Dissertation

The Role of Platelet-rich Plasma (PRP) in the Treatment of Athletes at Risk of Tendinosis and Tendinopathy

submitted by

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Declaration

I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other material used. Throughout this dissertation and in all related publications I followed the guidelines of "Good Scientific Practice".

Graz, Date

Signature

Acknowledgements

First, I want to express deep thanks to Patrick Vavken, MD MSc FRSPH and Martha M. Murray, MD PhD for introducing me into the aspects of platelets in tissue engineering. As I had a focuss on anterior cruciate ligament (ACL) research, which started evaluating the outcome differences of single versus double bundle ACL reconstruction, I come across their work on the possibility of the ACL´s biological repair. I immediately found the idea fascinating to aid in biological repair and wanted to visit their team at Boston.

After submission of various grants, finally, the Association for Orthopaedic Research (AFOR) offered me a fellowship to join Dr. Murray´s and Vavken´s team at Childrens Hospital Boston. Since then, Dr. Vavken has become one of my most important research partners within the following years and I am excited about future projects. Fortunately, this PhD thesis and the underlying publications were produced and published in collaboration with the Childrens Hospital Boston at Harvard Medical School in the Journal of Orthoapedic Research and our findings gained recognition as Prof. Per Aspenberg, from Scandinavia, feeled obligated to publish a letter on our work.

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3. Abbreviations

PRP	platelet rich plasma
BMP	bone morphogenic proteins
IGF	insulin-like growth factor
VEGF	vascular endothelial growth factor
IL1-β	interleukin 1 beta
TGF-β	transforming growth factor-beta
GAG	glycosaminoglycan
ACL	anterior cruciate ligament
PDGF	platelet-derived growth factor
FGF	fibroblast growth factor
EGF	epidermal growth factor
IL-8	interleukin 8
KGF	keratinocyte growth factor
CTGF	connective tissue growth factor
DNA	deoxyribonucleic acid
AFOR	association of orthopaedic research
SMD	standardized mean difference
RCT	randomized controlled trial
CENTRAL	cochrane central register of controlLed trials
CDSR	cochrane database of systematic reviews
NCBI	national center for biotechnology information
PRISMA	preferred reporting items for systematic reviews and meta-analyses
QUOROM	quality of reporting of meta-analyses
CONSORT	consolidated standards of reporting trials
CD 31	cluster of differentiation 31
DAB	brown diaminobenzidine
PRPFM	platelet rich plasma fibrin matrix
JAMA	The Journal of the American Medical Association
MTS	mechanical testing machinge
CINHAL	cumulative index to nursing and allied health

4. Summary

The aim of this PhD thesis was to assess the impact of platelet-rich plasma (PRP) on athletes at risk of tendinosis with a special focus on the Achilles tendon and rotator cuff. We therefore evaluated existing studies on animal and human trials with a focus on the Achilles tendon to raise a conclusion in a meta-analysis, and, as data on the human rotator cuff was not sufficient to get pooled, created an in vitro investigation of PRP on the human rotator cuff.

In order to systematically review the current in-vivo evidence for the use of platelet-concentrates (PRP) in the treatment of Achilles tendinopathy and Achilles tendon a systematic search of PubMed, CINAHL, EMBASE, and CDSR was performed for animal and human studies using the terms ‘‘Achilles tendon and platelet.’’ The systematic search revealed a total of 149 papers. After excluding duplicates and cases of overlapping data, studies not focusing on in vivo evidence in terms of treatment or outcome, studies without any intervention, studies with unacceptable high attrition, one Chinese and one Swedish study, the remaining 14 manuscripts were included. The key finding of our study is evidence in support of a statistically significant effect of platelet concentrates in the treatment of Achilles tendon ruptures in vivo in animal models and human application, consistent with a medium to large sized effect. This effect is most likely attributable to fastened and enhanced scar tissue maturation. There was no evidence for a beneficial effect of platelets in Achilles tendinopathy.

In order to assess the in vitro effect of platelet-rich plasma (PRP) on biological activity of the human rotator cuff fibroblasts and to describe the optimal dose-response to maximize cellular stimulation while reducing potential risk, rotator cuff (RC) fibroblasts of n = 6 patients (mean age of 65.2 years) undergoing arthroscopic cuff tear reconstruction were cultured in vitro for 21 days and stimulated with PRP in three different concentrations (1-, 5-, and 10-fold). Samples were obtained for DNA and glycosaminoglycan (GAG) measurement at 1, 7, 14, and 21 days. The biological outcomes were regressed on the PRP concentration. The application of PRP significantly influenced the fibroblast proliferation and activity of the human rotator cuff with elevated GAG and DNA levels. The dosage of PRP had the significantly

highest impact on this proliferation using a onefold or fivefold application. These findings showed that PRP has a significant effect on fibroblast proliferation of the human rotator cuff in vitro with an optimal benefit using a onefold or fivefold PRP concentration. This study justifies further in vivo investigations using PRP at the human rotator cuff.

As an overall conclusion, PRP might offer interesting solutions in tissue engineering, in general. However, it is too early to recommend it in clinical application as PRP has not been definitely proven to be beneficial in clinical settings yet.

5. Zusammenfassung

Ziel dieser PhD Arbeit war eine Beurteilung des Einflußes von PRP auf Tendinosen bei Athletinnen und Athleten unter besonderer Berücksichtigung der Achillessehne und der Rotatorenmanschette. Als höchste Evidenzebene war dafür eine systematische Metaanalyse sinnvoll, die jedoch aufgrund der mangelnden vorliegenden Evidenz lediglich im Bereich der Achillessehne sinnvoll durchgeführt werden konnte. Daher wurde zur weiteren Beurteilung an der Rotatorenmanschette eine *in vitro* Studie durchgeführt.

Um den Einfluß von PRP an der Achillessehne zu untersuchen wurde in den Suchportalen „PubMed, CINAHL, EMBASE, CCTR und CDSR“ nach den Begriffen ‘‘Achilles tendon and platelet’’ gesucht. Dabei wurden insgesamt 140 Treffer gefunden und nach Ausschluss von doppelten Nennungen und Studien ohne Intervention oder hoher Attrition wurden 14 Studien entgültig in die Analyse eingeschlossen. Als Ergebnis zeigte sich ein signifikanter Effekt von PRP in Tierstudien zur Behandlung von Rupturen der Achillessehne, jedoch keinerlei Evidenz auf einen Nutzen in Studien an Patientinnen und Patienten.

Um die Evidenz an der Rotatorenmanschette zu erweitern wurden Fibroblasten der menschlichen Rotatorenmanschette von 6 PatientInnen, die einer arthroskopischen Rekonstruktion unterzogen wurden, entnommen um in vitro die optimale Dosis-Wirkungs-Kurve zu beschreiben. Die Zellen wurden für 21 Tage kultiviert und mit einer einfachen, fünffachen und zehnfachen Konzentration von PRP stimuliert. DNA- und Glykosaminoglykanmessungen wurden nach einem, sieben, 14 und 21 Tagen durchgeführt. Dabei zeigte sich ein signifikanter Einfluß von PRP bei einer einfachen und fünffachen Konzentration.

Ich schlussfolgere aus den Ergebnissen dieser PhD-Arbeit, dass es noch zu früh sein mag PRP tatsächlich im klinischen Setting unseren Patientinnen und

Patienten zu empfehlen obwohl sich in Tierstudien und *in vitro* Studien bereits signifikant postive Ergebnisse gezeigt haben. Dennoch gibt es viele relevante Fragestellungen, die noch zu klären sind, bevor definitive Empfehlungen abgegeben werden können. Unklarheit besteht etwa noch hinsichtlich des Zeitpunktes der Anwendung, der Art der Herstellung und der Menge der Applikation von plättchenreichem Plasma.

6. General introduction

The focus in orthopaedic surgery is changing. Whilst in the previous decades, we surgeons tried to reconstruct destroyed structures, nowadays the idea of biological repair of defect tissues gains more and more importance. The biological alternative of a total or partial knee arthroplasty might be a high tibial osteotomy. The benefit is obvious –patients still have their own knee joint, with all possible advantages, such as a more natural feeling or ability for natural recovery.

This idea of a biological way to keep our own structures has been expanded to the ligaments and cartilage as well. Brittberg and Petersen et al. have developed methods to harvest, culture, and replant patients´ cartilage after small and clearly defined defects [1]. In terms of tendon and ligament healing, orthopaedic scientists tried to stimulate healing using various growth factors. It was the influence of other specialities, such as dental surgeons, which led to the idea to use platelet-rich plasma (PRP).

Our platelets induce growth factors, which are essential for physiological healing [2]. In order to cumulate these factors, the principle idea is to administer plasma, which is rich of those autologous platelets. The proclaimed benefit might be a cummulation of these growth factors. Martha M. Murray and Patrick Vavken have successfully tested and evaluated the possible impact of PRP on the anterior cruciate ligament (ACL) [3-7]. As I focused on clinical and radiological aspects of ACL research, I came across their work and immediately got in contact. Getting granted by the Association of Orthoapedic Research (AFOR), I visited their team at Childrens´ Hospital Boston and started a fruitful collaboration since then.

However, whilst Martha and Patrick only focused on the ACL, we wanted to further elucidate the topic in Graz in order to evaluate the impact on athletes at risk of tendon injuries and therefore started a new project evaluating the impact of PRP on the human rotator cuff joint and an accurate analysis of PRP for Achilles tendon

injuries. These two projects could both be published and were further discussed in the Journal of Orthopaedic Research and are the basis of this PhD- thesis.

6.1 Definition of platelet-rich plasma

Platelet-rich plasma (PRP) is defined as autologous blood plasma, which has been enriched with platelets using centrifugation. A synonyme is autologous conditioned plasma (ACP). The postulated effect of PRP is gained due to several different growth factors, which stimulate the healing of soft tissues (such as ligaments), and bones or cartilage [8].

6.2 Historical background

Schulte et al. first described possibly benefical effects of PRP in the 1960s [9, 10]. They did not pool the plasma but used conventional plasma for healing of wound defects. Therefore, only autologous blood without real centrifugation was used and the work did not gain international recognition. In 1993, Yamamoto et al. described the use of PRP for haemostasis and after cardiac surgery [11]. A detailed description of PRP preparation was published in 1996 [12] and in 1997, the first clinical study was published in the field of oral surgery [13]. Thereafter, the use of PRP was popular amongst dental surgeons within the following years.

In 2006, Murray et al. published the impact of a collagen-platelet rich plasma scaffold to stimulate healing of a central defect in the canine ACL [14]. This research group expanded the knowledge gained from PRP on various aspects of ACL reconstruction.

Whilst scientists have agreed, that PRP has the potential to gain significant influence on tissue repair in musculoskeletal surgery, its benefical impact remains to be proven in large randomized controlled trials. In addition, various co-factors such as, the method of preparation and the time of administration might have significantly high influence on our patients.

6.3 Production process of PRP

There exist various devices for PRP preparation with different outcomes but the basic principles remain the same and are hereby explained:

At least 60 cc of whole blood are drawn per patient. In order to prevent coagulation of the whole blood sodium citrate is added before the process of centrifugation. Using centrifugation, it is possible to separate the PRP from platelet-poor plasma and erythrocytes (Figure 1).

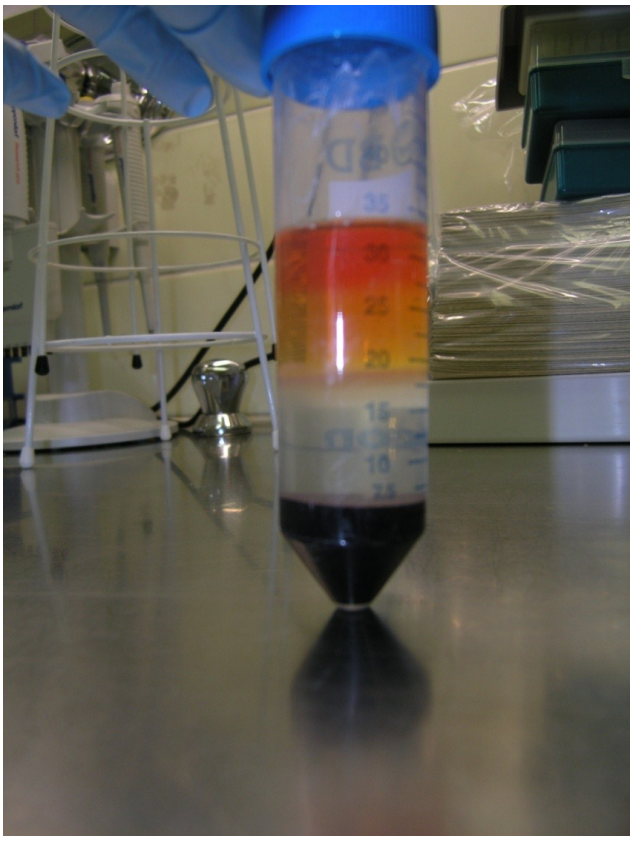

Figure 1 – Platelet rich plasma is harvested in the laboratory of the Department of Orthoapedic Surgery, Medical University of Graz, Austria.

For clinical application in patients, a 5-fold concentration of the typical baseline blood platelet count is applied (1 000 000 per µl). Once injected, PRP might be further activated using various types of thrombin or collagen. Different companies have produced devices, which make harvesting of the PRP easier after the process of

centrifugation by having installed a small syringe into the centrifuged syringe (Figure 2).

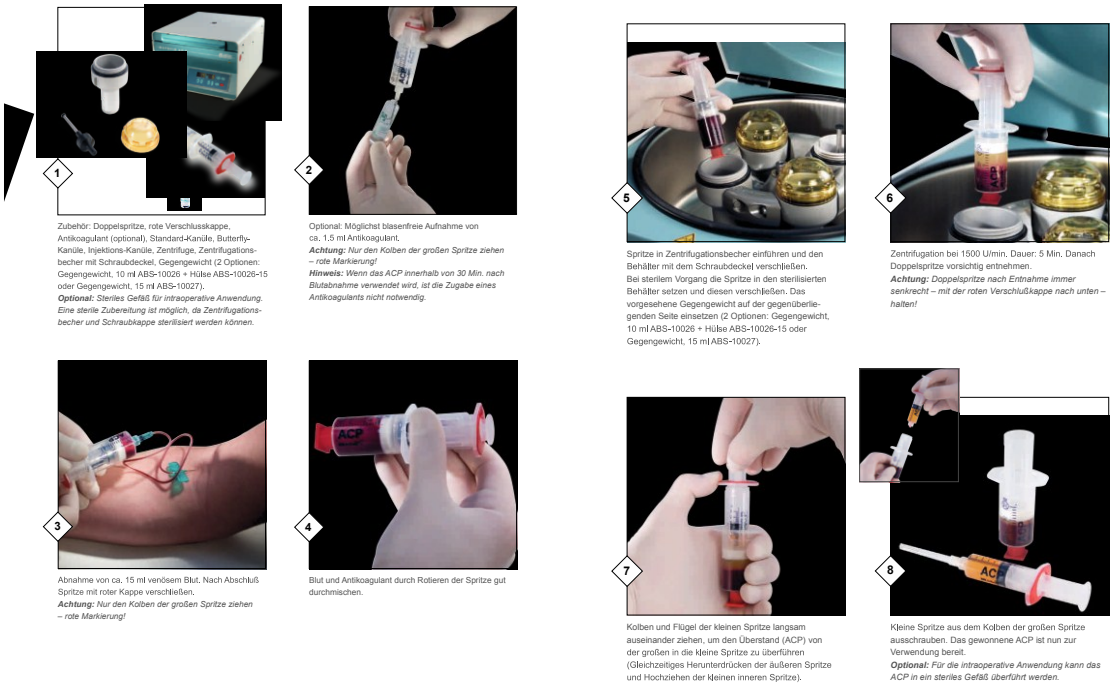

Figure 2 – Preparation of PRP using the system (Arthrex, Naples, FL) (www.arthrex.com/tags/prp, last accessed the 23rd of June 2013)

6.4 Physiological mechanism of PRP

PRP releases various growth factors, which stimulate healing once activiated. These growth factors are hereby listed:

platelet-derived growth factor (PDGF)
transforming growth factor beta (TGF-beta)
fibroblast growth factor (FGF)
insulin-like growth factor 1 (IGF-1)
insulin-like growth factor 2 (IGF-2)
vascular endothelial growth factor (VEGF)
epidermal growth factor (EGF)
Interleukin 8 (IL-8)
keratinocyte growth factor (KGF)

connective tissue growth factor (CTGF)

Under physiological conditions, these growth factors aid in wound healing and tissue regeneration after trauma. The underlying principle of PRP usage is to pool those factors to achieve a higher than normal effect. In addition, it is a more cost-effective method, than producing the different factors.

7. PRP for Achilles tendon treatment

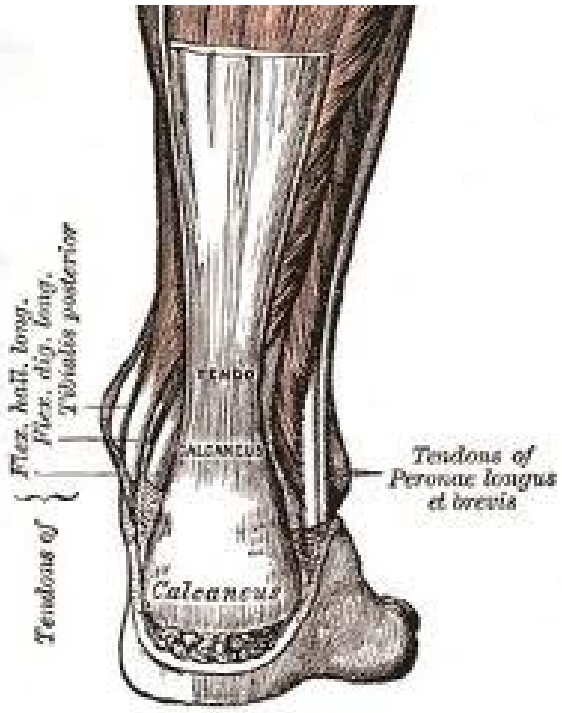

Figure 2 – Achilles tendon. From Richard M. Tibbitts out of "Gray´s Atlas der Anatomie. Urban & Fischer".

7.1 Rationale

Ligament and tendon healing is an important topic in orthopedics and orthopedic sports medicine. Tears and chronic damage of these tissues – including but not limited to the anterior cruciate ligament, the rotator cuff, the patellar tendon and the Achilles tendon - occur at high incidences and have long and potentially serious sequelae. Consequently there is substantial research done in this area in order to improve techniques of tissue repair and tissue regeneration [6].

Among the most promising approaches is the use of platelet concentrates such as platelet-rich plasma (PRP). Platelets have two beneficial effects that support and enhance wound healing. On the one hand, they are a source of a plethora of growth factors that stimulate healing [6]. On the other hand, platelets clot and form a temporary matrix that fills defects sites and serves as a matrix for cell migration and tissue remodeling [6]. Platelet concentrates are being used to enhance current or create new treatments for tendon and ligament diseases such as ruptures of the ACL, epicondylitis, rotator cuff tears, or treatments of the Achilles tendon.

The Achilles tendon is one of the most vulnerable tendons of the human body [15, 16] and it is estimated that Achilles tendon injuries are involved in 30% -50% of all sports-related injuries. [17]. The diagnosis of Achilles tendinopathy and tears can be made easily in the presence of a painful, swollen tendon with impaired function, which is evaluated using the Simmonds-Thompson test [18].

Achilles tendon tears may become chronic because of their lack of regenerative capability and once chronic they are characterized by increased vascularization, disorganization and degeneration of their collagen fibers, and irregular cellularity on histological analysis. With a lack of signs of classic inflammation in this pathological setting, this disease is classified as tendinopathy rather than tendinitis [19-24].

Platelets have been used to fix Achilles tendon ruptures and Achilles tendinopathy in *in vivo* settings [25, 26]. However, the benefit of platelets in regeneration of Achilles tendinopathy and Achilles tendon tears is still elusive as this is a relatively new treatment option with uncertain treatment regimes and their effectiveness is still not comprehensively analyzed and described.

7.2 Objectives

The objectives of this meta-analysis and systematic review were twofold. The primary objective was to systematically review the current *in vivo* evidence for the use of plateletes for the treatment of Achilles tendon rupture and perform a meta-

analysis. The secondary objective was to systematically review the current *in vivo* evidence for the use of platelet-concentrates for the treatment of Achilles tendinopathy and perform a meta-analysis.

7.3 Materials and Methods

This systematic review was performed in accordance to the PRISMA (*P*referred *R*eporting *I*tems for *S*ystematic reviews and *M*eta-*A*nalyses) statement, an evidence-based, established guideline for systematic reviews published by the CONSORT group (www.consort-statement.org) [27, 28]. The PRISMA statement is essential to systematically structure and analyse a study question such as defined.

7.3.1 Eligibility criteria

Studies were included if they reported on the use of platelets in Achilles tendon treatments, in either humans or animals, in a controlled trial. All types of treatments were admitted, but there had to be a defect or injury model. Studies on PRP use in healthy tendons were not eligible, neither were longitudinal or cohort studies. There was no limitation for follow-up duration.

7.3.2 Data sources

The online databases PubMed, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR) were searched. All dates and languages were included. The last search was performed on June 30th, 2010.

7.3.3 Search

The search algorithm was (**Achilles tendon AND platelet)** and was replicated using the keywords as MeSH terms as well. All searches were unlimited to language and publication date. In addition, the bibliographies of the included studies were reviewed by hand to identify further publications.

7.3.4 Study selection

Both title and abstracts from all search results were screened for eligibility in duplicate. Studies were excluded if title and/or abstract clearly invalidated eligibility. Full text articles were obtained for all studies matching the inclusion criteria or with unclear eligibility, and the full text papers were reviewed in duplicate. All study selections were cross-referenced. Disagreement was resolved by consensus or with the help of the senior author.

7.3.5 Data collection process

All data were extracted in duplicate by at least two independent reviewers and entered into a pre-defined datasheet. Data consistency was checked after extraction by a third, independent investigator. Disagreement was resolved by consensus.

7.3.6 Data items

We extracted data on the study design characteristics, and on the type of model and treatment(s) used for descriptive purposes. The main endpoints for the analysis were biomechanical, histological, and clinical outcomes, as well as results from imaging assessment. Numerical outcomes that were reported in more than one study and with methodological consistency (same scales, same scores, etc) were extracted for data synthesis. These outcomes were biomechanics for Achilles tendon rupture studies and clinical scores for tendinopathy studies.

7.3.7 Risk of bias in individual studies

We assessed the risk of bias in the included studies using a modified Jadad scale [29]. This score assesses randomization, concealment of allocation, and attrition/power with one point each, thus resulting in a score between 0 (worst results, high risk of bias) and 3 (best result, low risk of bias). Additionally, we categorized all included papers by level-of-evidence.

7.3.8 Data synthesis

Publication bias among the included studies was assessed graphically using funnel plots and mathematically using Egger's weighted regression [30]. This "desk drawer bias" is obvious, when scientists tend to publish positive results, whereas negative studies remain in their desks unpublished. However, this leads to a false positive outcome in a majority of meta-analysis, if not correctly accounted for. Therefore, publication bias is one of the most common methodological flaws of structured meta-analysis.

The presence of between-study heterogeneity was qualified by Cochrane's Q test, using a p-value of 10% to adjust for the low power of this test in small samples, and quantified using the I^2 index [31]. To assess the potential sources of such heterogeneity, meta-regressions were performed [32, 33].

To pool data, standardized mean differences (SMD) were calculated for biomechanical outcomes. SMD calculate differences in means between the experimental and the control group and divide this number by the standard deviation of the difference, thereby standardizing it. This cancels out units (such as Newton or Pascal) and allows for a valid comparison across different scales. SMD is also know as "effect size" or Cohen's d, and can be categorized as small (SMD <0.3), medium (<0.5) or large (>0.8). Regardless of size, any of these values can be statistically significant from zero (no effect) or not, i.e. statistical significance does not automatically imply clinical meaning [34].

For clinical scores (VISA-A), weighted mean differences were calculated, i.e. difference in points VISA-A score accounting for different sample size and different variance in the outcomes of the pooled studies. Inverse variance was used to weigh the individual studies.

All calculations were performed using Intercooled STATA® 10 (StataCorp LP, College Station, TX, USA). The level of significance for pooled estimates was set at *5%.*

7.4 Results

7.4.1 Study selection

Our search produced 149 papers in total. Fifty publications were obtained and reviewed based on the criteria described above. No additional papers were identified by bibliographic cross-reference. Two papers (one in Chinese and one in Swedish) could not be obtained. Finally, 14 papers were included in this study. (Figure 4) These papers were published between 2003 and 2010 in English.

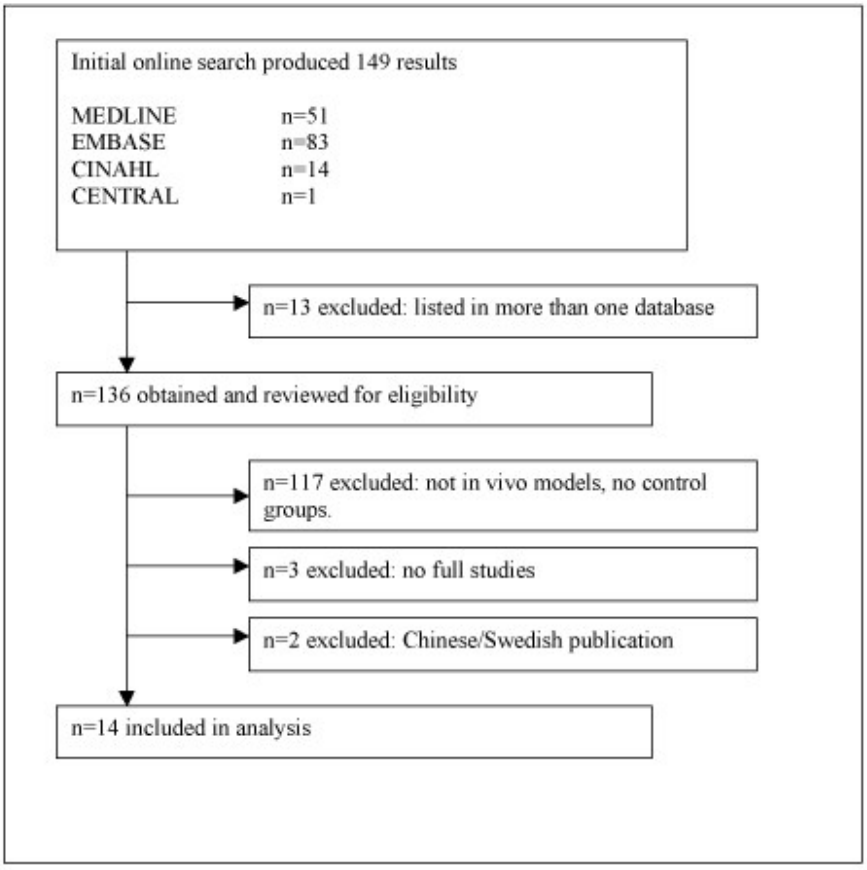

Figure 3 – Trial flow of study identification.

7.4.2 Characteristics of the included studies

Thirteen studies published in 14 papers were included for final analysis [25, 35-47]. Ten papers focused on models and trial of Achilles tendon rupture repair, and four papers focused on with Achilles tendinopathy.

Aspenberg et al. [35] investigated, whether a platelet concentrate injection would improve Achilles tendon repair in an established rat model in 20 rats, which were randomized in a platelet and a control group. They transected the tendons transversely and injected 50 ml of platelet concentrate 6 hours postoperatively. After 8, 11, 14, 21 or 28 days the rats were sacrificed and tendons were histologically examined with respect to their callus. In addition the maximum peak force, stiffness and energy uptake was tested using a material testing machine (100 R, DDL Inc. Eden Praire, MN, USA).

The paper of Lyras et al. [36] reports about 48 New Zealand rabbits, which received either PRP or were used as the untreated control group. Equal numbers of animals were sacrificed at the 1st, 2nd, 3rd and 4th weeks. Surgery included a transverse incision to transect the Achilles tendon and an injection of 1 ml of PRP into the tendon mass in the intervention group. For comparison, histological and immunohistochemical evaluations with anti-TGF-ß antibodies were performed.

In a further study, Lyras et al. [37] investigated new vessel numbers by image analysis for angiogenesis in the same study setting using a monoclonal antibody against CD31 (Daco Co) because poor vascularity plays a major role in limited capacity of tendon healing.

In 2011, Lyras et al. [38] investigated whether a single PRP application would alter expression of IGF-I in the early phase of tendon healing in the same setting (48 rabbits, one intervention versus one control group) using an anti IGF-I primary antibody. They evaluated the density of brown diaminobenzidine (DAB) staining for quantitatively analysis.

Sánchez et al. [39] performed a laboratory case control level III study in 12 athletes who either received open suture repair after complete Achilles tendon tear

with a preparation rich in growth factors (PRGF) or no treatment for retrospective comparison. Outcome was evaluated using range of motion (ROM), functional recovery, and complications, and Achilles tendons were measured by ultrasound approximately 50 months after intervention.

In the study from Sarrafian et al. [40] a cross-linked accellular porcine dermal patch (ADP), as well as platelet-rich plasma fibrin matrix (PRPFM), and a third control group were evaluated for repair of acute Achilles tendon rupture in a sheep model. Sheeps were euthanized at 24 weeks after the repair and tendons were tested biomechanically (tensile strenght) and histologically for comparison.

Schepull et al. [41] performed a level II RCT in 30 consecutive patients with Achilles tendon ruptures. During surgery tantalum beads were implanted proximal and distal to the rupture and before skin suture after reconstruction, 16 patients were injected with 10 ml PRP whereas 14 were not in a randomized setting. The distance between beads was measured using roentgen stereophotogrammetric analysis at 7, 19, and 52 weeks, and additionally at 1 year the functional outcome was evaluated, including the heel raise index and Achilles Tendon Total Rupture Score.

In 2006 Virchenko et al. [42] investigated how one platelet injection after tendon injury leads to a tronger tendon after 4 weeks in a rat model. Achilles tendons received either PRP or a control injection and were either unloaded by Botox injections into the calf muscles or mechanically stimulated in activity cages, or not. Mechanical testing was performed using a materials-testing machine (100R; DDL Inc., Eden Praire, MN) measuring tendons´ force, stiffness, energy, area, and stress.

In the same year, the same authors [43] compared 5 treatment options in 60 female Sprague-Dawley rats using (1) platelet gel, containing thrombin-activated platelets and added calcium, (2) platelet gel supplemented with Hirudin, (3) injectable platelet concentrate without thrombin, (4) thrombin in saline solution, and (5) saline solution alone. Ten rats were used as PRP donors and 50 further tested among the five treatment options after 14 days using a materials testing machine (100R; DDL Inc., Eden Praire, MN). Stress and transverse areas were calculated.

Zhang et al. [44] published on the effect of vascular endothelial growth factor on rat Achilles tendon healing in 2002. Fifty Sprague-Dawley rats were included. In the intervention group, the Achilles tendon was transected and repaired with the modified Kessler suture technique with an additional VEGF injection. The contralateral Achilles tendon served as a control. After 1, 2, and 4 weeks the animals were killed and tendons were evaluated for tensile strength using a tensionmeter (Sintech 2/G, MTS, Minneapolis, MN, USA) and gene expression (IGF-1, TGF-ß, bFGF, and PDGF mRNAs).

Three studies report results for the use of platelets in human Achilles tendinopathy treatments [25, 45, 46]. De Jonge et al. [25] investigated 54 patients with chronic Achilles tendinopathy in the American Journal of Sports Medicine in a randomized control trial (RCT) by providing either a blinded injection containing platelet-rich plasma or saline (placebo group) in addition to an eccentric training program. They evaluated main outcome using the Victorian Institute of Sports Assessment-Achilles score (VISA-A). Furthermore, they recorded patient satisfaction and ultrasound examination at follow-up of 1 year. De Vos RJ et al. [45, 46] published analyses from the population in JAMA and the British Journal of Sports Medicine, focusing on clinical scores and ultrasonographic assessment.

Suwalsi et al. [47] showed in an accelerated Achilles tendon healing by PDGF gene delivery with mesoporous silica nanoparticles in tenocytes, which were obtained from adult Achilles tendon explants of adult Wistar rats. They investigated histological quality (transmission electron microscope) and biomechanical quality (with a conventional mechanical test machine (MTS Synergie 400, Eden Prairie, MN, USA) of the tendons after application.

Table 1 further summarizes the characteristics of study designs, table 2 of the platelet concentrate parameters.

Author	randomized*	blinded assessment*	power calculation*	Jadad Score	LoE	follow-up (mo)	Mean Age Platelet Group	Mean Age Control Group	% female or animal study	F
Aspenberg et al. 2004	yes	yes	no	2		1	n.a.	n.a.	Animal (rats)	
DeJonge et al. 2011	yes	yes	yes	3		12	49.7	49.7	Human, n.a.	
DeVos et al. 2010	yes	yes	yes	3		12	49.7	49.7	Human, n.a.	
Lyras et al. 2009	yes	yes	Yes	3		1	n.a.	n.a.	Animal (rabbits)	
Lyras et al. 2009	yes	yes	Yes	3		1	n.a	n.a.	Animal (rabbits)	
Lyras et al. 2011	yes	yes	yes	3		1	n.a.	n.a.	Animal (rabbits)	
Sanchez et al. 2007	no	no	no	0		12	36.2	32.1	Human, n.a.	
Sarrafian et al. 2010	yes	No	yes	2		1	> 3.5	> 3.5	Animal (sheep)	
Schepull et al. 2011	yes	yes	no	2		12	39.8	39.4	20 % female	
Suwalski et al. 2010	no	no	no	0		.5	n.a.	n.a.	Animal (rat)	5
Virchenko et al. 2006	yes	yes	no	2		.5	n.a.	n.a.	Animal (rat)	1
Virchenko et al. 2006	yes	yes	no (post hoc)	2		<1 (14 days)	n.a.	n.a.	Animal (rat)	
Zhang et al. 2003	yes	yes	no	2		< 1 (4 weeks)	n.a.	n.a.	Animal (rat)	

* reported in paper. n.a. = not applicable

Table 1 – Characteristics of the included studies

Author	PRP Technique	PRP Concentration	PRP injection (volume)	Volume Blood Drawn	Anticoagulant
Aspenberg et al. 2004	-	$1.5 * 10^{12}$ platelets/L	50µL	5 mL	Citrate phosponate dextrose (CPD) (0.15mg CPD(mL)
DeJonge et al. 2011	Recover Platelet Separation Kit (type Gravitational Platelet Separation III)	-	4 mL	54 mL	Citrate (6mL)
DeVos et al. 2010	Recover Platelet Separation Kit (type Gravitational Platelet Separation III)	-	4 mL	54 mL	Citrate (6mL)
Lyras et al. 2009	PRP Fast system		1 mL	8 mL	
Lyras et al. 2009	PRP Fast system		1 mL	8 mL	
Lyras et al. 2011	PRP Fast system		1 mL	8 mL	
Sanchez et al. 2007	PRGF System II, BTI, Vitoria-Gasteiz, Spain		4 mL	40 mL	Trisodium citrate (5mL)
Sarrafian et al. 2010	PRPFM (Cascade Autologous Platelet System-4, Musculoskeletal Transplant Foundation	5 times higher than non centrifuged autologous blood	-	9 cc of centrifuged autologous blood	-
Schepull et al. 2011		10 times	6 + 4 mL	450 mL	Citrate phosphate dextrose
Suwalski et al. 2010		n.a.	50 mL (pDNA/MSN 2:5 ratio)	n.a.	n.a.

Table 2 – Platelet concentrate parameters of the included studies

7.4.3 Risk of bias in the included studies

The average Jadad score for the included studies was 2.1 ± 1.0 pts, which is representative of musculoskeletal studies. The most commonly neglected quality item was an a priori power assessment, which is particularly troublesome in field characterized by a higher percentage of negative studies. No study reported on unusually high attrition rate, which disperses concerns about selection or response bias.

7.4.4 Platelets in Achilles tendon ruptures

Nine studies presented results for the use of platelets in Achilles tendon rupture treatment, seven from animal experiments and two from human trials. Six of the animal studies used a rat model, and one used an ovine model. All animal

studies, using biomechanical and histological assessment, showed a beneficial effect of platelets.

In the statistical assessment of these studies, there was no evidence for publication bias (p=0.079). There was no evidence for mathematical heterogeneity for stiffness (p=0.493), but some evidence for heterogeneity for load (p<0.001), based on the outlying results of Virchenko et al. from 2006 [43]. Overall, there was no evidence for heterogeneity across these three outcomes (p=0.179).

The pooled estimates for the biomechanical outcomes showed a significant, favorable effect of platelets on load (p<0.001), but not on stiffness (p=0.185) or tensile strength (p=0.890). Overall, there was strong evidence for statistically significant, favorable effect of platelets on biomechanical outcomes (p=0.001). (Figure 5)

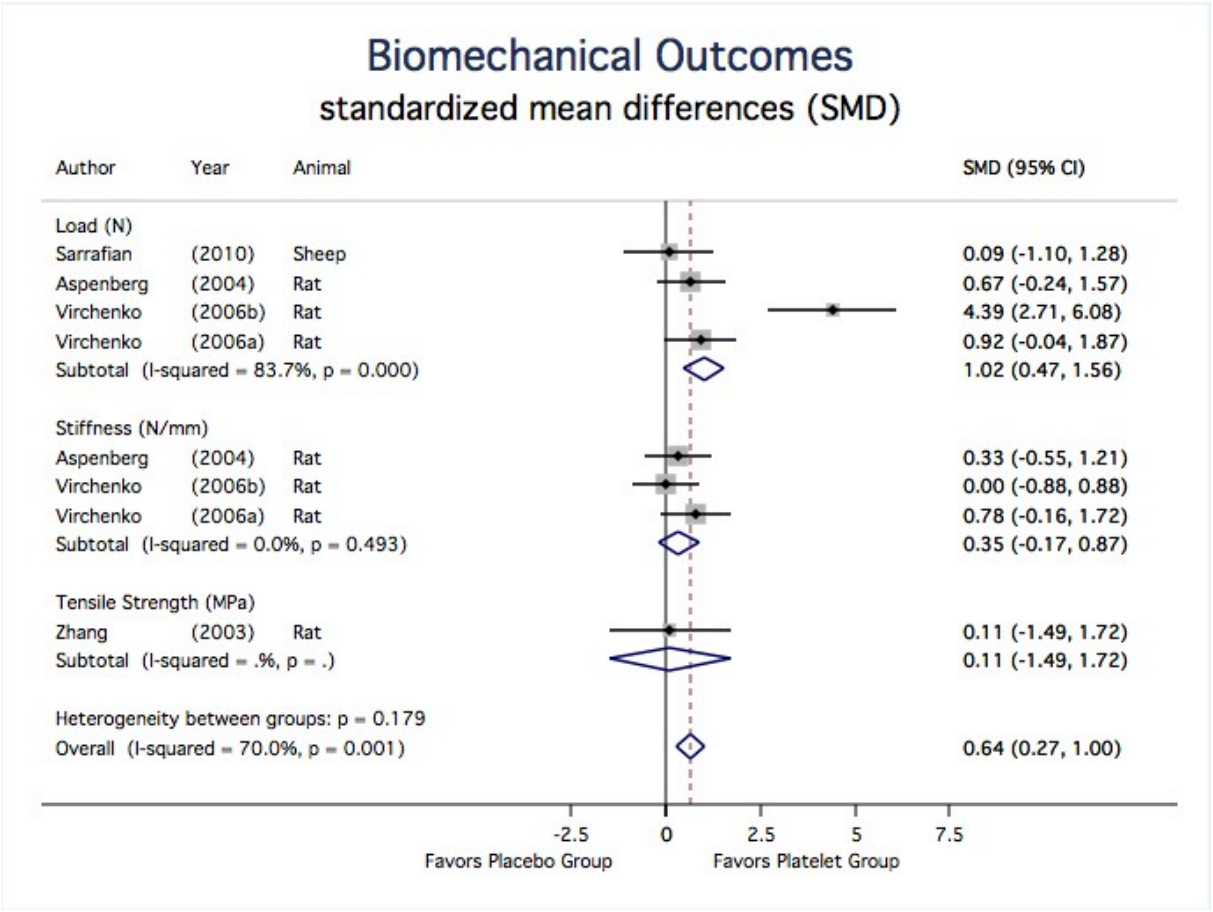

Figure 4 – Pooled estimates for biomechanical outcomes of Achilles tendon lesions treated with platelet-rich plasma (PRP)

Five studies present histological results from rat and rabbit models. Sarrafin et al. [40] showed that in an ovine Achilles tendon suture repair model, tendon repair occurs via increased thickness and by addition of horizontally arranged fibers, whereas in a repair model with an added platelet concentrate, there was only little tendon thickening and a higher level of fiber organization. Similar results were reported by Aspenberg et al. [35], in a rat model, showing a higher level of maturation in those animals treated with a platelet concentrate. Interestingly, these difference manifested only late in the study (21 days) but not during the earlier time points (11 days). Lyras et al. [36] showed in their first of three rabbit studies improved scar maturation too, with less vascularity and less inflammatory cells than in a control group without platelets although there was a stronger, early angiogenetic response in the PRP group. Lyras et al. [37, 38] could also demonstrate that, immunohistochemically, there was a higher expression of IGF and TGF-beta in those animals treated with platelets.

Lastly, there were two human studies that tested the effect of platelets on the treatment of Achilles tendon rupture using imaging techniques and clinical results. In a human study of 30 patients Schepull et al. [41] found no effect of platelets on radioisometrical wound contraction or clinical outcomes. Sánchez et al. [39] found nearly identical results as were seen in animal studies in a group of 12 athletes treated with PRP augmented suture repair at 32 months. In ultrasonographic assessment, there was less tendon thickening, there were higher concentrations of TFG-beta and other growth factors and patients regained range of motion faster and returned to sports (gentle running) earlier.

7.4.5 Platelets in Achilles tendinopathy

Three studies reported on the use of platelets in human Achilles tendinopathy [25, 45, 46]. All three studies used platelets as an adjunct to eccentric exercises. Two studies provide data for clinical scoring using the Victorian Institute of Sports

Assessment-Achilles (VISA-A) score, which is a validated outcome tool for Achilles tendinopathy [25, 45]. (Figure 6)

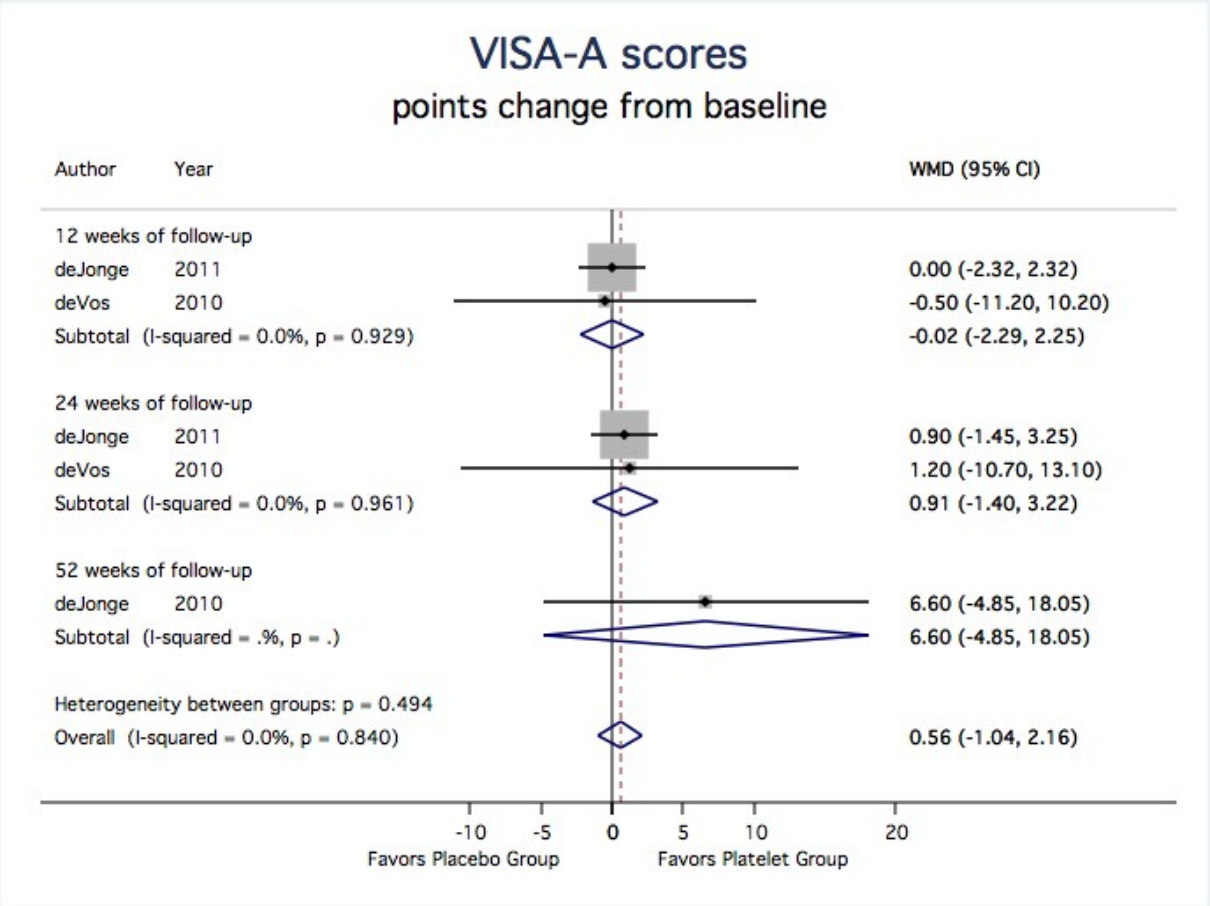

Figure 5 – VISA-A scores of Achilles tendinopathies, treated with plaetelt-rich plasma (PRP)

Mathematically, there was no evidence for publication bias or heterogeneity among these studies (p=0.929). The weighted mean differences (WMD) showed no effect of platelets at any point during follow-up, nor overall with a WMD of 0.56 pts (95%CI -1.04 to 2.16).

Both authors also offered results from ultrasonographic assessment. There was a significant improvement in both the experimental and the control groups over time, but no across group differences in neovascularization, echo-type, or tendon structure.

7.5. Discussion

7.5.1 Summary of evidence

This study assessed the role of platelets in Achilles tendon treatments. Achilles tendon rupture and Achilles tendinopathy were combined in one paper since there is a pathogenetic continuum across these diseases, and because this study wanted to provide a complete and comprehensive summary of the current evidence. Based on biomechanical, histological and clinical data from human and animal studies, the current best evidence suggests a strong effect of platelets in enhancing outcomes after Achilles tendon rupture treatment, but not for Achilles tendinopathy.

The current best evidence suggests a beneficial effect of platelet use in the treatment of Achilles tendon ruptures. The animal data shows, consistently across different animal models, that platelets improve biomechanical outcomes by about half a standard deviation. There was one outlier, the second study by Virchenko et al. [43] in 2006, yet this paper does not contradict the findings of the other studies, but lies, in agreement, even further on the “favorable” side of the forest plot (Figure 2). These biomechanical findings are largely supported by histological assessment, showing better scar maturation in those groups treated with PRP. Interestingly, these findings were considerably consistent across different species.

Finally, there are two human studies that provide data for the effect of platelets in Achilles rupture treatment. Schepull et al. [41] found no beneficial effect, but there are two important, maybe interrelated, issues to consider in this study. First, they used a 17x PRP (17 times the physiological concentration of platelets), which might have lead to overstimulation of the tenocytes and thus a poorly organized response [26, 48, 49]. Second, this study was affected by a very high inter-patient variability in outcomes, suggesting that some confounding co-variable might have influenced its results [50]. The other human study was published by Sánchez et al. [39] and showed results that were equivalent with the findings from the earlier published

animals studies – faster healing, less thickening of the tendon, and high levels of growth factors in the wound site. It is important to note that this agreement across different studies in different species is a strong indicator for a biological effect. Furthermore, the group of Sánchez et al. [39] has also performed research on the use of PRP in ACL reconstruction, and found similar results. In this 2010 study they were able to show a significantly better maturity index for ACL grafts treated with PRP than for untreated grafts ($p=0.024$) and a significantly better synovial coverage of the treated grafts ($p=0.023$), as well as a faster healing time ($p=0.014$) [39]. These findings were confirmed in a recent systematic review [6]. This consistency of effectiveness across different procedures, on top of the consistency across different species for the same procedure, is further support for a true biological effect.

As far as Achilles tendinopathy is concerned, the current evidence does not suggest a beneficial effect of platelet concentrates. Both deVos and deJonge published level-I, randomized, controlled clinical trials and found no evidence for improved clinical outcomes [25, 45, 46]. A point could be made that both studies suffered from considerable variance in their outcomes, and that a larger sample size would reduce this variance, thus leading to significant p-values, but the absolute differences in outcomes on the VISA-A score was not consistent with a clinically meaningful result. The same is true for ultrasonographic assessment in these studies that showed significant improvement over time, but not across intervention groups. An important point to consider is that PRP was used as an adjunct to an eccentric training program and the effect of this program could have diluted the effect of PRP. Given the early use of human trials and the lack of a Achilles tendinopathy animal model, it is not surprising that there is a paucity of animal data for PRP treatments of this disease. For the purpose o this study, we categorized the study published by Suwalski et al. [46] as tendinopathy model. In this study the investigator created three Achilles tendon defects by puncture wounds, which is not a perfect tendinopathy model, but more so than a transection model. This study found that the use of platelet-derived growth factor (PDGF) improved biomechanics and fastened histological healing at 21 days postoperatively. After mentioning the paucity of Achilles tendinopathy animal studies it is worth noting that there are “non-Achilles tendon “animal studies investigating the effect of PRP on tendon healing. For example, Bosch et al. [51] showed that intratendinous PRP treatment improves the

functional strength of healing equine superficial digital flexor tendons, but the differences between the Achilles tendon and digital flexor tendons are sufficient to render such models ineligible for this meta-analysis.

A very interesting extension of PRP treatments of the Achilles tendon is the use of PRP with a cellular component, such as bone marrow derived stem cells. For example Okamoto et al. [52], in 2010, used mesenchymal stem cells to enhance natural healing in a transection model in rats and found significantly better results in biomechanics and histology at 28 days. The addition of (stem) cells is particularly interesting since the hypocellualrity of the Achilles tendon is not only a reason for its high injury risk, but also a problem in its healing. Chong et al. [53] present data from a rabbit Achilles tendon repair augmented either with fibrin and bone marrow stem cells or with fibrin alone and found significantly better fiber organization and elastic modulus at 3 weeks postoperatively. Future studies in this area might produce very interesting insight.

7.5.2 Limitations

There are potential shortcomings in our study. First, like any systematic review, our study's validity depends on the quality of the primary studies that were included. For this particular study, the quality of the primary studies was in the mid range, but this finding is not unusual for surgical and musculoskeletal research.

Another shortcoming is heterogeneity among the primary studies, i.e. mathematical and methodological differences among the primary studies. The methodological differences, such as animal models or human studies, or the type and concentration of platelet concentrate used were described in the text to allow the reader to come to an own judgment. Concerning the mathematical side of heterogeneity, which jeopardizes the validity the results of a meta-analysis, we used standardized mean differences to combine results. As mentioned above, this method uses mean differences divided by SDs, i.e. all results are given as "how many times SD" the result is away from no effect. This measure is also known as effect size. Thus our result can only be interpreted as, for example, a 1.02x SD improvement, or

a large effect size, in load with addition of a platelet concentrate to a ruptured Achilles tendon.

Lastly, it should not go unnoticed that PRP is an “umbrella term” for a wide range of preparations. Concentrations and constituents of PRP vary significantly, and some of the included studies used individual growth factors associated with PRP rather than an actual platelet-concentrate. However, we chose to include all this study to give a comprehensive overview of all available data. Furthermore, if there is a true biological effect of PRP it should be, at least partially, visible in all PRP preparation, but of course with varying strength, and we really did find evidence for a – varying but visible - overall effect of PRP on Achilles tendon rupture treatment.

7.5.3 Conclusion

The current evidence provides strong evidence in support of a statistically significant effect of platelet concentrates in the treatment of Achilles tendon ruptures *in vivo*, consistent with a medium to large sized effect. This effect is most likely attributable to fastened and enhanced scar tissue maturation. There was no evidence for a beneficial effect of platelets in Achilles tendinopathy.

8. PRP for rotator cuff treatment

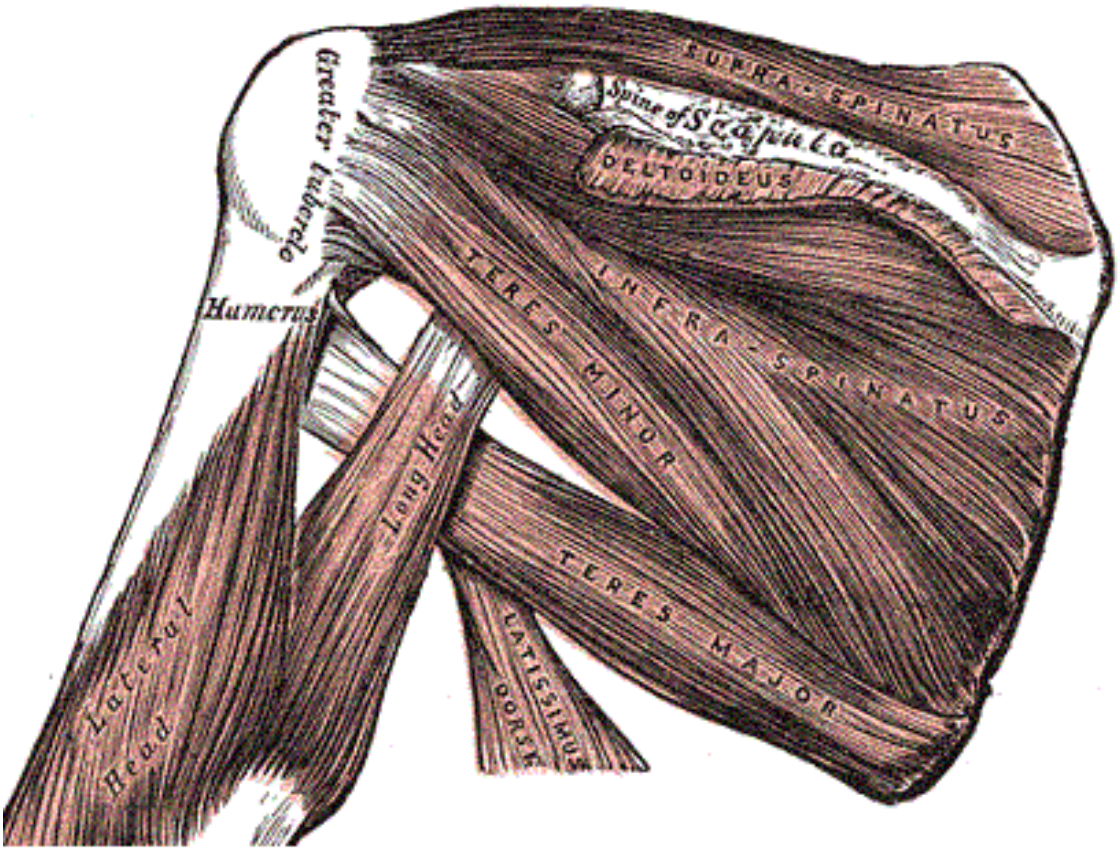

Figure 6 – Shoulder joint with rotator cuff muscles. From Richard M. Tibbitts out of "Gray´s Atlas der Anatomie. Urban & Fischer".

8.1 Introduction

Tissue engineering of ligaments and tendons is an upcoming topic in orthopaedics surgery and regenerative medicine. The involved injuries, e.g. ruptures, tears, and chronic tendinopathy of the rotator cuff (RC), the anterior cruciate ligament (ACL), the patellar tendon (PT), and the Achilles tendon (AT) have long and potentially serious sequelae and occur at high incidences [6, 26, 54, 55]. Consequently there is a substantial amount of research done in this area in order to improve techniques of tissue repair and tissue regeneration [6].

Among the most promising approaches is the use of platelet concentrates such as platelet-rich plasma (PRP) [6, 26, 54]. Platelets have two beneficial effects that support and enhance wound healing. On the one hand, they are a source of a plethora of growth factors that stimulate healing [54]. On the other hand, platelets clot and form a temporary matrix that fills defect sites and serves as a matrix for cell migration and tissue remodeling [54]. Platelet concentrates have been investigated for their effect on the ruptured ACL, chronic epicondylitis, or treatments of the Achilles tendon [39, 49, 56].

However, the biology and effects of the growth factors released from PRP on the human rotator cuff are still elusive und not fully understood. Two recent *in vitro* studies by Jo et al. and Hoppe et al. have tried to further address to this topic without adequately investigating a dose-response or long period of time after PRP stimulation [57, 58]. The scientific literature on the clinical impact of PRP on the human rotator cuff in *in vivo* studies is therefore still insufficient leading to a need of further investigation of the topic [59-64]. Evidence from *in vitro* and animal studies suggests that the pro-inflammatory agents of PRP might have negative effects, and its use and dosage should be chosen deliberately while carefully weighing benefits with potential detrimental effects such as muscle fibrosis after injury [65].

The authors therefore want to elucidate the effects of PRP on rotator cuff fibroblast growth and bioactivity, with special attention on the dose-response relationship between PRP concentration and these outcomes.

This study has two aims: (1) To assess the *in vitro* effect of platelet-rich plasma (PRP) on biological activity of the human rotator cuff fibroblast (DNA expression, collagen and glycosaminoglycan (GAG) production over DNA ratio). (2) To describe the optimal dose-response relationship of PRP concentration on human rotator cuff fibroblast proliferation to maximize cellular stimulation while reducing potential risk.

8.1.1 Study hypothesis

The study hypothesis was that an application of PRP would significantly influence the fibroblast proliferation and activity of the human RC using PRP, and, that the dosage of PRP would have significant impact on this influence.

8.2 Methods

8.2.1 Cell Culture and Tissue Preparation

Human rotator cuff (RC) fibroblasts were obtained from n=6 patients with degenerative rotator cuff tears (above 50 years of age) undergoing elective arthroscopic or mini-open assisted rotator cuff repair (The study protocol was approved by the local ethics committee (24-427 ex 11/12)).

RC tissue was harvested, washed, minced, and explant cultures were used to obtain fibroblast cells. Once sufficiently high cell numbers were obtained, 500 000 cells were seeded onto 6-well plates and stimulated with PRP once. Coagulation was triggered by an activator (thrombin/CaCl2 mixture v/v). 250 ml activator was added per 750 µl PRP. All cells incubation were carried out at 37°C in a humidified atmosphere of 5% CO_2 in a medium consisting of DMEM (Gibco® Invitrogen, Darmstadt, German), 10% foetal bovine serum (FBS; (Gibco® Invitrogen), 2 mM L-glutamine (Gibco® Invitrogen), 100 U/ml penicillin and streptomycin (Gibco® Invitrogen), 0.25 µg/ml amphotericin B (PAA, Pasching, Austria), and 0.025 mg/ml ascorbic acid (Sigma Aldrich, Vienna, Austria). At 1, 7, 14, and 21 days samples were obtained for immediate testing or snap freezing for further processing.

8.2.2 Processing of Platelet-rich Plasma (PRP)

Per volunteer sixty cc of blood were drawn and spun down to isolate blood constituents. To avoid coagulation sodium citrate was used as anticoagulant. While erythrocytes were discarded, the blood plasma and a buffy coat of PRP were harvested to prepare PRP. Therefore platelets were thereafter counted and adjusted to a 1-, 5, or 10-fold concentration of the initial blood sample using the harvested plasma. The platelet-concentrate was stored on ice until application to the RC fibroblasts.

8.2.3 Analysis of biological response to Platelet-rich Plasma (PRP)

All samples obtained for DNA and or procollagen measurements were digested using a standardized papain protocol (St. Louis, MO) [65]. Briefly, samples were dried, weighed, and 1 mL papain in phosphate buffer (0.125 mg/mL papain) was added. Subsequently, all samples were digested on a shaker at 60°C for 3 hours. Triplicates of samples were assessed immediately after digestion using the PicoGreen assay (Quant-iT PicoGreen assay, Molecular Probes, Eugene, OR, USA) [66]. The procollagen content in the cell culture supernatant samples was assessed using a commercially available ELISA kit for the procollagen Type I C-peptide (PIP EIA kit Takara Bio Inc., Shiga, Japan) [67]. A procollagen assay, rather than a collagen assay was used for two reasons. First of all, procollagen is the original product of the cell and reflects cellular metabolism independent from extra-cellular protein processing. Secondly, our collagen assay is not sensitive enough to validly measure the small amounts of newly synthesized collagen against the strong background of the RC. All results were adjusted for dry weight and normalized for empty samples.

8.2.4 Sample size

A number of previous studies showed consistently that an effect size of 1.1 was to be expected for all outcomes. Based on this assumption a sample size of n=6 per group is needed to obtain 95% power in a fixed effects ANOVA analysis with an alpha of 5%.

8.2.5 Statistical Analysis

Fixed effects ANOVA was used to compare outcomes over time or over PRP concentration in DNA levels and glycosaminoglycan over DNA ratios. Multilevel, generalized linear mixed regression modeling was used to assess the effect of time and PRP concentration, including potential interaction, on RC proliferation and biosynthetic activity. Intercooled Stata 12.1 was used for all assessment.

8.3 Results

Fibroblasts of the human rotator cuff could be harvested from 6 patients undergoing elective arthroscopic rotator cuff repair. These fibroblasts kept their typical bipolar spindle phenotype unchanged in all 3 groups (1-, 5-, and 10-fold concentration of PRP) within the whole time period until day 21 (Figure 8).

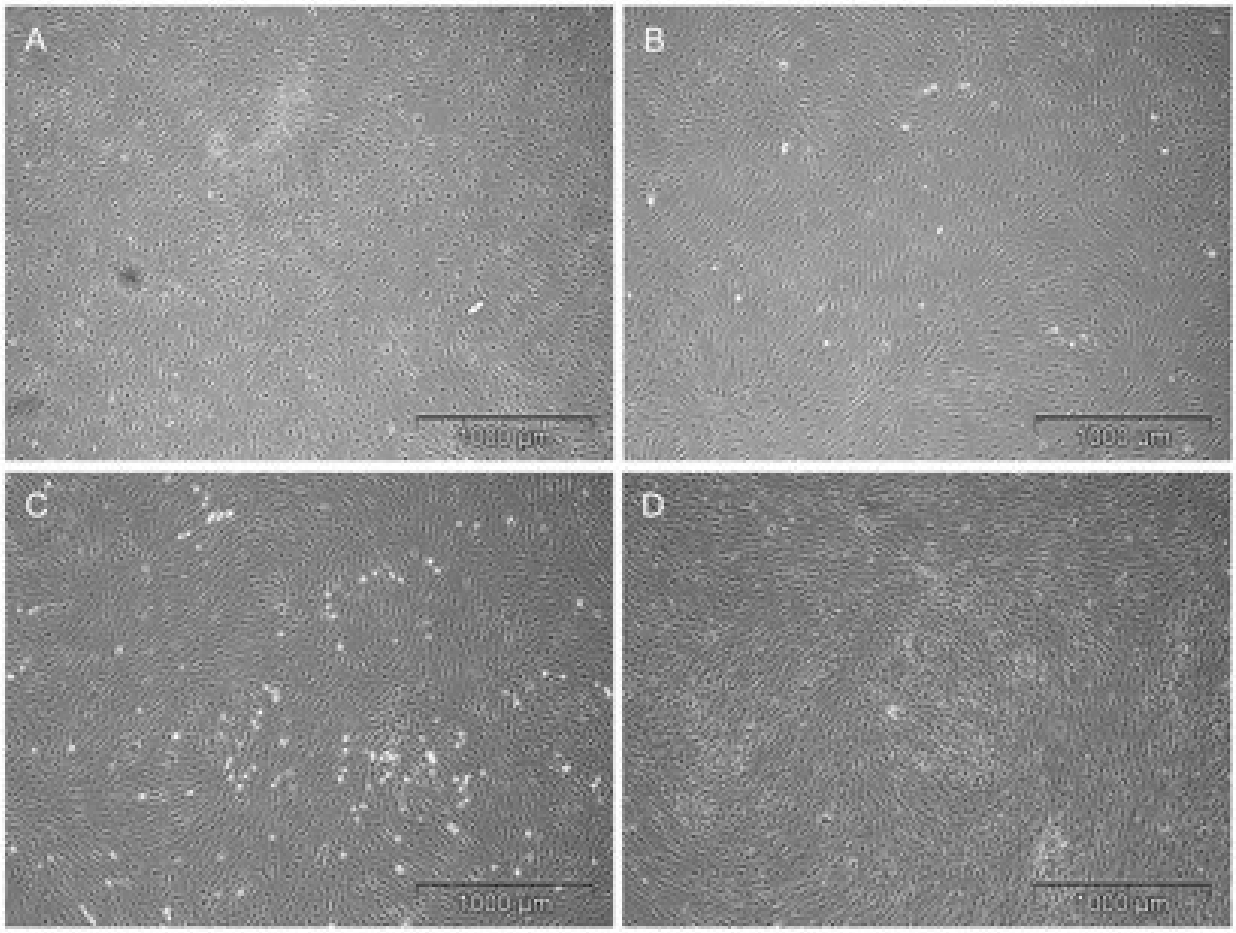

Figure 7 – Cell growth analysis of human rotator cuff fibroblasts. According the DNA expression levels after 14 days of A) untreated control cells, bright field microscopy demonstrated the increasing cell growth after the treatment with B) 1-fold, C) 5-fold, and D) 10-fold concentration of platelet-rich plasma (PRP). All pictures are shown in 100x magnification.

DNA expression

The DNA expression was equal with 100% in the control group, the 1-fold, 5-fold, and 10-fold PRP concentration group each at day 1, respectively. At the following days 3, 7, 14 and 21, the DNA expression was significantly highest in the group with a 1-fold concentration of platelet-rich plasma. However, the groups with a 5-fold and 10-fold PRP concentration revealed higher levels of DNA expression at every single time point in contrast to the control group. These data are further illustrated in Table 3.

	PRP concentration			
Time point	Control group	1-fold**	5-fold	10-fold
1 day	100%	100%	100%	100%
	0.0 CI*	0.0 CI	0.0 CI	0.0 CI
3 days	217.8%	318.4%	290.4%	303.4%
	15.6 CI	39.8 CI	77.9 CI	85.7 CI
7 days	314.2%	457.6%	395.0%	364.6%
	93.9	135.1	81.3	67.7
14 days	362.3%	542.4%	465.9%	460.9%
	80.5 CI	137.7 CI	77.1 CI	72.3 CI
21 days	403.8%	589 %	523.4%	468.8%
	84.7 CI	127.3 CI	90.4 CI	89.4 CI

*Confidence interval (CI)
**1-fold platelet-rich plasma (PRP) concentration

Table 3 – Fibroblasts of the human rotator cuff were stimulated *in vitro* using different concentrations of platelet-rich plasma (PRP). The percentages of DNA expression after 1, 3, 7, 14, and 21 days, indicating biological response, were measured in a control group, a 1-fold, a 5-fold, and a 10-fold concentration of PRP at all time points. ANOVA analysis revealed the significantly highest DNA expression in the 1-fold PRP concentration at all measured time points ($p<0.0001$).

DNA over glycosaminoglycan ratio

The DNA over glycosaminoglycan ratio was almost equal at day 1 between groups. At day 3 it was highest in the control group (with 4.7), followed by the group with a 1-fold PRP concentration (2.8), and the group with the 5-fold concentration (1.8). At the

remaining time points (day 7, day 14, and day 21) the group with a 5-fold concentration of PRP revealed the highest ratios (6.9, 5.9, and 2.8, each). This is further illustrated in Table 4.

	DNA over GAG ratio			
Time point	Control group	1-fold**	5-fold	10-fold
1 day	0.3	0.3	0.4	0.1
	0.2 CI*	0.2 CI	0.2 CI	0.1 CI
3 days	4.7	2.8	1.8	1.3
	1.0 CI	0.2 CI	0.5 CI	0.2 CI
7 days	4.8	4.4	6.9	4.9
	3.3 CI	2.5 CI	3.2 CI	1.3 CI
14 days	2.3	3.9	5.9	4.2
	3.1 CI	5.0 CI	5.0 CI	3.6 CI
21 days	1.3	2.3	2.8	1.8
	1.6 CI	3.1 CI	3.3 CI	2.0 CI

*Confidence interval (CI)
**1-fold platelet-rich plasma (PRP) concentration

Table 4 – Fibroblasts of the human rotator cuff were stimulated *in vitro* using different concentrations of platelet-rich plasma (PRP). The ratios of DNA expression over glycosaminoglycanexpression after 1, 3, 7, 14, and 21 days, indicating relative biological response, were measured in a control group, a 1-fold,a 5-fold, and a 10-fold concentration of PRP at all time points. ANOVA analysis revealed the significantly highest ratio in the 1-fold PRP concentration at 3 days, and in the 5-fold PRP concentration at 1, 7, 14, and 21 days with $p<0.0001$, each.

Overall, the application of PRP significantly influenced the fibroblast proliferation and activity of the human RC with elevated DNA levels and an elevated glycosaminoglycan over DNA ratio. The dosage of PRP had the significantly highest impact on this proliferation using a 1-fold concentration with respect to DNA expression and 5-fold concentration with respect to the DNA over glycosaminoglycan ratio at days 7, 14, and 21. The 1-fold and 5-fold concentration revealed superior results over a 10-fold application, respectively.

8.4 Discussion

This study had two aims: (1) To assess the *in vitro* effect of platelet-rich plasma (PRP) on biological activity of the human rotator cuff fibroblast (DNA expression, collagen and glycosaminoglycan (GAG) production over DNA ratio) and (2) to describe the optimal dose-response relationship of PRP concentration on human rotator cuff fibroblast proliferation to maximize cellular stimulation while reducing potential risk.

The study hypothesis was that an application of PRP would significantly influence the fibroblast proliferation and activity of the human RC using PRP, and, that the dosage of PRP would have significant impact on this influence.

To the best of our knowledge, this is the first study in the literature showing, that an application of PRP significantly influenced the fibroblast proliferation and activity of the human RC using PRP, and, that the dosage of PRP had the significantly highest impact on this proliferation using a 1-fold or 5-fold concentration.

The importance of sufficient rotator cuff repair after traumatic or degenerative ruptures is a main focus of orthopaedic sports medicine in order to preserve range of motion (ROM) and to avoid long term salvage procedures as reverse total shoulder arthroplasty [68, 69]. As the outcome of rotator cuff repair is worthy being improved, substantial research is done on the procedure itself and further adjuvant treatment options. PRP has been shown to provide additive strength in terms of ACL and Achilles tendon ruptures in animal models [5, 54], without this effect being proven in humans [45, 46].

However, according to the translational model of orthopaedic research, new treatment options should be investigated in an animal setting, before starting with human *in vitro* applications, and human *in vivo* applications, finally. The usage of PRP on mesenchymal cells in animal studies has been extensively investigated and been proven beneficial in various investigations [70-72]. Although relatively early in its use, the *in vivo* effect of PRP on the human rotator cuff is still unclear with no

consensus or meta-analysis on this topic [59-64]. Exact *in vitro* analysis is therefore undertaken [8, 9] and mandatory before getting to the very next steps.

The authors are the first to prove, that an ideal dosage of a 1-fold PRP concentration leads to the significantly highest biological response with respect to DNA expression and a 5-fold concentration with respect to the DNA over glycosaminoglycan ratio at days 7, 14, and 21 in an *in vitro* setting in human RC cells. Thereafter, with respect to these results, we would recommend a 5-fold PRP concentration for further use in humans. The authors have undertaken this *in vitro* evaluation of the effect of PRP on biologic response of the human RC to expound the fundamental research on its effect, after various clinical studies have failed in demonstrating meaningful significance [57-61]. Our findings suggest a further use of PRP in cuff tear reconstruction; however, future studies should focus on the correct application dosage

.

8.4.1 Limitations

This study has the following limitations. First, PRP is an “umbrella term”, summarizing a variety of growth factors, which individually contribute to the aspect of healing. Next, the authors model had a potential ceiling effect, with a 10-fold dosage of PRP as the highest option. However, the optimal dosage was between a 1-to 5-fold concentration.

We want to underline the significant benefit, that the authors present the first study in the literature, evaluating the effect of PRP on the target cell of the human rotator cuff in a dose-dependent setting and that the presented results were published and discussed in the Journal of Orthopaedic research [54, 73, 74].

8.4.2 Conclusion

Platelet-rich plasma has a significant effect on fibroblast proliferation of the human rotator cuff in *in vitro* settings with an optimal benefit using a 1- to 5-fold PRP concentration. This study justifies further *in vivo* investigations using PRP at the human rotator cuff.

9 Overall conclusion

Overall, I want to come to the conclusion, that PRP might offer interesting solutions in tissue engineering, in general. However, with respect to a definite recommendation in terms of clinical application, I am in line with Prof. Aspenberg, who commented on our publication and underlined the fact, that PRP has not been proven to be beneficial in clinical settings yet.

10. References

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11. Curriculum Vitae

Dr. med. (Ludwig-Maximilians University Munich)
Dr. med. univ. (Medical University of Graz)
Patrick Sadoghi, MD

Date and place of birth:	26th of January 1984 in Graz, Austria
Main residence:	Argenotstrasse 50a, 8047, Graz, Austria
E- mail:	patrick.sadoghi@medunigraz.at
Phone:	0043 650 5237591

Scientific Expertise

Joint Replacement/ Adult Reconstructive Surgery
Orthopaedic Sports Medicine/ Shoulder Surgery
Knee Surgery

Clinical Career

January 2013:	Assistant Professorship at the Department of Orthopaedic Surgery, Medical University of Graz, Austria
March 2012:	Graduation (Dr. med., MD, “magna cum laude”) at the Department of Orthopaedic surgery, Ludwig-Maximilians University Munich, Prof. Dr. Dipl.-Ing. Volkmar Jansson, MD
November 2011:	Postdoctoral Visiting Research Fellow, Sports Medicine Research Laboratory, Children's Hospital Boston, Harvard Medical School, Boston, USA, Prof. Dr. Martha M. Murray, MD
2010 – 2012:	Resident in Orthopaedic Surgery, Medical University of Graz, Austria, Prof. Dr. med. univ. Andreas Leithner, MD
2009 - 2010:	Postdoctoral Research Fellow, Laboratory for Biomechanics and experimental Orthopaedics, Ludwig-Maximilians University Munich, Prof. Dr. med. Wolfgang Plitz
2009 – 2010:	Resident in Orthopaedic Surgery, Ludwig-Maximilians University Munich, Germany, Prof. Dr. med. Dipl.-Ing. Volkmar Jansson, MD
2009 – 2010:	Chiropractic degree of the Austrian Medical Chamber
2009:	Intern in Trauma Surgery, AUVA Trauma Center Linz, Austria, Assoc. Prof. Dr. Albert Kröpfl, MD
2008:	4th of December: Graduation (Dr. med. univ, MD) at the Medical University of Graz, Austria
2003 – 2008:	Medical study at the Medical University of Graz, Austria, and the George Washington Medical University, US-MD in 10.5

semesters.

2002: Final examination at secondary school Petrinum in Linz, Austria with distinction

Awards, Scholarships, and Prizes

2013: AGA – Smith & Newphew Shoulder Fellowship (Freddie F. Fu, Jon JP Warner, Michael Terry)

2012: Outgoing Scientist program (Bank Austria) to visit the Cartilage Repair Center, Prof. Dr. Tom Minas, MD, Department of Orthopaedic Surgery, WBH, Harvard Medical School, Boston

2011: GOTS (Gesellschaft für Orthopädisch-Traumatologische Sportmedizin) Young Investigator Award

2011: AFOR (Association for Orthopaedic Research) scholarship

2011: Scientific Research Grant of the (ÖGO) Austrian Society of Orthopaedic Surgeons

2011: Incoming Scientist program (Bank Austria) for Prof. Dr. Plamen Kinov, MD, Department of Orthopaedic Surgery, University Hospital of Sofia

2010: Incoming Scientist program (Bank Austria) for Dr. Patrick Vavken, MD, Harvard Medical School, Boston, USA

2009: Leonardo DaVinci scholarship of the Austrian Medical Chamber

2008: Traveling scholarship of the Medical University of Graz for the George
Washington University, Washington DC, USA

2007: Traveling scholarship of the Medical University of Graz for the University Clinic of Cairo, Kasr Alaini Hospital, Egypt

2004: Scholarship of excellence of the Medical University of Graz, Austria for finishing 5th after the first part of the medical studies.

Degrees of the Austrian Medical Chamber

ÖÄK – degree for chiropractic medicine

Memberships in Professional Societies

AGA – German Society of Arthroscopy and Joint Surgery

ÖAMM – Austrian Society for Chiropractic Medicine

GMC - General Medical Council- Medical Chamber of the UK

DKOU – German Society for Orthopaedic Surgery and Trauma Surgery / Section: basic research

ÖGO – Austrian Society of Orthopaedic Surgery

GOTS – Society of Traumatology and Sports Medicine

ICRS – International Cartilage Repair Society

Editorial Boards

WORLD JOURNAL OF META-ANALYSIS: Editorial Board Member

ORTHOPAEDIC JOURNAL OF SPORTS MEDICINE: Editorial Board Member

Reviewer for scientific journals

THE JOURNAL OF ARTHROPLASTY

WORLD JOURNAL OF ORTHOPEDICS

CONNECTIVE TISSUE RESEARCH

MINERVA ORTOPEDICA E TRAUMATOLOGICA

OSTEOARTHRITIS AND CARTILAGE

SARCOMA

JOURNAL OF ORTHOPAEDIC RESEARCH

INDIAN JOURNAL OF ORTHOPAEDICS

EUROPEAN ORTHOPAEDICS AND TRAUMATOLOGY

IRISH JOURNAL OF MEDICAL SCIENCE

ARCHIVES OF MEDICAL SCIENCE : AMS

THE AMERICAN JOURNAL OF SPORTS MEDICINE

KNEE SURGERY SPORTS TRAUMATOLOGY ARTHROSCOPY

INTERNATIONAL ORTHOPAEDICS

Reviewer for funding organizations

Alessandro Liberati Programme - Programma di ricerca Regione-Università – Agenzia sanitaria eSociale regionale – Italy (served as a reviewer for 5 grants on 1 250 000 € in total)

Language skills

English, French, and Spanish

11.1 External Funds

Sum:	123 712€ in total

Principal Investigator or main applicant:

Traveling scholarship of the MeduniGraz (Egypt)	650 €
Traveling scholarship of the MeduniGraz (GWU, Washington DC)	1 500 €
Scholarship of the MeduniGraz	778 €
Leonardo DaVinci scholarship	1 684 €
Incoming Scientist program (BACA, Vavken)	2 000 €
Incoming Scientist program (BACA, Kinov)	2 000€
AFOR scholarship & grant	2 000 €
ÖGO research grant	15 000€
GOTS Young Investigator Award 2011	1 000 €
Outgoing Scientist program (BACA, Minas)	2 000€
AFOR grant	10 000€
DePuy Johnson & Johnson industry grant	60 000€

Co-investigator:

Unfallchirurgischer Fortbildungsverein (AUVA)	19 000 €
Unfallchirurgischer Fortbildungsverein (AUVA)	6 100€

Organizer of scientific conferences, Chairs

2012: Journalclub sports medicine and arthroscopic surgery (granted by the Austrian Medical Chamber) (Organizer)

2012: Journalclub arthroplasty (sponsored by DePuy, granted by the Austrian Medical Chamber) (Organizer)

2012: Orthopaedic medical education of the Medical University of Graz (granted by the Austrian Medical Chamber) (Organizer)

2011: Orthopaedic medical education of the Medical University of Graz (granted by the Austrian Medical Chamber) (Organizer)

2009: SICOT Trainee, Kolobrzeg, Poland (Chair)

11.2 Publications

Summary:

46 pubmed-listed publications

23 of these 46 as a first author (12 top 20% nach JCR)

3 of these as a last author

Sum of impact factor (with accepted publications): approx. 95

** SCI/ pubmed-listed publications

(alphabetically listed after first author)

First authored papers:

**** Sadoghi, P**; Leithner, A; Dorotka, R; Vavken, P , 2013. Effect of Pulsed Electromagnetic Fields on the Bioactivity of Human Osteoarthritic Chondrocytes. Orthopedics. 2013; 36(3):e360-e365

**** Sadoghi, P**; Müller, PE; Valderrabano, V; Lidder, S; Leithner, A; Vavken, P; Musculoskeletal Clinical and Cost-effectiveness Outcome Study Group, 2013

Musculoskeletal Clinical and Cost-effectiveness Outcome Study Group.

Orthopedics. 2013; 36(3): 174-174.

** Ferlic, PW; **Sadoghi, P**; Singer, G; Kraus, T; Eberl, R, 2013 Treatment for ischial tuberosity avulsion fractures in adolescent athletes. Knee Surg Sports Traumatol Arthrosc. 2013; (Ferlic and Sadoghi contributed equally first)

Müller, AM; **Sadoghi, P; Lucas, R; Audige, L; Delaney, R; Klein, M; Valderrabano, V; Vavken, P, 2013 Effectiveness of bracing in the treatment of nonosseous restriction of elbow mobility: a systematic review and meta-analysis of 13 studies. J Shoulder Elbow Surg. 2013; (Müller and Sadoghi contributed equally first)

****Sadoghi, P;** Leithner, A; Labek, G, 2013 Overcoming Boundaries of Worldwide Joint Arthroplasty Registers: The European Arthroplasty Register Minimal Dataset. J Arthroplasty. 2013;

****Sadoghi, P**; Liebensteiner, M; Agreiter, M; Leithner, A; Böhler, N; Labek, G, 2013

Revision Surgery After Total Joint Arthroplasty: A Complication-Based Analysis Using Worldwide Arthroplasty Registers. J Arthroplasty. 2013;

****Sadoghi, P**; Lohberger, B; Aigner, B; Kaltenegger, H; Friesenbichler, J; Wolf, M; Sununu, T; Leithner, A; Vavken, P, 2013 Effect of Platelet-Rich Plasma on the Biologic Activity of the Human Rotator-Cuff Fibroblasts: A Controlled In Vitro Study.

J Orthop Res. 2013; 31(8):1249-1253

****Sadoghi, P**; Thaler, M; Janda, W; Hübl, M; Leithner, A; Labek, G, 2013 Comparative Pooled Survival and Revision Rate of Austin-Moore Hip Arthroplasty in Published Literature and Arthroplasty Register Data. J Arthroplasty. 2013;

****Sadoghi, P**; Janda, W; Agreiter, M; Rauf, R; Leithner, A; Labek, G, 2013

Pooled outcome of total hip arthroplasty with the CementLess Spotorno (CLS) system: a comparative analysis of clinical studies and worldwide arthroplasty register data. Int Orthop. 2013; 37(6):995-999

****Sadoghi, P**; Kastner, N, 2013 Size measurement and flexion gap balancing in total knee arthroplasty-new benefits of the Attune™ system? Int Orthop. 2013;

** **Sadoghi, P**; von Keudell, A; Vavken, P Effectiveness of Anterior Cruciate Ligament Injury Prevention Programs. J Bone & Joint Surgery Am 2012;94(9):769-76

** **Sadoghi, P**; Kröpfl, A; Jansson, V; Müller, PE; Pietschmann, MF; Fischmeister, MF Impact of tibial and femoral tunnel position on clinical results after anterior cruciate ligament reconstruction. Arthroscopy. 2011; 27(3):355-364

** **Sadoghi, P**; Borbas, P; Friesenbichler, J; Scheipl, S; Kastner, N; Eberl, R; Leithner, A; Gruber G Evaluating the Tibial and Femoral Insertion Site of the Anterior Cruciate Ligament using an Objective Coordinate System: A Cadaver Study. Injury 2012 http://dx.doi.org/10.1016/j.injury.2012.07.004

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