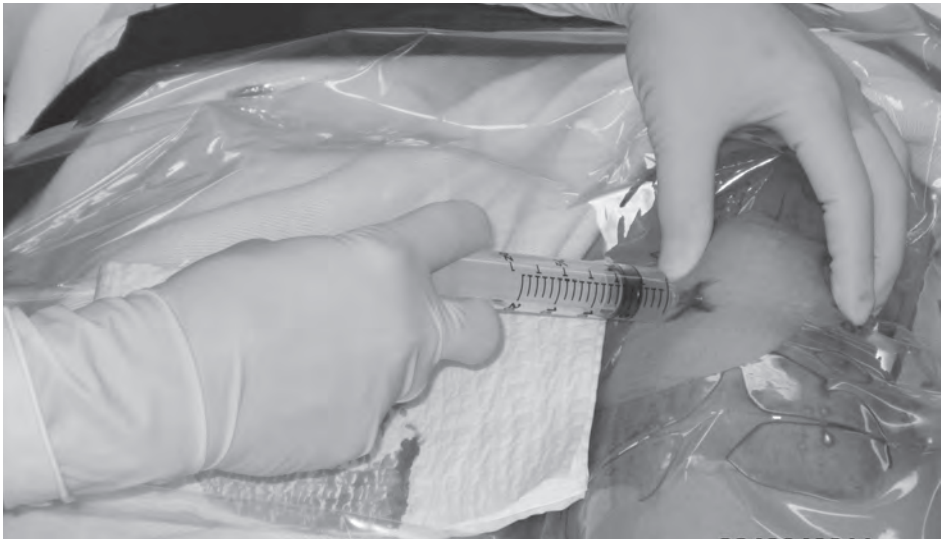
Activation of PRP is critical when obtaining the blood using anticoagulation. PRP activation may take place immediately before application or can occur after application in-vivo within the injected tissues. Currently, there is no consensus over the timing of PRP activation.

PRP can be activated outside of the tissue in-vitro (done in a laboratory) and then injected into the tissue. The major in-vitro activating factors are calcium chloride and autologously-prepared thrombin.

PRP can be activated in the tissue in-vivo (done with a live body) and placed directly where needed to allow the local environment to activate it immediately at the injection site. By relying on the collagen activation in the tissue, PRP can be injected while inactive and then become activated by the presence of collagen in the tissue during the procedure or surgery.

Following application, the platelets actively secrete proteins from the granules within ten minutes of clotting. The majority of these proteins are growth factors and they are secreted within the first hour. After the initial outburst of growth factors, the platelets synthesize and secrete additional growth factors for the remaining days of their lifespan.

10. Actual injection of PRP.



11. Application of dressing.

12. Return to the recovery room and discharge instructions:

(a) 24-hours of immobilization
(b) Avoidance of Aspirin, Advil and similar products
(c) Prescription of analgesics
(d) Physical therapy as per protocol

13. Follow-up visit.

A course of physical therapy will be determined following PRP.

This is done to improve function, increase strength and improve the outcome of the injection procedure.

Additional injections may be recommended.

The goal is to avoid surgical procedure and to speed up the recovery process.

Chapter 10

Future Studies on PRP Therapy

As we have discussed, the medical literature as of 2012 has relatively few credible and large studies on PRP therapies. Since extensive data is difficult to find and interpret, evaluation of PRP has been challenging.

Why has so little been written and published on the subject, despite the fact that this effective noninvasive therapy has been available for a quarter of the century?

Is it possible that a potential conflict of interest exists within the pharmaceutical industry, due to its lack of interest in the development of technology that cannot be patented, and then used for profit?

The simple answer to these two critical questions might be that PRP is a blood product and not a drug.

There is no incentive to promote a pharmaceutical product obtained directly from the patient's own blood. This has resulted in the lack of funding for past and present studies and will continue to hinder future medical trials.

At one time a recombinant growth therapy using growth factors was proposed. The process of chemical and biological synthesis of molecules was involved in regeneration and healing. Unfortunately, these efforts failed due to the extremely high cost of recombinant synthesis of the growth factors and their inability to achieve good therapeutic results with a single growth factor application (growth factors usually work in conjunction with one another).

Without the resources and funds available, it is very difficult to perform clinical trials on a larger scale. Domestic institutions and non-profit organizations like the National Institute of Health, the National Cancer Institute, or government agencies, should be involved in facilitating this type of research, but they are not.

In an article published in The American Journal of Sports Medicine in 2005, "Outcome of Surgery for Chronic Achilles Tendinopathy", Cheryl Tallon and co-authors (1) suggest that for any future studies to be considered credible, the following guidelines should be included:

1. Studies should be large-scale, randomized, controlled and prospective.
2. The patient selection criteria should be specific and well documented. The number of patients who do not complete the study should also be considered.
3. Post procedural/postoperative evaluation should include MRI, ultrasound and other objective studies such as histo-

logical assessment - in addition to clinical evaluation.

4. When evaluating the results of the pain relief and improved range of motion studies, the quantitative research should be documented in order to ensure its objectivity.
5. Postoperative rehabilitation should be documented in detail. This would provide a full description of the protocol and patient compliance. Postoperative rehabilitation is extremely important and may play a vital role in the rehabilitation process following the PRP injection.

It seems that at present the pharmaceutical industry may not contribute to the growth of PRP treatment and significant clinical studies will not become available. However, I intend to diligently continue documenting the positive results patients have achieved with PRP therapy in conjunction with physical therapy (PT). I also intend to recommend PRP therapy to three groups of patients who may benefit most from it.

1. Surgical candidates:
   When surgery is presented as the only option, a trial of the PRP therapy may be successful and the surgery may be avoided altogether.
2. Young athletes:
   Since greatest healing potential exists in younger patients, this is where PRP shows most promise.
3. Injury victims:
   The majority of studies done on injured tendons, joints, and muscles have validated the benefit of PRP.

Whether you are a patient considering surgery, an injured athlete or recovering from an injury, PRP used in conjunction with physical therapy is a viable and cost effective option. It has benefited many individuals seeking to be active again.

References

1. Tallon, Ch. et al. Outcome of Surgery for Chronic Achilles Tendinopathy, The American Journal of Sports Medicine, Vol.29, No. 3, p.315-320.

PART III

A NEW PARADIGM

Chapter 11

Regenerative Medicine

As previously mentioned, the classical approach in Orthopedic Medicine and Surgery relies mainly on stabilizers or immobilizers such as ace bandages, slings, casts, plates, and screws, which are used to immobilize broken bones, hurt joints, and painful tendons. Even the most advanced surgical technique called ORIF (**O**pen **R**eduction **I**nternal **F**ixation) depends on fixation and stabilization with mere plates and screws.

The recovery phase of the classical approach, during which the body gradually repairs the damage, is slow and inefficient. In time, along with some consistent physiotherapy, the body recovers its former efficiency and patients regain their previous physical fitness.

For years, this long and painstaking healing process was the only one available.

This is not the case any longer. Recently the medical world has given birth to a new paradigm of regenerative medicine.

Regenerative Medicine is a science, which seeks to strengthen the healing process and create new tissue. This tissue repairs, replaces and restores the function and the structures that have been lost due to injury or disease.

Repair refers to the healing of injured tissue or replacement of lost tissue by cell proliferation and synthesis of new extracellular matrix. Unfortunately, repaired tissue generally fails to replicate the structure, composition, and function of the normal organ.

In this context, regeneration refers to the formation of entirely new tissue that essentially duplicates the original organ.

Regenerative Medicine focuses on two principal techniques:

1. To significantly enhance and increase normal therapeutic properties.
2. To reproduce the previously damaged and irreparable tissue or organs in order to replace them.

The first approach (enhancing and increasing normal healing) uses platelets and depends upon growth factors obtained from cells responsible for repair and regeneration.

This can be accomplished in clinical medicine through PRP injections and PRP therapy.

The second approach (reproducing the previously damaged and irreparable tissue or organs) depends upon omnipotent cells available to regenerate the area of irreparable damage. These cells are known as stem cells.

The injection of stem cells obtained from bone marrow or fat aspirate facilitates the regeneration of the damaged tissue.

Although in the past, stem cell therapy has been riddled with controversy, platelets and growth factors have been used successfully for many years to accelerate the healing process. This process, at least partially, depends upon the recruitment and activation of stem cells from the periphery and from blood circulation. As a result, stem cell therapy has recently become part of mainstream medical therapy.

New frontiers have been tested with injections that target specific cells. It is possible that omnipotent stem cells can be utilized to regenerate specific tissues rather than to provide nonspecific healing properties. Direct stem cell injections, as well as the recruitment of stem cells from the bloodstream, are the latest process in development.

Chapter 12

Facts, Concepts, and Frequently Asked Questions

Now that you have a solid understanding of the reasons why Platelet Rich Plasma (PRP) is an important pain management option, this brief summary will help you tie all of the concepts together.

First, ten simple facts to remember:

1. PRP stands for Platelet Rich Plasma injection and the substance is derived from the patient's own blood.

2. PRP has a higher than normal concentration of platelets.

3. PRP is used to deliver above normal concentration of growth factors to the patient's cells.

4. PRP has been used by many medical and surgical specialists including Sports Medicine Specialists, Orthopedic Surgeons, Pain Management Specialists, Oral Surgeons, Podiatrists, and Plastic Surgeons.

5. PRP application in Sports Medicine has increased over the past few years with high-profile athletes receiving extensive media coverage after treatment.

6. PRP supports and speeds up the healing of muscle strains, tendon and ligament sprains, and tendinopathy.

7. PRP usage in Pain Management may decrease pain and hasten recovery from common pain syndromes.

8. PRP clinical studies in Veterinary Medicine and Animal Research show promising results.

9. PRP usage in human studies is underway and has already shown highly satisfactory and promising clinical results.

10. PRP application can benefit a broad range of medical specialists including pain management specialists, orthopedic surgeons, sports medicine physicians, physiotherapists, chiropractors, and acupuncturists.

Secondly, six key aspects of PRP and how it works:

1. PRP is a blood product derived from the patient's own blood. To increase the concentration of the existing blood platelets and growth factors, the blood is centrifuged at a high speed and spun to separate the red blood cells from platelets and plasma. This is done immediately before application of the PRP; the resulting substance is used within minutes of its preparation.

2. Any contamination during the preparation of PRP is very unlikely as there is minimal contact with the outside environment. The blood is collected, processed and reinjected within minutes in the same physical location.

3. As part of PRP, both platelets and plasma contain fundamental growth factors.

4. After injury the pain area has low or minimal blood flow. The level of delivered nutrients and healing factors decreases, and the healing process slows down. The injection of PRP directly to the site of injury increases the supply of growth factors and nutrients which enhance and stimulate healing of the wound.

5. The extensive range of medical applications comes from the ability of PRP to support the healing of many tissues. Specifically, PRP enhances fibroblast events involved in tissue healing including chemotaxis, cell proliferation, proteosynthesis, repair, extracellular matrix deposition, and tissue remodeling.

6. By providing additional growth factors, PRP accelerates the regeneration process. This in turn may enhance the recovery process and the patient's faster return to normal activities. PRP has also been successfully used to improve the outcomes of surgical procedures in orthopedic, podiatric, spinal, maxillofacial, and cosmetic surgery.

Finally, important answers to the most essential and frequently asked questions.

What is the science behind PRP?

The science of wound healing and tissue repair is complex and occurs on multiple levels. The molecular response is a chemical process mediated by many factors. These factors are released from plasma and platelets after an activation phase. The presence of an increased level of growth factors significantly speeds up the process of regeneration.

How is PRP prepared and applied?

A sample of the patient's blood is obtained in the same way any blood sample is extracted for blood analysis. After antiseptic skin preparation, a tourniquet is applied, and a needle is inserted into the peripheral vein.

The tube is labeled with the patient's name and placed in the centrifuge. The spinning of the sample at a high speed takes minutes after which the PRP is ready for injection. The PRP will remain with the patient until it is subsequently injected by the physician.

Typically, patients are seen every four to six weeks until healing is complete. Generally, two to six visits are necessary for each area being treated.

There are many systems used for PRP preparation. They vary in the amount of blood they use and the centrifuging peak and trough times.

In my clinical experience, using the Cascade Platelet Rich Plasma Therapy System of Musculoskeletal Transplant Foundation in Edison, New Jersey has been successful. This product has led to quick recovery and greater patient satisfaction.

What are the results?

The clinical use of PRP is gaining acceptance and popularity because of its effectiveness and simplicity. The regenerative effects of PRP on human tissues and organs translate into clinical benefits. This alternative to surgical intervention has greatly benefited the general public as well as athletes, both occasional and professional. The biological effect of PRP is being researched further to determine if there are even greater clinical applications.

Is PRP good for all types of injuries?

PRP is good for less severe injuries where there is no complete separation of the tendon or ligament tissue. A complete rupture will require surgery, while an incomplete rupture, sprain or strain will be well served by a regenerative PRP injection.

Is PRP good for arthritis?

PRP is helpful for pain relief. If viscosupplementation therapy with Synvisc® and steroid injection with Depomedrol® fails, PRP may be a viable option. The same is true if the patient refuses surgery or is a poor candidate for joint replacement therapy.

How long will it take for the PRP results to be visible?

Because PRP therapy is a regenerative process, it takes time - one to two months - before the results are clearly visible. Repeated PRP procedures may be necessary before complete healing occurs.

Why PRP and not surgery?

While surgery is more expensive and requires much more time for recovery, in well-selected cases, PRP offers similar results at a lower cost and in significantly less time.

Chapter 13

The Safety and Success of the PRP Procedure

PRP is an autologous preparation. This means that the donor and recipient are the same person, which prohibits an immunogenic reaction and disease transmission. It is safe as it is generated from the body of the same individual (1).

The blood preparation is collected in a sterile container and remains there throughout the entire process of preparation. Only after antiseptic skin preparation has been completed is the tourniquet applied and the needle inserted into the vein. It is also highly unlikely that a PRP preparation would become contaminated since there is minimal contact with the outside environment.

There is no evidence of any systemic effects of local PRP injections (2).

The aforementioned clinical studies conducted on patients validate a wide range of success and safety. The results of these studies include:

- PRP treatment has helped patients to reduce pain and enjoy greater mobility as compared to the results of those patients receiving steroid injections.

- PRP has helped patients with Achilles tendinopathy function better with fewer complications.

- Patients enjoyed both short and long-term improvement in knee function and mobility. PRP is safe and may be an effective approach to treating early signs of aging in the knees.

- Tissue regeneration in the knee was improved with an increased potential of pain relief. This is another example of PRP accelerated healing.

- PRP has proved very effective in the treatment of elbow tendonitis. It is a viable alternative to surgery.

- PRP has also been clinically used for backaches. There were no side effects of PRP therapy when combined with hydrogel to effectively treat intervertebral disc degeneration.

The role of PRP in tissue healing and regeneration introduces a new era in regenerative medicine. Standards regarding the effectiveness of PRP in a clinical setting are being established for future applications. These standards support the use of PRP for the healing of muscles, tendons, ligaments, cartilage and other pain generating and deteriorating tissue. In the future, this healing will be done by omnipotent cell lines, growth factors and bioactive proteins.

Combining biological advancements with the art of medicine (knowledge, experience, clinical judgment, and intuition) is central for proper transition of these new therapies and their future implementation in routine medical care.

References

1. Foster T. et al. Platelet-rich Plasma. From Basic Science to Clinical Applications. The American Journal of Sports Medicine, Vol.37, No 11:2259-2273.
2. Redler L. et al. Platelet-Rich Plasma Therapy: A Systematic Literature Review and Evidence for Clinical Use. The Physician and Sportsmedicine, Feb. 2011, No1, Vol39, 42-51.

Glossary

Achilles Tendon Injury
The Achilles tendon is the tendon extension of two muscles, gastrocnemius and soleus, that passes behind the ankle. It is the thickest and strongest tendon in the body. The most common Achilles tendon injuries are Achilles tendinosis and Achilles tendon rupture. Achilles tendinosis is the soreness or stiffness of the tendon, generally due to overuse. Achilles tendinitis, inflammation of the tendon, was thought to be the cause of most tendon pain, until scientists discovered no evidence of inflammation. The clinical term of tendinopathy should be given to the combination of tendon pain, swelling and impaired performance. Treatment of damage to the tendon is generally nonoperative. Orthotics can provide early relief to the tendon by the correction of misalignments. Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally to be avoided as they make the more common tendinopathy (degenerative) injuries worse although they may infrequently be indicated for the tendinitis (inflammatory) injuries which are rare. Physiotherapy by eccentric calf stretching under resistance is commonly recommended, usually in conjunction with podiatric insoles or heel cushioning. The pain in Achilles tendinopathy arises from the nerves associated with neovascularization. PRP injections show promise in non-healing Achilles tendon injury when other therapies have failed. Steroid injections should be avoided as they may weaken the Achilles tendon and lead to rupture. Surgical intervention is reserved for total rupture of the Achilles tendon.

Actin
A protein found in muscle, which together with myosin, functions in muscular contraction and relaxation.

Allogenic
Being genetically different although obtained from the same species.

Autologous
Derived or transplanted from the body of the same individual.

Cartilage
A strong but flexible connective tissue found in various parts of the body, including the joints, the outer ear, and the larynx. During the embryonic development of most vertebrates, the skeleton forms as cartilage before most of it hardens into bone.

Cell
The smallest living units of the body which group together to form tissues and help the body perform specific functions.

Chemotaxis
Directional movement of an organism or cells in response to the influence of chemical stimulation. Chemotaxis is a cellular function, particularly of neutrophils and monocytes, whose phagocytic activity is influenced by chemical factors released by invading microorganisms.

Epicondylitis
Painful inflammation of the muscles and soft tissue around an epicondyle.

- lateral epicondylitis, lateral humeral epicondylitis, tennis elbow - painful inflammation of the tendon at the outer border of the elbow resulting from overuse of lower arm muscles (as in twisting of the hand).

- medial epicondylitis, golfer's elbow is an inflammatory condition of the medial epicondyle of the elbow.

Epithelization
The healing process of covering (a wound, for example) with epithelial tissue.

Fibroblast
A cell in connective tissue that synthesizes collagen.

Function
The physiological activity of an organ or body part. Special, normal, or proper operation of any part or organ.

Hyaluronic Acid
A gellike aminoglycan that is found in the tissue space, the synovial fluid of joints, and the vitreous humor of the eyes; acts as a binding, lubricating, and protective agent.

Inflammation
A response of body tissues to injury or irritation, characterized by pain, swelling, redness and heat.

Injection noun
In medicine, a fluid injected into the body, especially for medicinal purposes.

Injection verb
The act of putting a liquid into the body by means of a syringe

- intradermal injection - an injection into the skin
- intramuscular injection - an injection into a muscle
- intravenous injection - an injection into a vein
- subcutaneous injection - an injection under the skin

Jumper's knee or Patellar Tendinopathy
(often incorrectly called Patellar tendinitis) It is a relatively common cause of pain in the inferior patellar region in athletes. It begins as inflammation in the patellar tendon where it attaches to the patella and may progress by tearing or degenerating the tendon. It is an overuse injury from repetitive overloading of the extensor mechanism of the knee. The microtears exceed the body's healing mechanism unless the activity is stopped. The injury occurs in many athletes, but is most common in sports such as soccer, volleyball, or basketball which require explosive movements. Early stages may be treated conservatively. PRP offers an excellent opportunity for noninvasive, nonsurgical option to aid a speedy re-

turn to normal activities. Uncommonly, it may require surgery to remove myxoid degeneration in the tendon.

Leukocytes White Blood Cells (WBCs)
Cells of the immune system involved in defending the body against infectious disease and foreign materials. There are five different and diverse types of leukocytes: 1.Neutrophils, 2. Basophils, 3. Eosinophils, 4. Monocytes 5. Lymphocytes. All of them are produced and derived from a multipotent cell in the bone marrow known as a hematopoietic stem cell. Leukocytes are found throughout the body, including the blood and lymphatic system.

Lysosome
Cellular organelles that contain acidic hydrolase enzymes (digestive enzymes) that break down waste materials and cellular debris.

Muscle
A body tissue composed of sheets or bundles of cells that contract to produce movement or increase tension. Muscle cells contain filaments made of the proteins actin and myosin, which lie parallel to each other. When a muscle is signaled to contract, the actin and myosin filaments slide past each other in an overlapping pattern.
• **Skeletal muscle** powers voluntary movement of the skeleton and is made up of bundles of elongated cells (muscle fibers), each of which contains many nuclei. • **Smooth muscle** provides the contractile force for the internal organs and is controlled by the autonomic nervous system. Smooth muscle cells are spindle-shaped and each contains a single nucleus. • **Cardiac muscle** makes up the muscle of the heart and consists of a meshwork of striated cells.

Myosin
The most common protein in muscle cells, responsible for the elastic and contractile properties of muscle. It combines with actin to form actomyosin.

Neutrophil
A cell, especially an abundant type of granular white blood cell, that is highly destructive of microorganisms. It is the chief phagocytic leukocyte.

Organ
A differentiated part of the body that performs a specific function.

Organelle
A differentiated structure within a cell, such as a mitochondrion, vacuole, or chloroplast, which performs a specific function.

Pain
An unpleasant sensory and emotional sensation occurring in varying degrees of severity as a consequence of injury, disease, or emotional disorder.

Phagocytosis
The process by which a cell, such as a white blood cell, ingests microorganisms, other cells, and foreign particles.

Plantar Fasciitis
A painful inflammatory or degenerative process of the plantar fascia – tendinosis structure at the bottom of the foot. Longstanding cases of plantar fasciitis often demonstrate more degenerative changes than inflammatory changes and are termed plantar fasciosis. The plantar fascia is a thick fibrous band of connective tissue originating on the bottom surface of the calcaneus (heel bone) and extending along the sole of the foot towards the five toes. This condition occurs in 10% of the population within the span of a lifetime and is associated with constant weight gain and obesity. Difficulty and decreased dorsiflexion of the ankle is also present. The pain is usually felt on the underside of the heel and may be debilitating.

Plasma
The clear, yellowish fluid portion of blood, lymph, or intramuscular fluid in which cells are suspended. It differs from serum in that it contains fibrin and other soluble clotting elements.

Platelet
Fragments of protoplasm found in vertebrate blood; essential for blood clotting and tissue regeneration.

Prolotherapy ("Proliferative Injection Therapy")
Involves injecting an otherwise nonpharmacological and nonactive irritant solution into the body, generally in the region of tendons or ligaments for the purpose of strengthening weakened connective tissue and alleviating musculoskeletal pain. Prolotherapy is also known as "proliferation therapy" or "regenerative injection therapy."

Regenerative Medicine
Advanced medicine described as the creation of tissue that provide, repair, replace or restore structures and functions absent or lost due to congenital defects, aging, disease, or damage. Regenerative medicine helps natural healing processes to work faster, or uses special materials to regrow missing or damaged tissue.

Rotator Cuff Syndrome
The tendons at the ends of the rotator cuff muscles (supraspinatus, infraspinatus, teres minor and subscapularis) can become stretched, sprained, or partially or completely torn, leading to pain and restricted movement of the arm. A torn rotator cuff can occur following a trauma to the shoulder or it can occur through the "wear and tear" of tendons, most commonly those of the supraspinatus under the acromion. It is an injury frequently sustained by athletes whose duties involve making repetitive throws. It is commonly associated with motions that require repeated overhead motions or forceful pulling motions. The purpose of the initial treatment is to reduce pain and swelling. As with all muscle injuries, R.I.C.E. is an acronym for initial response and therapy recommended by health providers.

- **R**est means ceasing movement of the affected area.
- **I**cing uses cold to reduce inflammation.
- **C**ompression limits swelling.
- **E**levation involves placing the area higher to reduce inflammation and swelling.

Initial therapy involves physical therapy modalities, strengthening exercises and range of motion exercises. If a partial tear is present, the rest may require more time for healing. If conservative measures fail PRP shows promise in all but the most severe cases of complete separation and may help to avoid surgical intervention through its regenerative properties. Depending on severity of symptoms, further imaging with radiograph or MRI may be warranted to see if an underlying bone injury exists. Partial rotator cuff tear may require PRP injection, while fracture and/or complete separation will require surgery.

Serum
Blood serum, a blood component which is collected after coagulation.

Stem Cell Treatments
A type of intervention strategy that introduces new cells into damaged tissue in order to treat disease or injury. Many medical researchers believe that stem cell treatments have the potential to change the face of human disease and alleviate suffering. The ability of stem cells to self-renew and give rise to subsequent generations with variable degrees of differentiation capacities, offers significant potential for generation of tissues that can potentially replace diseased and damaged areas in the body, with minimal risk of rejection and side effects (1).

Syndrome
A group of symptoms that collectively indicate or characterize a disease or abnormal condition.

Syndromes:

Tennis Elbow
A condition where the outer part of the elbow becomes sore and tender. The condition is also known as lateral epicondylitis ("inflammation of the outside elbow bone"), a misnomer as histologic studies have shown no inflammatory process. Other descriptions for tennis elbow are lateral epicondylosis, **lateral epicondylalgia**, or simply lateral elbow pain. Tennis elbow is an overuse injury occurring in the lateral side of the elbow region, more specifically, occurring at the common extensor tendon that originates from the lateral epicondyle. While the common name tennis elbow suggests that people who play tennis may develop this condition, other activities of daily living may also cause it. The main factor precipitating tennis elbow is overexertion. Athletes as well as those who use the same repetitive motion for many years, especially in their profession, suffer from tennis elbow. It is also common in individuals who performed motions they were unaccustomed to and occurs most commonly in the right arm.

Golfer's Elbow or medial epicondylitis
This is an inflamatory/degenerative condition of the medial epicondyle of the elbow.

Jumper's Knee (see above)

Sports Medicine
An area of health and special services that applies medical and scientific knowledge to prevent, recognize, manage, and rehabilitate injuries related to sport, exercise, or recreational activity.

Synovium
A thin membrane in synovial (freely moving) joints that lines the joint capsule and secretes synovial fluid.

Tendon
A band of tough, inelastic fibrous tissue that connects a muscle to its boney attachment.

Tendinosis
Sometimes called chronic tendinitis, chronic tendinopathy or chronic tendon injury. It is damage to a tendon at the cellular level (the suffix "-osis" implies a pathology of chronic degeneration without inflammation). It is thought to be caused by microtears in the connective tissue in and around the tendon, leading to an increase in tendon repair cells. This may lead to reduced tensile strength, thus increasing the chance of tendon rupture. Tendinosis is often misdiagnosed as tendinitis.

Tendinitis
Meaning inflammation of a tendon (the suffix "itis" denotes diseases characterized by inflammation), is a type of tendinopathy. The term tendinitis should be reserved for tendon injuries that involve large-scale acute injuries accompanied by inflammation.

Tissue
Part of an organism consisting of an aggregation of cells having a similar structure and function.

Statement:

Dr. Dariusz J. Nasiek, M.D. has no conflicts of interest to disclose. No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this publication.

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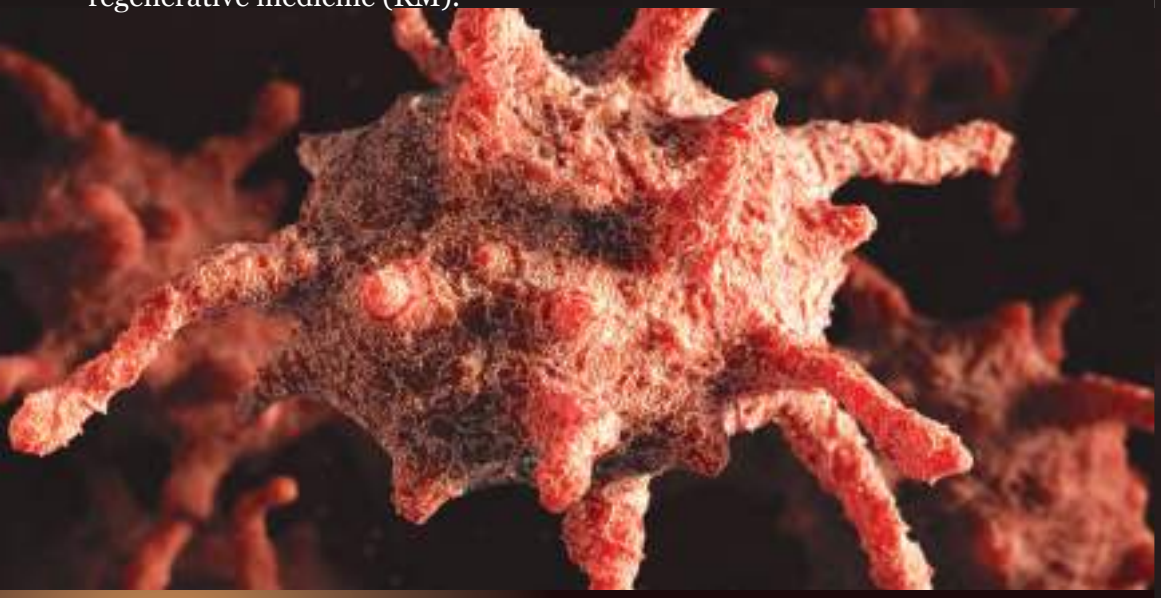

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ISBN 978-0-9885190-0-8
$14.95
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