# Thesis

**The use of platelet preparations to enhance the outcome of dental implant therapy: A systematic review**

For obtaining the academic degree

**Doctor of Dentistry**

**(Dr. med. dent)**

At the

**Medical University of Vienna**

Executed at the

Department of Oral Biology

Under the supervision of

**Prof. Reinhard Gruber**

Submitted by

**Lama Hamisch**

Mat. Nr. N 1542220

Vienna, on the _____ Signature: _____

## A word of thanks

I would like to express my gratitude toward Medical University of Vienna, which allowed me to be a part of it, which is for me a great honor. My gratitude will not end and stay with me forever. My special thanks go to Prof. Reinhard Gruber, who has patiently taken over the scientific support and supervision of the thesis and has introduced me to the team and basic research of medicine. I am eternally grateful to my family, which always supported me, without their support, this work would never have been achieved. In addition, I would like to thank my mother, the strong and gentle soul, who taught me to work hard to achieve my goals. I would like to thank my father who was a doctor and taught me, that the medical work is the highest human work. Finally, my special thanks to everyone, who supported me during my studies, to my friends, and colleagues.

# Content

## Zusammenfassung

### Ziel der Studie

Vergleich der Ergebnisse beim Einsetzen von Zahnimplantaten mit Platelet-Rich Plasma (PRP) und ohne Thrombozyten Verabreichung. Die Fragestellung lautet wie folgt: verbessert die Verwendung von Thrombozyten das Ergebnis der Zahnimplantat-Therapie?

### Forschungsmethode

Die Recherche auf der PubMed-Datenbank erfolgte nach folgenden Kriterien: Thrombozyten *UND Dental-Implantate UND Mensch. Diese Recherche fand im September 2017 statt. Die Abstracts der Artikel wurden dem Inhalt nach auf kontrollierte klinische Studien überprüft. Relevante Artikel wurden nach den folgenden Kriterien analysiert: (i) Anzahl, Alter und Geschlecht der Patienten, (ii) klinische Indikationen, (iii) Methode der Thrombozyten Vorbereitung und Verwendung, (iv) Beobachtungszeitraum, (V) klinische Behandlungsergebnisse. Die Daten wurden in einer Tabelle dargestellt. Aufgrund der Heterogenität zwischen den Studien konnte keine Meta-Analyse durchgeführt werden. Neun Studien befassten sich mit Sinusbodenaugmentationen. Der Implantatstabilitätsquotient war in drei dieser neun Studien ein Richtwert und zeigte ein positives Ergebnis.

### Ergebnisse

Fünfzehn kontrollierte klinische Studien erfüllten die Einschlusskriterien. Sie verglichen Knochen-und Weichgewebe Augmentationen mit und ohne den Einsatz von Thrombozyten Vorbereitung. Aus einer anfänglichen Suche wurden 280 Titel ausgewählt und Daten extrahiert. Alle Studien wurden von Chirurgen in spezialer und klinischer Umgebung durchgeführt. Die Auswirkungen der Thrombozyten auf Implantatstabilität war in drei von fünf Studien positiv. Vier von sechs Studien wiesen positive Resultate auf was den Einsatz von PRP auf Knochenaufbau, Knochenhöhe und periimplantäre Knochenregeneration, angeht. Eine von zwei Studien beschrieb einen wesentlichen Einfluss der PRP auf marginalen Knochenverlust. Neun Studien befassten sich mit der Sinusbodenaugmentation. Der

Implantatstabilitätsquotient war ein Parameter von drei dieser neun Studien und hatte ein positives Ergebnis.

**Schlussfolgerungen**

Die hohe Heterogenität unter diesen Studien machte es schwierig eine eindeutige Schlussfolgerung zu finden. Einige Studien zeigten klinische und radiographisch positive Effekte was die Verwendung von PRP bei Implantationsoperationen betrifft. Weitere Studien, die den Effekt von PRP auf Knochenaufbau und Weichgewebe und Implantatsstabilität untersuchen, sind erforderlich.

## Abstract

**Aim:** To compare the outcome of dental implant therapy with platelet-rich plasma (PRP) as well as without platelet preparations. The focused question was as follows: Does the use of platelet preparations enhance the outcome of dental implant therapy?

**Methods:** A search on PubMed database was performed using the following criteria: platelet* AND dental implants AND human. This search was in September 2017. Abstracts were screened for articles on controlled clinical studies. The relevant papers were analyzed for the following criteria: (i) number; age and gender of patients; (ii) clinical indication; (iii) method of platelet preparation and application; (iv) observation period; (v) clinical outcome and parameters. The data were presented in a table. Due to heterogeneity in between the studies, no meta-analyses could be performed.

**Results:** Fifteen controlled clinical trials met the inclusion criteria. They compared bone and soft tissue augmentation with and without the use of platelet preparation. From an initial search, 280 titles were selected and data extracted. All studies were performed by surgeons in specialized clinical settings. The impact of platelets on implant stability quotient was positive in three out of five studies. Four out of six studies showed a positive effect of the use of PRP on bone formation and bone height and peri-implant regeneration. One out of two studies had a significant effect of PRP on marginal bone loss. Nine studies were on sinus floor augmentation. The implant stability quotient was as a parameter of three out of these nine studies and it had a positive result.

**Conclusions:** The high heterogeneity among these studies made it difficult to give a clear conclusion. Some studies demonstrated clinical and radiographic positive effect of PRP use in implant surgery. Further studies evaluating the use of PRP on bone and soft tissue formation and implant stability remain necessary.

# 1. Introduction

The purpose of this systematic review is to report the knowledge and the effects of use platelet rich preparation with implant insertion. There were many systematic reviews in the last decade (2007-2017) about PRP were published (Lemos et al., 2016), (Pocaterra et al., 2016), (Simonpieri et al., 2012), (Agrawal, 2017), (Huang et al., 2017), (Mihaylova et al., 2017), (Rosello-Camps et al., 2015), (Panda et al., 2016), (Al-Hamed et al., 2017), (Castro et al., 2017a), (Castro et al., 2017b), (Miron et al., 2017a), (Moraschini et al., 2016). We provide an update on this topic. The aim of this systematic review is to collect and review the data from different studies and write a conclusion about the effects of PRP on implant stability, on bone preservation, and on marginal bone around the implant. In total, the initial search strategies generated 280 articles. Of the initial search 53 articles were retained for further investigation. In total 32 articles were excluded based on our search criteria. In total 21 articles were kept for further evaluation (Fig 1). Finally, 15 studies were kept for analyzing. In these articles various surgical procedures have been done before implants were inserted. Nine studies were on sinus floor augmentation.

## 1.1 Sinus augmentation

A sinus augmentation, or "sinus lift," is a surgical procedure for bone grafting methodology that is performed in the maxillary sinus. The point when a few patients need such little sums for existing bone over these regions that insert can't embed without addition structuring from claiming new bone, (Pal et al., 2012). There are two separate approaches for sinus floor elevation A) parallel antrostomy concerning illustration on offering on that one alternately two ventures methodology similarly as immediate technique. B) Osteotome system with an crestal approach similarly as indirect way (Pal et al., 2012). Toward crestal approach, there need aid of a number surgical methods similarly as a sinus lift, without interference the integument of the sinus floor, alternately toward utilizing Osteotomes, alternately by utilizing an inflatable sinus lift technique, or surgical protocol about sinus lifting throughout extraction of the upper molar, alternately by those intra-lift piezotips, alternately toward the surgical protocol from claiming intra-lift A) Get ready of the pilot gap. B) Growing of the gap, c) Push out of the membrane. D) Scattering of the graft (Cordaro, 2003).

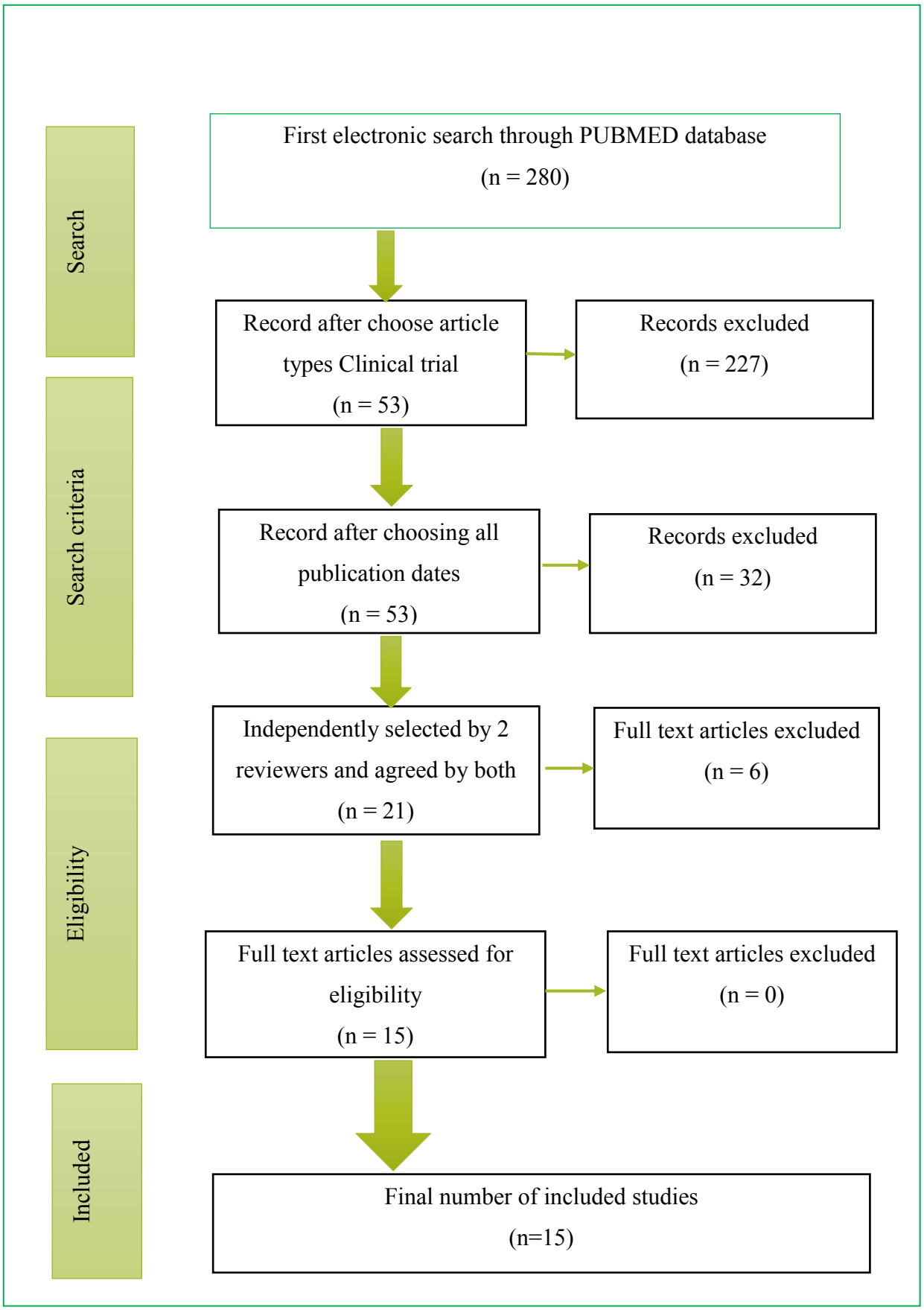


**Fig 1:** Flowchart of the screened relevant publications.

Per using parallel antrostomy a little buccal window will make on the parallel divider of the maxillary sinus, utilizing a round diamond under sterile saline watering system. The Schneiderian membrane will be divided from those inward surfaces of the maxillary sinus until those parallel dividers were totally segregated. (Gassling et al., 2013).

## 1.2 Study parameters

Depending on clinical and histological analysis of these studies, were many parameters. This systematic review described the bone defects and the results about these investigations by numbering these investigations to rearranging its examination. Each study had two groups, PRP group or test group, and a control group which required just bone graft material, without PRP preparation. Every group for these investigations had the same surgical procedure and the same specialist. The aim of this systematic review is to define the effect of PRP on osteointegration and on implant success.

## 1.3 List and description of studies included in this systematic review

1. (ArRejaie et al., 2016)
2. (Öncü et al., 2015)
3. (Hamzacebi et al., 2015)
4. (Kutkut et al., 2013)
5. (Gassling et al., 2013)
6. (Kutkut et al., 2012)
7. (Dasmah et al., 2013)
8. (Cabbar et al., 2011)
9. (Badr et al., 2010)
10. (Torres et al., 2009)
11. (Aimetti et al., 2008)
12. (Consolo et al., 2007)
13. (Thor et al., 2005)
14. (Monov et al., 2005)
15. (Raghoebar et al., 2005)

### 1.3.1 (ArRejaie et al., 2016)

Dehiscence was the bone defect of this study, which considers as one of the major bony defects. The dehiscence occurs on the buccal or palatal and lingual wall of the tooth and the most of dehiscence started from the tooth without bone loss in a interproximal area, (Nevins et al. 2006) The defect is known as “dehiscence” when the root is uncovered with bone and only covered with the overlying gingiva and periosteum, and the denuded areas extend through the marginal bone. The risk factors for these defects are age, tooth malposition, trauma, and strong occlusal forces, (Patterson et al, Weine FS et al). The outcomes in this study were marginal bone level, bone density, horizontal depth of defect at 2 mm, and at 6 mm apical to crest, defect height, horizontal bone width also at 2 mm, and at 6 mm apical the crest. Using a CBCT these parameters have been defined.

### 1.3.2 (Öncü et al., 2015)

In this study, there was no bone defect. After tooth extracted the implants were inserted. Resonance frequency measurements were made at 1 week and 1 month postoperatively after implant placement. The stability of the implants was evaluated with resonance frequency analysis (RFA). The measurements were carried out with the Osstell device (Fig 2), by connecting the transducer to the implant (Öncü et al., 2015). Initial stability at placement time (primary stability) and the development of osseointegration in the following healing process (secondary stability) were the two important factors for implant success, Al-Jetaily et al., 2011.

**Fig 2:** Osstell, Park, et al., 2009

### 1.3.3 (Hamzacebi et al., 2015)

The bone defects are infra-bony periodontal defects, buccal dehiscence, buccal and lingual dehiscence, circumferential bone resorption, horizontal bone resorption. The parameters were probing depth, clinical attachment level, amount of keratinized mucosa, mucosal recession distance between the restoration margin and peri-implant mucosal margin, presence of dental plaque along the mucosal margin, for up four peri-implant sites in each, for up to 15 seconds after gentle probing, and suppuration for peri-implant were recorded with a Michigan measuring 0.5mm in diameter (Hu-Friedy) Hamzacebi et al., 2015. The bone defect was evaluated intra-surgically and classified according to the peri-implant classification criteria proposed by Schwarz et al.( 2006).

### 1.3.4 (Kutkut et al., 2013)

This study is about bone preservation following the tooth extraction. Alveolar bone preservation following tooth extraction has the major advantage of the esthetic outcome of final restorative the extraction. The implants in this study were placed after 3 months of the grafting. Clinical parameters of the implants were checked at baseline and at 12 months after definitive restorations for pain, occlusion, and prosthesis mobility. Success criteria for implant survival were: The presence of clinical implant stability, absence of radiolucency around the implant, absence of peri-implantitis mucositis or inflammation, and absence of pain. A radiographic evaluation was reported, the parameters were mean mesial and distal bone loss. In this study esthetic outcomes were reported as changes in the position of papillae. Papillae height measurements were referenced clinically to the incisal edges of adjacent teeth and performed prior to tooth extraction and 12 months after definitive restoration(Cooper et al. 2010).

### 1.3.5 (Gassling et al., 2013)

The surgical procedure of this study is sinus augmentation which was described in this systematic review. The sinuses were grafted bone-substitute material (Bio-Oss) mixed in a 1:1 ratio with autologous bone. Due to the osteoinductive and osteoconductive properties of the

autologous bone was the gold standard for sinus floor augmentation procedures for a long time (Cordaro, 2003). Bone-substitute material Bio-Oss is a carcinogenic bone-substitute consisting of sterilized anorganic bovine bone in the form of granules with a particle size of 0.25- 2.0 mm. collagen membrane conventionally used non-cross-linked collagen membrane. Bio-Gide (porcine collagen types I and III), was used for the covering of the buccal window of the maxillary sinuses. The parameter of this study was graft specimens which were evaluated for the percentage of vital bone, and the percentage of residual graft material. In all samples the histomorphometric examination of specimens revealed vital bone of a woven type adjacent to the bone-substitute particles.

### 1.3.6 (Kutkut et al., 2012)

After extraction of teeth, eight selected patients randomly received collagen resorbable plug dressing material (control group), and eight selected patients randomly received medical grade calcium sulfate hemihydrate mixed with PRP in the extraction sockets (test group), and after 3 months later from the time of extraction (at implant surgery), socket dimensions were measured in horizontal and vertical level. The study evaluated clinical and histological outcome. Histology slides were prepared, and an examination was performed at 400 magnifications to the cores revealed a new bone formation in all grafted sockets. A new formation of vital trabecular bone was found in all the examined sections. The new bone was organized in trabeculae, with collagen fibers arranged in a meshwork pattern and a randomly distributed of osteocytes within the trabecular in large spindle-shaped lacunae. The collagen fibers in the new vital bone were arrayed in a parallel organized manner. The trabecular spaces were filled with a loose fibrous tissue with thin vessels. Denser trabecular bone patterns were observed in the test group. Other parameter was the vertical buccal wall height, which compared between both groups test and control group.

### 1.3.7 (Dasmah et al., 2013)

The osseous tissue defect was sinus atrophy, and the surgical procedure was grafted autogenous bone an onlay block and particulate osseous tissue from the iliac crest, tip have been used in sinus-lift procedure in order to rehabilitate patients with extremely resorbed maxillae. After elevation of a full thickness flap via a midcrestal incision and vulnerability of

the upper jaw bone, a cortical window was outlined on the front-anterior aspect of the maxillary sinus wall bilaterally. The Schneiderian membrane was gently lifted and pushed medially together with the bony window. Particulate bone mixed with PRP was placed and compressed in the anterior and lower part of the left maxillary sinus and the right side was grafted with the same procedure, using particulate bone without PRP in the control group, and with PRP in the examination group. The parameter in this study were men of marginal bone, resonance frequency analysis, stability of alveolar consonant implant both at positioning and during function is an important criterion for the success of dental implants. Quantitative methods, including RFA can yield valuable information (Nystrom et al., 1996).

### 1.3.8 (Cabbar et al., 2011)

The purpose of this study was to compare Unilab Surgibone (USB) (Mississauga, Ontario, Canada), a bone xenograft (bovine) with PRP use and USB without PRP to augment the human maxillary sinus in preparation to receive dental implants. Bone defect was sinus atrophy. Parameters were the amount of soft tissue, residual graft material, new bone, the trabecular bone volume, and the mean ISQ values which were compared between both groups.

### 1.3.9 (Badr et al., 2010)

The bone defect was sinus atrophy, and the surgical procedure in this study was maxillary sinus grafted with particulate bone (lateral window approach) with iliac crest bone. Outcome measures were implanted integration, implant stability, soft tissue healing, graft resorption. Implant stability measurements were recorded at placement and exposure using a resonance frequency analysis device. Patients were followed up to abutment connection.

### 1.3.10 (Torres et al., 2009)

This study evaluated whether or not PRP improves the efficacy of anorganic bovine bone in sinus floor augmentation. The maxillary sinus-lift surgical technique increases the bone height in the posterior area, and enables the placement of implant-supported prostheses (Tatum, 1986). The osteotomy of the lateral wall of the maxilla was performed under local anesthesia, and the entire buccal wall was removed before the elevation of the sinus membrane and the

implantation of the assigned graft material. No membranes were used to cover the lateral wall defect after the bone substitute was placed. In the two-stage sinus augmentation procedure, a healing time of 6 months was allowed before implant placement (Zinner et al., 1996). The parameters were implant survival, which was defined as the implant remaining in situ during the entire observation period, and treatment success rate which was defined as the rate of patients that presented no complications during the observation period. Another parameter in this study was residual bone height mobility. We found differences between the one- and two-stage surgery groups, indicating that the residual height could affect the survival rate. The other parameter of this study was a histomorphometric analysis, which was performed only on 5 patients.

### 1.3.11 (Aimetti et al., 2008)

The surgical procedure was a sinus augmentation after sinus atrophy and finally implants insertion. The parameters were clinical and radiographic healing patterns, histology and histomorphometry, marginal bone loss in the first year, bone implant contact (BIC).

### 1.3.12 (Consolo et al., 2007)

The surgical procedure is overlap flap, a modification of the original Langer et al. (1990), technique. Tatum (1986) was performed to gain access to the maxillary sinus and to prepare it for the floor augmentation. The modification for the most part consisted in an incision effected distant from the sinus access, which guarantees a wide coverage of both the grafting site and alveolar ridge. Moreover, surgery was planned to avoid ostium obstruction (Langer et al. 1990). Five and six months after surgery, the histological differences between autologous bone grafts and bone plus PRP were not only less noticeable but sometimes even reversed (Consolo et al., 2007). The clinician aims to preserve an adequate and viable bony mass (architecture and volume) to meet implant-prosthetic requirements. Biopsy hounsfield units densitometric values were taken from sinuses before and after augmentation. The parameters were densitometric values and histology documents with bone activity.

### 1.3.13 (Thor et al., 2005)

In this study a particulate autogenous bone were grafted in maxillary sinuses, the right side without PRP and the left side with PRP. The left side of the anterior maxilla was grafted with particulate bone graft with PRP and the right side with bone blocks without PRP. In addition, 10 of the patients received particulate bone grafts to the floor of the nose on the left side with PRP (test group) and the other side without PRP (control group). After 6 months of healing dental implants were placed, and abutments were connected after another 6 months. After 1 year the patients were finally examined of loading. The parameters in this study were histology, resonance frequency analysis, and marginal bone level measurements. The stability of the dental implants was assessed by RFA (Osstell).

### 1.3.14 (Monov et al., 2005)

Using a one-stage surgical protocol, a total of 34 Branemark Mk-III Ti-Unite implants with a length of 13mm and a diameter of 3.75mm were inserted in 10 edentulous mandibles (Monov et al. 2005). Radiographic examinations jaw bone density and quantity were judged from preoperative radiographs and during drilling, according to the classification of (Lekholm). The RFA values of implant stability were high in the mandible and showed minor differences from the day of implant placement until the end of study period.

### 1.3.15 (Raghoebar et al., 2005)

This study evaluated the use of PRP on sinus floor augmentation using autologous bone graft from iliac crest. A biopsy after one month from bone grafting were taken using a trephine from the arranged insert locales (N = 30) to evaluate the new bone formation. A camera was linked to a personal computer equipped with a frame grabber. The magnified microradiographs were stored as images with a size of 640 to 480 pixels and with a resolution of 256 (gray) values ranging from 0 (white) to 256 (black). The parameter was the average density on the microradiographs at the first premolar and first molar region. All sections were studied to evaluate bone-marrow light microscopically on the following items: quality of bone biopsy, ratio, bone-bone marrow, a type of bone marrow when there were no connective tissues), the presence of hematopoietic tissue, presence of bone formation, and presence of bone cell and resorption. A biopsie was been taken for a histomorphometric analysis using

Leica Qwins image analysis software (Leica Microsystems Image Solutions, Leica, Switzerland). The biopsy was been taken in posterior area no density data has been derived because light microscopic evaluation.

## 1.4 Platelet rich plasma (PRP)

According to Harrison et al. (1993) the platelets are part of cytoplasmic of megakaryocytes, which formed in the marrow and its diameter is 2 μm it contains more than 30 bioactive proteins, many of it have a main role in tissue healing or hemostasis (Schilephake, 2002).

### 1.4.1 Classification

As stated by the arrangement suggested toward Dohan Ehrenfest et al., 2009. Four primary groups for arrangements can be defined, relying upon their mobile substance also fibrin construction modeling.

1. Immaculate (P-PRP) or leucocyte-poor PRP results are arrangements without leucocytes what's more with a low-thickness fibrin organize actuation.
2. Leucocyte- and PRP (L-PRP) products are preparations with leucocytes and with a low density fibrin network after activation. It is in this group that the largest number of commercial or experimental systems exists. Many protocols have been developed in the last years, for simplify the handling a specific kit was required, that allows maximum standardization of the preparation and minimum handling of the blood samples.
3. A leucocyte-poor platelet-rich fibrin preparation or pure platelet-rich fibrin (P-PRF) are without leucocytes and with a high-density fibrin network. Without traditional fibrin glues these products cannot be injected or used because it is existed only in a strongly activated gel form.
4. According to Dhurat et al. ( 2014) leucocytes with a high-density fibrin network (L-PRF) or second-generation PRP products will be prepared.

### 1.4.2 PRP vs PRF

According to Kobayaschi et al. (2016) study, which compares growth factor release over time from platelet-rich plasma (PRP), and platelet-rich fibrin (PRF), the results show that the advantage of PRP is the release of significantly higher proteins at earlier time points whereas

PRF displayed a continual and steady release of growth factors over a 10-day period. Furthermore, in general, it was observed that the new formulation of PRF (A-PRF) released significantly higher total quantities of growth factors when compared to traditional PRF. Based on these findings, PRP can be recommended for fast delivery of growth factors whereas a PRF is better-suited for long-term release. The preparation of PRP requires the addition of anticoagulants like a bovine thrombin during initial blood collection in opposite of PRF which obtained by centrifugation without anticoagulants, and is therefore strictly autologous. According to Choukroun the time of preparation and cost of preparation are both significantly lower as PRF does not necessitate the direct activation with additional factors such as bovine thrombin or extrinsic anticoagulants.

### 1.4.3 PRP proteins

According to Dhurat et al. (2014) fibrin, fibronectin and vitronectinwhich already were included in PRP as three proteins in blood known to act as cell adhesion molecules, PRP is obtained from a sample of patients' blood drawn at the time of treatment. A 30 cc venous blood draw will yield 3-5 cc of PRP depending on the baseline platelet count of an individual, the device used, and the technique employed.

### 1.4.4 PRP preparation

Differential centrifugation of PRP is the way to prepare it, by this process acceleration force is adjusted to sediment certain cellular constituents based on different specific gravity (Dhurat et al. 2014). Buffy-coat method is one of many ways of preparing PRP. It can also be prepared by the method an initial centrifugation to separate red blood cells is followed by a second centrifugation to concentrate platelets, which are suspended in the smallest final plasma volume. In (Fig 3), flow chart describes a double centrifugation process of PRP. In a tube, a whole blood was collected that contain anticoagulants to start with turn venture may be performed at consistent acceleration on differentiating RBCs from those remaining WB volumes. Following the primary turn step, the WB separates under three layers an upper layer that holds mostly platelets and WBC, an intermediate dainty layer that is known as the buffy cover also that is rich in WBCs, and a lowest part layers that comprises mostly from claiming RBCs for the processing from claiming (P-PRP), upper layer also shallow buffy cover need

aid exchanged with a void sterile tube. To the handling about (L-PRP), that whole layer about buffy covered the few RBCs which needs aid exchanged. The second spin step is then performed. For the second spin which should be just adequate to aid in formation of soft pellets (erythrocyte-platelet) at the bottom of the tube. The upper portion of the volume that is composed mostly of PPP is removed. Pellets are homogenized in lower 1/3rd (5 ml of plasma) to create the PRP.

*Buffy coat method*

1. The 20°C to 24°C temperature is required for whole blood centrifugation.
2. High speed is a condition for centrifugation.
3. Three layers are formed because of its density: 1. The bottom layer consisting of RBCs.2. The middle layer consisting of platelets and WBCs. 3. The PPP layer at the top.
4. Remove supernatant plasma which exists in the top of tube.
5. Transfer to another tube.
6. Use leucocyte filtration filter.

According to Scherer et al. (2012) exactly creators initiate platelets for thrombin or calcium, while others apply platelets without being formerly activated, contending that better effects need aid obtained. However, there were different variables with respect to these various protocols have been optimized the preparation of PRP. The process, such, number of spins, time period of centrifugation, as volume and sampling of processed whole blood and range of centrifugal acceleration. Despite these variations, all protocols follow a generic sequence that consists of blood.

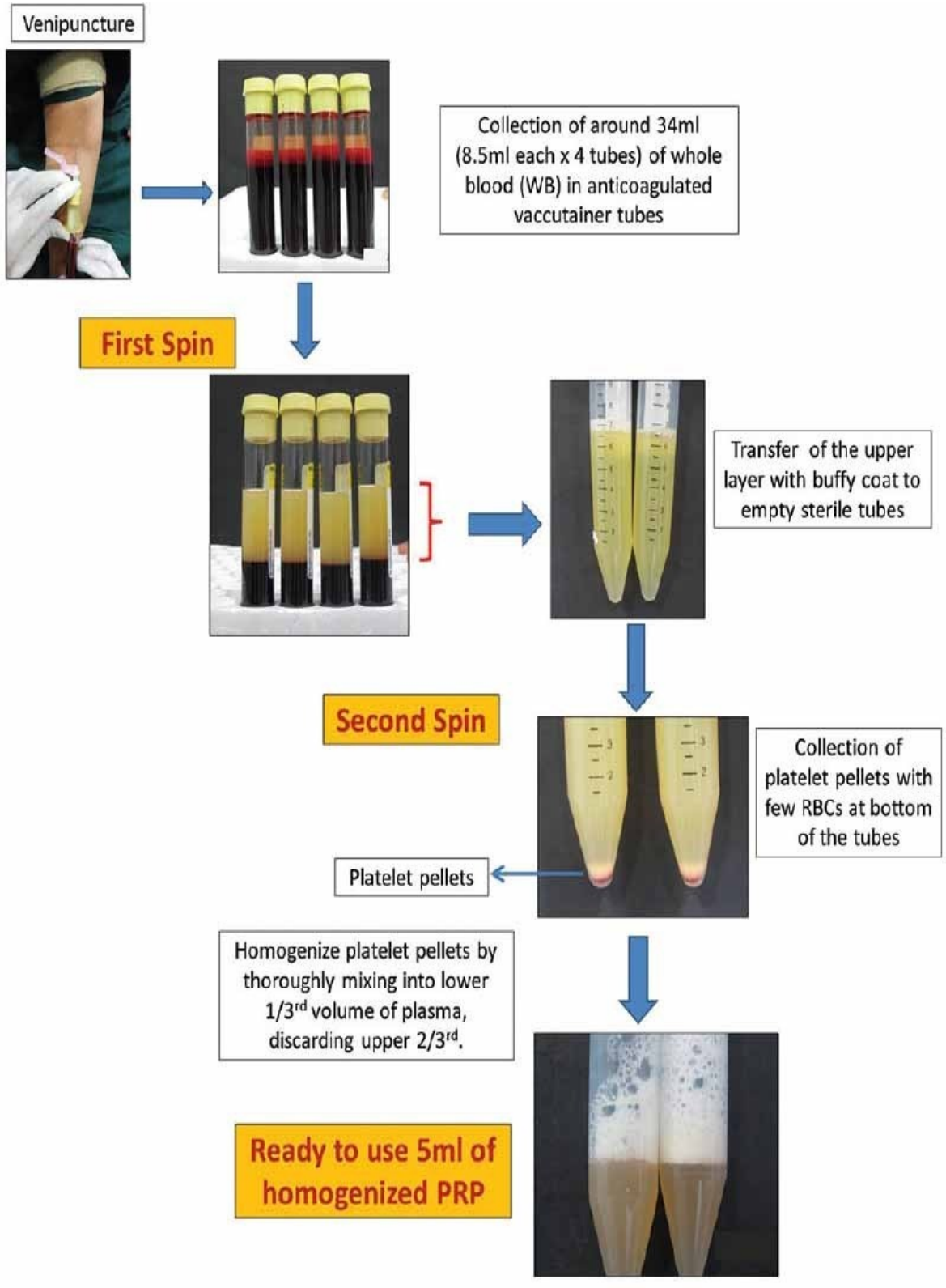


**Fig 3:** Flowchart describing preparation of PRP Dhurat et al. ( 2014) Buffy coat method

According to Amable et al., (2013) an initial centrifugation is needed to separate RBCs, subsequent centrifugations to concentrate platelets, and other components and also an activation of the sample is needed by adding a platelet agonist. This Study studied variations as a relative centrifugal force, temperature, and time for optimizing conditions for platelet isolation and also quantification of cytokines and growth factors in PRP before and after platelet activation.

### 1.4.5 Procedure of PRP standardization

To obtain an optimum PRP concentrate there are many factors influence PRP yield. The following points are helpful in Dhurat et al.( 2014) study.

1. Draw blood in anticoagulant vacutainer tubes using Eclipse blood collection needle (Ref: 368607; BD Biosciences, India), (Fig 4.)Set separated 1-2 ml to benchmark mobile numbering including RBCs, platelets, WBCs and hematocrit. Contributor percent hematocrit (the proportion of the volume from claiming RBCs of the downright volume about blood) will be pertinent with plasma yield streamlining. Blood with a low percent hematocrit needs more plasma accessible thereby diluting the fixation for platelet-rich-plasma.

**Fig 4:** Venipuncture using BD Eclipse blood collection needle Dhurat et al. ( 2014).

2. Blood specimens that are gathered clinched alongside tubes ought further bolstering be altered 5-10 times the fitting blending of the anticoagulant. Assuming that tube is not mixed little fibrin clots might form, making a dishonestly diminished platelet check.
3. After first spin, measure the platelet check over RBCs and the supernatant to guarantee ideal detachment from claiming platelets starting with the whole blood.
4. Assuming that this doesn't happen, change the parameters such as rpm and time.
5. Following initial spin, if big volume of plasma is obtained, that point it might require higher speed velocity.
6. After the second spin, measure that platelet check for PPP and PRP after enough racking the tubes.
7. If high or low concentration of platelets then the parameters are not optimal.
8. According to Schilephake et al, (2002) study the PRP must be divided from the PPP soon after centrifugation because the concentrated platelets will slowly diffuse into the PPP over time and would reduce the platelet count of the PRP preparation.
9. According to Amable et al., (2013) to numbering those platelets in the last PRP concentrate it must be re-suspended to no less than 5-10 min on considering rise to circulation from claiming platelets in front of numbering.

## 1.5 Endpoints

Although all these studies have the same topic which was to compare between the use or not of PRP preparation during surgical procedures, and implant insertion. The endpoints of these studies were different. It has been differed depending on surgical procedures, and parameter or outcomes that have been measured. These studies have different analysis, radiography, clinically, histology and histomorphometer. In ArRejaie et al. (2016) study the parameters were taken using cone beam computer tomography, horizontal depth of defects at 2, 6 mm apical the crest determined from the outermost labial surface implant or bone to the outline of the implant fixture. The clinical parameters were defect height, horizontal depth of the defect, horizontal bone width, horizontal bone width at end of the implant, with using radiography parameter could the author compare the mean marginal bone loss at the mesial and distal sites between both groups (PRP, without PRP). The endpoint of the second study, Öncü et al.

(2015) was comparing implant stability quotient at the end of the fourth week between both groups. The third study Hamzacebi et al. (2015) were probing depth (PD) >5mm, and radiology, bone loss>2mm using the implant abutment as reference, clinical attachment level, amount of keratinized mucosa, mucosal recession distance, between the restoration margin and peri-implant mucosal margin, presence of dental plaque along the mucosal margin, blood of probing for up four per-implant sites in each implant, for up to 15 seconds after gentle probing, and suppuration for peri-implant.

The parameter of fourth study Kutkut et al., (2013) where the success criteria for implant survival, which were clinical implant stability, absence of radiolucency around the implant, absence of pain. The endpoint was Papilla height measurements were referenced clinically to the incisal edge of adjacent teeth. Average papilla recession for mesial and distal site in the one year follow up. The radiology evaluation was the vertical bone loss which radiology assessed between both groups. The endpoint of fifth study Gassling et al., (2013) were histomorphometry, which evaluated the percentage of vital bone, and the percentage of residual graft material. For endpoints of the sixth study, Kutkut et al., (2012) a histomorphometric analysis was performed on three fields for each section using specialized software. The study parameters were percentages of vital bone and also mean value of the newly formed vital bone. The clinical measurements were soft-tissue healing of the grafted areas was uneventful and visually assessed. Other endpoints were the difference in radiographic measurements for mesial and distal vertical bone resorption.

The seventh study Dasmah et al., (2013) endpoints were the mean marginal bone levels in the first year, and after 5 years. The eighth study Cabbar et al., (2011) endpoints were histomorphometric measurements using a computer and software performed in the 3 zones. The volumes of soft tissue (percentage of soft tissue area total measured area), new bone formation (percentage of newly formed bone area to total measured area), the correlation between new bone volume and trabecular bone volume (percentage of graft particle area to total measured area), ISQ, which measurements were performed with the Osstell Mentor the arithmetic mean of the 3 values was recorded as the ISQ value, the mean height of the residual alveolar crest. The Badr et al., (2010) study parameters were gingival healing index used score 4 = excellent healing with pink gingiva, no bleeding, no granulation tissue, and no

dehiscence; score 3 = good healing with only slight to moderate gingival redness; score 2 = poor wound healing with significant erythema bleeding on palpation, granulation or dehiscence; score 1 = very poor healing with suppuration and or spontaneous bleeding. The other endpoint of this study was implanted stability quotient. Torres et al., (2009) endpoints were implanted survival, and residual bone height. The Aimetti et al., (2008) study parameters were bone implant contact, which was calculated as the ratio between the implant length in direct contact with newly mineralized bone and the total implant length. The Consolo et al., (2007) study parameters were densimetric values and histology documents with bone activity (mean trabecular bone volume approximately). Thor et al (2005) study parameters were mean marginal bone, and implant stability question. Monov et al., (2005) study parameters were (ISQ) values for implant stability. Raghoebar et al., (2005) study parameters were the average area occupied by bone in augmentation area.

## 2 Existing Systematic Reviews on Plates and Dentistry.

Although there were many systematic reviews about PRP preparation and dental implant, they are no longer up to date, and not all studies analyzed the use of PRP in hard and soft tissue augmentation, and implant success. Although many studies showed that the application of PRP in implant placement enhance the implant stability, but there was no definitive recommendation to use PRP. Our systematic review collected all relative studies related the use of PRP with implant, and soft, and hard tissue augmentation, many bone defects, and many surgical procedures which give our systematic review its advantage and its strength.

Castro et al., (2017)a, and Castro et al., (2017) b, systematic reviews, both of them consider as a good systematic review, but they took a part of defect. Part A was about the regenerative potential of leucocyte- and platelet-rich fibrin L-PRF during periodontal surgery, and part B was about the effect of L-PRF on bone regeneration procedures and osseointegration, and this theme considers as a very important in dental implantology field, but still a narrow way to talk about the benefits of PRP. Another good systematic review I would like to introduce it is Miron et al., (2017) review, which is a new one, and has been searched in (PRF) and soft tissue wound healing, part of it in vitro, in vivo, and clinical literature utilizing PRF for soft tissue regeneration, augmentation, and/or wound healing. In this study there was no implant

has been used, no hard tissue augmentation, it focused only on one soft tissue defect. Miron et al., (2017) systematic review was about PRF in regenerative dentistry, human good studies were selected, but the difference between our systematic review and this one is the use of implants. Moraschini et al., (2016) chose PRF in treatment recession to conducted his systematic reviews on 7 RCTs, but the end conclusion was, that PRF membranes did not improve the KMW, or CAL in the treatment of Miller Class I and II gingival recessions compared with the other treatment modalities, this opens the door for new systematic reviews. Lemos et al., (2016) systematic reviews evaluated the effect on bone formation and implant survival of combining PRP with bone grafts in maxillary augmentation, he ended up with 13 studies about focus in hard tissue and implant survival, without any mention of soft tissue effect, which can be affected the surgical procedure the total study results.

Pocaterra et al., (2016) gave also a good review. The studies included in his systematic reviews, and meta- analysis were 6 studies, its parameters were bone to implant contact, and histomorphometric parameter was bone formation at least 3 months after the bone graft. The clinical parameter was implant survival at least 12 months after implant insertion at the patient and implant levels. Although that this systematic reviews, analysis studies about bone augmentation procedures, such as the sinus lift technique, and implant survival, but it has missed the aspect of soft tissue parameter, that was a motivation for us to do our systematic reviews. Simonpieriet al., (2012) published knowledge about the role of PRP and PRF in implant placement as surface treatment for the stimulation of osseointegration, the treatment of peri-implant bone defects like peri-implantitis, during implantation in an insufficient bone volume or during the immediate post-extraction or post ovulation implantation, the sinus lift procedures and various complexes implant-supported treatments, also like the previous systematic reviews, there were not enough parameters and results to prove or not the effects of PRP, which always create the need of new systematic reviews, which gave our review the justification to conduct it.

Agrawal et al., (2017) review there was no comparing between use or not the PRP, no control or test group. The author focused on compilation of different platelet concentrates, their discovery and different protocols available. It was a descriptive review, which was completely different from our review. Huang et al., (2017) presented a new idea, which was the effect of

PRP in neural degeneration. Its hypothesis was that after teeth extraction mechanoreceptors in the periodontal ligament are subject to immediate degeneration. A novel idea to stimulate peripheral nerve regeneration after tooth loss would be to add a multitude of growth factors from autologous PRP together with an implant placement immediately after tooth extraction to overcome degenerative neural processes. The topic of this systematic review was completely different from ours, which gave us also another justification to conduct a new one. Mihaylova et al., (2017) overview was about present work employs an extensive critical overview of the literature on the development and application of platelet concentrates. The topic of this overview also was completely different from ours.

Rosello-Camps et al., (2015) systematic review aim was to assess the influence of PRP on the regeneration of periodontal intra-bony defects the author evaluated the means of radiographic and clinical outcomes in prospective human clinical trials, which was considered as a good review, and were similar with ours, but the author selected studies about periodontal intra-bony defects without the use of implant or hard tissue augmentation, and that was evaluated in our systematic review. However, this review evaluated 18 good articles about periodontal defects, although it had soft and hard tissue parameters, still the main focus on periodontal parameters the hard tissue parameter were as attachment parameters to evaluate the periodontal defects.

Panda et al., (2016) systematic review evaluated 15 articles about the additive effect of autologous platelet concentrates (APCs) in treatment of intra-bony defects when used along with other regenerative procedures and when used alone in clinical and radiological outcomes. In Panda et al., (2016) study there was no implant had been inserted in those articles that has been evaluated in this systematic review, this consider the main difference between our systematic review and this one. Al-Hamed et al., (2017) systematic reviews evaluated 5 studies on the effects of PRF after mandibular third molar extraction, its parameters were alveolar osteitis, periodontal pocket depth, bone healing. This was a simple review, with few aspects, which created the need for further systematic reviews. Finally, always still a need for new studies, our goal was to highlight the effects of PRP, and to be like a basis stone for further studies.

# 3 Materials and Methods

## 3.1 The study's eligibility criteria

A detailed protocol including all aspects of a systematic review methodology was developed prior to initiation of this review. A search on PubMed database was performed using the following criteria: platelet* AND dental implants AND human. This initiated search gave 280 hints (May 2017). After the selection of article types: Clinical trial, the number of studies, which were subject to these criteria is 53 studies. Abstracts will be screened for articles on controlled clinical studies. The relevant papers will be analyzed for the following criteria: (i) number, age and gender of patients; (ii) clinical indication; (iii) method of platelet preparation and application; (iv) observation period; (v) clinical outcome parameters. The data will be presented in a table. Considering the different study designs, it is unlikely to perform a meta-analysis. This protocol included PICO definition: (patient, intervention, comparison, outcomes) question.

## 3.2 PICO question

Population (patients) (P) = systematically healthy human in need of implant with (hard or soft) tissue augmentation, or socket preservation.
Intervention (I) = Surgery dental treatment (bone or soft tissue augmentation, socket preservation, implant insertion).
Comparison (C) = defined the different treatments with/ without use of PRP.
Outcome (O) = implant success, soft or hart tissue gain, implants stability.

## 3.3 Defining the focused question

The following focused question was defined: "Does the use of platelet preparations enhance the outcome of dental implants therapy?"

## 3.4 Search strategy

A Medline (PubMed) search was performed for human studies, including all articles published on (PubMed) without limiting in publication dates. The English language was a

condition for included studies. The search was complemented by manual searches of the reference list of all selected full-text articles. In addition, full text articles of reviews published in the same time period were obtained. A double check was performed by two authors.

## 3.5 Search terms

The following search terms were selected: “platelet* AND dental implants AND human.

## 3.6 Inclusion criteria

The systematic review selected only clinical trial studies with implant insertion. Studies published in English, describing the human clinical evaluation of PRP for the above-indicated search strategies.

## 3.7 Exclusion criteria

Studies not meeting all inclusion criteria were excluded from the review. Pre-clinical (animal) studies, studies without control groups, studies with a low number of patients if is no good, not clinical trial studies, no implant has been inserted, interviews and charts were excluded from the review as well studies were excluded not meeting all inclusion criteria.

## 3.8 Selection of studies

Studies derived from this broad search were independently screened by two authors (RG, LH) Disagreements were resolved by discussion, based on the inclusion criteria. The abstracts of all titles that has been agreed on by both authors were obtained, and screened for meeting the inclusion criteria. Finally, the selection based on inclusion, exclusion criteria were made for the full-text articles. For this purpose, materials and methods, results and discussion of these studies were screened by two reviewers, (Thoma et al., 2015)

## 3.9 Data extraction

Two reviewers independently extracted the data using data extraction tables. Any disagreements were resolved by discussion aiming for consensus, (Thoma et al., 2014).

# 4 Quality assessment

A quality assessment of the included RCTs and controlled clinical studies was performed independently by two reviewers (RG, LH). All variables were analyzed in each study, and classified into subgroups.

# 5 Statistical analysis

No meta-analyses could be performed due to heterogeneity in between the studies (different indications, control groups, observation periods, study designs).

# 6 Selected studies

## 6.1 Exclusion of studies

The first search gave 280 studies. After choosing clinical trial in article type filter. We end up with 53 studies. The full text evaluation was conducted on these 53 studies. From these 53 studies 32 studies were excluded depending on include criteria. Details are provided in Table 1.

**Table 1. Excluded studies with reason for exclusion**

| Author | Reason for exclusion |
|---|---|
| 1. (Movahedianet al., 2017) | No implant has been used |
| 2. (Taschieri et al., 2016) | No control group |
| 3. (Kanayama et al., 2016) | No control group |
| 4. (Periayahet al., 2015) | No control group, No implant has been used |
| 5. (Thomaet al., 2015) | Animal study |
| 6. (Eskanet al., 2014) | No implant has been used |
| 7. (Lorean et al., 2013) | No control group |
| 8. (Amorfiniet al., 2013) | Different used material between groups |
| 9. (Korpiet al., 2013) | No control group |

| | |
|---|---|
| 10. (Saini et al., 2013) | No implant has been used |
| 11. (Inchingolo et al., 2010) | No control group |
| 12. (Jayakumar et al., 2011) | No implant has been used |
| 13. (Torres et al., 2010) | Different bone materials |
| 14. (McAllister et al., 2010) | No implant has been used, no control group |
| 15. (Nevins et al., 2009) | No control group |
| 16. (Nevins et al., 2009) | Many groups with different bone materials |
| 17. (Griffin et al., 2009) | No implant has been used |
| 18. (Nevins et al., 2009) | No control group |
| 19. (Yamada et al., 2008) | No control group |
| 20. (Ueda et al., 2008) | No control group, no PRP |
| 21. (Lee et al., 2008) | No control group |
| 22. (Schaaf et al., 2008) | No control group |
| 23. (Filho et al., 2007) | No control group |
| 24. (Anitua et al., 2007) | Animal study |
| 25. (Steigmann et al., 2005) | No control group |
| 26. (Bettegaet al., 2005) | Article in French language |
| 27. (Gelbartet al., 2005) | No control group |
| 28. (Kassoliset al., 2005) | Different material used between both groups |
| 29. (Basa et al., 2005) | No PRP |
| 30. (Robionyet al., 2002) | No control group |
| 31. (Froumet al., 2002) | No control group |
| 32. (Anitua et al., 1999) | No control group |

## 6.2 Included studies

From 21 studies that met the inclusion criteria 15 were selected and presented in Table 2

**Table 2. Included studies with reason for exclusion**

1. (ArRejaie et al., 2016)
2. (Öncü et al., 2015)
3. (Hamzacebi et al., 2015)

4. (Kutkut et al., 2013)
5. (Gassling et al., 2013)
6. (Kutkut et al., 2012)
7. (Dasmah et al., 2013)
8. (Cabbar et al., 2011)
9. (Badr et al., 2010)
10. (Torres et al., 2009)
11. (Aimetti et al., 2008)
12. (Consolo et al., 2007)
13. (Thor et al., 2005)
14. (Monov et al., 2005)
15. (Raghoebar et al., 2005)

## 6.3 Final excluded studies by eligibility

**Table 3: Excluded studies with reason for exclusion**

| Author | Reason for exclusion |
|---|---|
| (Mozzatiet al., 2015) | No data, only classifications |
| (Angelo et al., 2015) | Only descriptive, no data |
| (Ntouniset al., 2015) | A lot of indicators, cannot be compared |
| (Forni et al., 2013) | Only descriptive, no data |
| (Nagataet al., 2012) | Only descriptive, no data |
| (Wiltfanget al., 2003) | Only descriptive, no data |

# 7 Results

## 7.1 Search outcomes

The initial search strategies generated 280 articles. After determining clinical trial criteria, 53 abstracts were retained for further investigation. From those, 53 articles were included in the full text review. 32 articles were excluded after full text screening, which was conducted independently by two reviewers (R.G., L.H.). The included articles were classified into subgroups, depending on the indication for the use of PRP (Tables):

1- Sinus floor elevation procedures n = 9, (Gassling et al., 2013), (Dasmah et al., 2013), (Cabbar et al., 2011), (Badr et al., 2010), (Torres et al., 2009), (Aimetti et al., 2008), (Consolo et al., 2007), (Thor et al., 2005), (Raghoebar et al., 2005)
2- Implant therapy: n = 2, (Monov et al., 2005), ( Öncü et al., 2015)
3- Alveolar ridge preservation: n = 2, (Kutkut et al., 2013), (Kutkut et al., 2012).
4- Implant with filling defects n = 1, (ArRejaie et al., 2016).
5- Treatment of peri-implantitis defect n =1, (Hamzacebi et al., 2015).

The total number of patients that were enrolled in the selected studies were 262, 149 were in sinus floor elevation studies, and 27 patients were in implant therapy studies, and 32 patients were in alveolar ridge preservation studies, and 35 patients were in implant with filling defects studies and 19 patients were in treatment of peri-implantitis defect studies. Various clinical studies outcomes were summarized in 1-5 Tables into subgroups depending on their common results. Most of these studies have more than one endpoints or parameter, for this, each study can be in more than one subgroups. Five out of the fifteen studies evaluated the use of PRP in peri-implant regeneration, sinus augmentation, and also in peri-implant bone loss respectively (ArRejaie et al., 2016), (Aimetti et al., 2008), (Raghoebar et al., 2005), (Cabbar et al., 2011), (Hamzacebi et al., 2015). These studies evaluated the effect of use PRP on peri-implant regeneration, bone height, and, new bone formation. The first study showed that the use of PRP could be successfully applicable for the treatment of dehiscence around an immediate dental implant (ArRejaie et al., 2016). The results of use PRP were significant for the primary outcome regarding bone fill, as well as the marginal bone level.

Nine out of the fifteen studies evaluated the use of PRP in sinus floor elevation, in same studies the results of bone quality were not significant, and seemed to be equal at both sites of the grafted sinuses, coverage of the lateral window with two different absorbable membranes had shown a similar amount of vital bone formation in both sites, (Gassling et al., 2013), and (Dasmah et al., 2013), studies showed that the change between use of PRP or not in sinus augmentation sites was not statistically significant. Moreover, in (Gassling et al., 2013) study a significantly higher degree of marginal alteration was during the first year of loading, compared with the examinations results after 5 years. In (Cabbar et al., 2011), the mean height of the residual alveolar crest was 5.6 ±1.4 mm in the control group and 4.7 ± 1.3 mm in

the study group, with no significant difference (P > .05), and no statistically significant differences were found between the two groups regarding soft tissue volume, new bone formation, residual graft volume, and trabecular bone volume (P >.05), also no statistically significant differences were observed between first and second controls and the mean differences in ISQ values between groups (P > .05).

In Badr et al., (2010) also there were no statistically significant differences observed for soft tissue healing indices (P = 0.4) and mean graft resorption (P = 0.5) between groups. All implants were found clinically integrated at time of exposure, and also there were no statistically significant differences in implant stability observed between groups at implant placement (P = 0.059). However, this difference was not clinically significant. In another hand (Torres et al., 2009) had found that the histological and histomorphometrical analysis in the bone augmentation was significantly higher in sites treated with PRP (p<.05), but the results did not show significant differences between densimetric values of the augmented areas between both groups. Other study showed that a higher bone-to-implant contact rate was observed on the implants was placed in bone and PRP than on those were placed in bone only. Aimetti et al., 2008, there were no clinically and radiographic differences between both groups after 5 years. Consolo et al., (2007) the clinical performance across both sites showed no statistical significance, but the densimetric values were higher at PRP sites (mean Hounsfield units almost + 57%), and the histology documents enhanced bone activities in sites treated with PRP, 4 months after surgery. A reduced bone activity was observed in both sites 5, 6 and 7 months after surgery. Bone amount, higher in sites treated with PRP, but decreased in both sites over time.

Another reported advantage to the use of PRP were tendency toward less resorption on PRP sites. RFA measurements showed statistically significantly higher implant stability quotient values for PRP sites at abutment connection in the anterior, but not in the posterior regions Thor et al., (2005). In another hand, the same study showed no significant differences of marginal bone level measurements. These results showed that it seems to be a different effect of PRP use depending on surgical area. Anyway, that increases the need for further studies to prove the effect of PRP. In Raghoebar et al., (2005) sinus augmentation in his systematic review showed that no beneficial effect of PRP on wound healing and bone remodeling was

observed. This study was posed that PRP has no additional value in promoting healing of grafted non-critical size defects.

## 7.2 Data extraction

The outcomes are: HDD from crest, DH, HBW, bone density mesial, bone density distal, ArRejaie et al. ( 2016). Mean ISQ in 4 weeks vs in 1 week Oncu et al. (2015). BOP, PD more at 5 mmm, radio bone lose more than 2 mm, CAL, KM, RC, PL, Hamzacebi et al. (2015). Esthetic papilla height measurements, Kutkut et al. (2013). Bleeding, mucosal recessions, PD, X-rays Gassling et al. ( 2013). MidM overall, differ ratio mesial, distal, histomorphometric analysis Kutkut et al. (2012).Stability of implant, RFA immediately Dasmah et al. (2013). Soft tissue residual graft, new bone, trabecular bone, mean ISQ second control. Ridge width, soft tissue healing index, RFA, average ISQ, Badr et al. (2010). Histological, histomorphometic analysis after 6 month, Torres et al. (2009). Vertical bone height, Aimetti et al.(2008). TBV Consolo et al. (2007). The mean marginal bone level mm, Thor et al. (2005). RFA Monov et al. (2005). Histomorphometrical (%; mean +SD), Raghoebar et al. (2005), follow-up also differed substantially, therefore a comparison between studies was difficult.

**Table 4: Effect of PRP on peri implant regeneration, bone height, new bone formation**

| Autor | Defect | Surgical protocol | Patient no. | Split mouth | Groups | Finaloutcome | Month | P Value |
|---|---|---|---|---|---|---|---|---|
| (ArRejaie et al., 2016) | Dehiscence | filling of defects | 16 | Yes | BioOss | HDD6 = 3.62±0.04 | | |
| | | | | | BioOss & PRP | HDD6 = 4.53±0.03 | 12 | .01 |
| | | | | | BioOss | DH = 1.87 ±1.04 | | |
| | | | | | BioOss, PRP | DH = 1.02 ±0.20 | 12 | .01 |
| | | | | | BioOss | HBW6 = 4.02±0.23 | | |
| | | | | | BioOss, PRP | HBW6 = 4.98±0.14 | 12 | .01 |
| | | | | | BioOss | HBWE = 4.52±0.408 | | |
| | | | | | BioOss, PRP | HBWE = 4.82±0.480 | 12 | .536 |
| (Aimetti et al., 2008) | Atrophy | sinus augmentation | 4 | Yes | Autogenousbone | BH = 1.95± 0.682mm | | |
| | | | | | Autogenous & PRP | BH = 2.13±0.63 mm | NA | NA |
| (Raghoebar et al., 2005) | Atrophy | Sinus augmentation | 5 | Yes | Autologous | BA = 41.1 ± 8.3% | | |
| | | | | | Autologous & PRP | BA = 38.4± 11.3%, | 3 | P>0.05 |
| (Cabbar et al., 2011) | Atrophy | Sinus augmentation | 10 | Yes | USB | VST = 57.8 ± 4.4 | | |
| | | | | | USB & PRP | VST = 59.9 ± 7.5 | 6-8 | NA |
| | | | | | USB | MHRAC = 5.6±1.4 | | |
| | | | | | USB & PRP | MHRAC =4.7±1.3 | 6-8 | P>0.05 |
| (Hamzacebi et al., 2015) | peri-implantitis | Access flap | 19 | Yes | Impl | REC (%)-0.20 ± 0.32 | | |
| | | | | | Impl & PRF | REC (%) 0.49± 0.51 | 6 | P<.001 |
| | | | | | Impl | KM (%) 0.05 ± 0.15 | | |
| | | | | | Impl & PRF | KM (%) -0.62± 0.58 | 6 | P<.001 |
| (Badr et al., 2010) | Atrophy | Sinus augmentation | 22 | No | Autogenousbone | MGHI = 3.3 ± 0.7 | | |
| | | | | | Autogenous & PRP | MGHI = 3.1 ± 0.75 | 2W | P=0.4 |

HHD6 = horizontal depth of defects at 6mm apical the crest; DH = depth height; HBW = horizontal bone width; HBWE = horizontal bone width at end of implant; BH = bone height; BA = bone augmentation; USB = Unilabsurgibone, a xenograft bone; VST = volume of soft tissue; KM = keratinized mucosa; REC = distance between the restoration margin and peri-implant mucosa margin; MHRAC = mean height of the residual alveolar crest; MGHI = mean gingival healing index;W = week; NA = not available.

**Table 5: Effect of PRP on ISQ**

| Autor | Defect | Surgical protocol | Patient no. | Split mouth | Groups | Finaloutcome | Month | P Value |
|---|---|---|---|---|---|---|---|---|
| (Oncu et al., 2015) | Extraction | Implant insert | 20 | Yes | Impl | ISQ = 70.5±7.7 | | |
| | | | | | Impl & PRP | ISQ = 77.1±7.1 | 1 | P=.001 |
| (Cabbar et al., 2011) | Atrophy | Sinus augmentation | 10 | Yes | USB | ISQ = 70.3 ± 5.7 | | |
| | | | | | USB & PRP | ISQ = 71.7 ± 4.5 | 6-8 | P=.043 |
| (Badr et al., 2010) | Atrophy | Sinus augmentation | 22 | No | Autogenousbone | ISQp = 64 ± 1.7 | | |
| | | | | | Autogenous & PRP | ISQp = 65 ±2.2 | 6 | P=.627 |
| (Monov et al., 2005) | Edentulous | Impl in mandibula | 10 | Yes | Imp | RFA = (6103–6230 Hz) | | |
| | | | | | Imp &PRP | RFA = (6167–6363 Hz) | 4weeks | P= >0.05 |
| (Thor et al., 2005) | Atrophy | Sinus augmentation | 19 | Yes | Autologous | ISQ = 61.5 | | |
| | | | | | Autologous & PRP | ISQ = 64 | 12 | P<0.05 |

---

ISQ = Implant stability quotient; Badr et al. (2010)) study ISQ in maxillaposterior (sinus augmentation); FRA = Resonancefrequencyanalysis.

**Table 6: Effect of PRP in implant failure or Impl loss, bone level, bone augmentation**.

| Autor | Defect | Surgical protocol | Patient no. | Split mouth | Groups | Final outcome | Month | P Value |
|---|---|---|---|---|---|---|---|---|
| (Hamzacebi et al., 2015) | peri-implantitis | Access flap | 19 | Yes | Impl | CAL = 1.84±0.81 | | |
| | | | 19 | | Impl & PRF | CAL = 3.31±1.08 | 6 | P<.01 |
| | | | | | Impl | BOP = 44.05± 36.17 | | |
| | | | | | Impl & PRF | BOP = 52.02± 32.32 | 6 | P<.001 |
| | | | | | Impl | PL = 20.31± 38.80 | | |
| | | | | | Impl & PRF | PL = 14.56± 33.09 | 6 | NA |
| | | | | | Impl | PD = 2.05 ±0.77 | | |
| | | | | | Impl & PRF | PD = 2.82± 1.03 | 6 | NA |
| (Kutkut et al., 2013) | Extraction | sockets graft | 16 | No | MGCSH | MR-1.1±0.7mm DR -0.6±0.6 | | |
| | | | | | MGCSH&PRP | MR -0.8±0.6mm DR -0.5±0.4 | 12 | P>0.05 |
| (Dasmah et al., 2013) | Atrophy | Sinus augmentation | 15 | Yes | Autogenous | MMB = 2.3±1.0 mm | | |
| | | | | | Autogenous & PRP | MMB = 2.0 ± 1.0 mm | 60 | NA |
| (Cabbar et al., 2011) | Atrophy | Sinus augmentation | 10 | Yes | USB | RG = 23.6 ± 5.9 | | |
| | | | | | USB & PRP | RG = 21.9 ± 6.6 | 13 | .572 |
| (Aimetti et al., 2008) | Atrophy | sinus augmentation | 4 | Yes | Autogenous | BIC = 46.75%± 13.6% | | |
| | | | | | Autogenous & PRP | BIC = 20.5%± 5.57% | 60 | NA |
| (Torres et al., 2009) | Atrophy | Sinus augmentation | 5 | Yes | ABB, | BV = 96.2% | | |
| | | | | | ABB & PRP | BV = 98.6% | 6 | P=<.05 |
| | | | | | ABB | HB = 9.4 ±0.7mm | | |
| | | | | | ABB & PRP | HB = 10.4 ±0.7mm | 6 | NA |
| (Thor et al., 2005) | Atrophy | Sinus augmentation | 19 | Yes | Autologous | MMBLP = 3.9 ±0.8 mm | | |
| | | | | | Autologous & PRP | MMBLP =3.7 ±0.9 mm | 12 | NA |

CAL = clinical attachment level; PD = probing depth; MGCSH = medical grade calcium sulfate hemihydrate; MMBLP = Mean marginal bone level posterior; RG = residual graft; ABB = anorganic bovine bone; BV = bone volume; HB = Height of augmentation bone.

**Table 7:Effect of PRP on bone quality (histomorphometic parameter), bone density(pixels), vital bone formation**

| Autor | Defect | Surgical protocol | Patient no. | Split mouth | Groups | Final outcome | Month | P Value |
|---|---|---|---|---|---|---|---|---|
| (ArRejaie et al., 2016) | Dehiscence | filling of defects | 16 | Yes | BioOss | BD = 106.46 ± 3.13 | | |
| | | | | | BioOss & PRP | BD = 129.34 ± 3.29 | 12 | .0008 |
| (Gassling et al., 2013) | Atrophy | sinus augmentation | 6 | Yes | BioOss, Bio-Gide | VB = 17.2% residual 17.3% | | |
| | | | | | BioOss, Gide & PRF | VB = 17.0% residual 15.9% | 5 | NA |
| (Kutkut et al., 2012) | Extraction | socket preservation | 8 | No | MGCSH | VB = 38.3% ± 9.3%. | | |
| | | | | | MGCSH & PRP | VB = 66.5% ±10.4%. | 3 | P<0.05 |
| (Aimetti et al., 2008) | Atrophy | sinus augmentation | 4 | Yes | Autogenousbone | VB = 20.5%±57.57%. | | |
| | | | | | Autogenous & PRP | VB = 46.75%±13.60%. | 60 | NA |
| (Consolo et al., 2007) | Atrophy | sinus augmentation | 16 | Yes | Autogenousbone | TBV = 29.2 ± 4 | | |
| | | | | | Autogenous & PRP | TBV = 39.3 ± 5.7 | 5 | P=0.046 |
| (Raghoebar et al., 2005) | Atrophy | Sinus augmentation | 5 | Yes | Autologous | BD = 84.6 ± 19.6, 90.7 ± 13.5 | | |
| | | | | | Autologous & PRP | BD = 91 ± 23.1, 71.8 ± 23.8 | 3 | P>0.05 |
| (Cabbar et al., 2011) | Atrophy | Sinus augmentation | 10 | Yes | USB | NB 16.1% ± 3.8% | | |
| | | | | | USB & PRP | NB 15.8% ± 4.8% | 6-8 | P=.0001 |
| | | | | | USB | TB = 64.7% ± 22.5% | | |
| | | | | | USB & PRP | TB = 69.1% ± 18.6% | 6-8 | P=.0001 |

BD = Bone density; VB = Vital bone; MGCSH = Medical grade calcium sulfate hemihydrate; TBV = Trabecular bone volume; NB = New bone; TB = Trabecular bone.

**Table 8: Effect of PRP on marginal bone loss**

| Autor | Defect | Surgical protocol | Patient no. | Split mouth | Groups | Final outcome | Month | P Value |
|---|---|---|---|---|---|---|---|---|
| (ArRejaie et al., 2016) | Dehiscence | filling of defects | 16 | Yes | BioOss | mean (mm) M = 1.60 ± 0.26 | | |
| | | | | | BioOss & PRP | mean (mm) M = 0.80 ± 0.24 | 12 | .000* |
| | | | | | BioOss | mean (mm) D = 1.50 ± 1.06 | | |
| | | | | | BioOss & PRP | mean (mm) D = 0.82 ± 0.71 | 12 | .000* |
| (Aimetti et al., 2008) | Atrophy | sinus augmentation | 4 | Yes | Autogenousbone | VB = 1.03± 0.05mm | | |
| | | | | | Autogenous & PRP | VB = 0.98± 010mm | 12 | NA |
| | | | | | Autogenousbone | MMBL = 1.97± 0.05mm | 60 | NA |
| | | | | | Autogenous & PRP | MMBL = 1.92± 0.10mm | 60 | NA |

M = mesial; D = distal;* = Differences were statistically significant; MMBL = mean marginal bone loss.

# 8 Discussion

Aim of this systematic review was to get an overview about the present research related to platelet concentration with respect to implant dentistry. The study was based on the systematic review based on search in the database PubMed. According to the relevant keywords 280 hits were found. After further analysis, we were excluding 227 leaving 53 papers for a detailed analysis. We ended up with 21 publications and later on, it turned out that 15 met the inclusion criteria and were selected for a detailed analysis. Nine out of the fifteen studies focused on the impact of platelet on sinus augmentation. The main readout were related to bone height, but also the implant stability based on ISQ and RFA measures. Overall, it turned out the impact of platelet on implant stability was positive with around three out of five studies reporting significant increase in this respect. Also, other studies related to socket preservation and flap related surgeries were part of the review. Some of the studies failed to include a statistical analysis and also the number of patients were considered low with some studies were having only 4 patients enrolled in the studies. Even though some studies showed the clinical change of the primary outcomes by the addition of platelet preparations, the clinical impact of this treatment is questionable. For example, in the work of Cabbar et al. (2011) PRP increases the ISQ from 70.3 to 71.7 which is rather moderate with respect to the clinical related stability. Also, Badr et al. (2010) showed ISQ values increased in mean from 64 to 65 which again can be considered too low. Overall the reader is left with a heterogeneous picture with some reports finding a significant difference in the use of PRP.

Studies reporting no significant differences supported the weak impact of platelet preparation on the respective clinical endpoints. A general problem with interpretation of findings is that the studies are controlled but not randomized. Most of these studies have a patient number between 20 and 4 patients; this is low statistically power. Another weakness of the studies is the uncontrolled preparation of PRP. Consistency the number of platelets in each preparation is not controlled and can show large variations which can impact the clinical outcomes. Moreover, the same preparation might lead to early platelet activation so the preparations in general were not standardized. Another limitation is that the studies are rather inhomogeneous with respect to the study design, the inclusion criteria, and the surgical protocol. Overall, we

are left with a rather unclear picture about the effect of platelet and platelet preparation on aspects related to implant dentistry which cannot be served as a basis for a strong clinical recommendation. Our knowledge, and the level of evidence on platelet preparation in the field of implantology can be considered moderate to low. Today, no clear recommendations can be offered to clinicians, and we are left with the question about the best clinical indication of the use of platelet preparation in the implant dentistry. Moreover, today beside platelet rich plasma also other protocols have been established. Most of all use platelet rich fibrin, and cannot be directly compared with PRP. Further research is necessary to gain a realistic and complete picture on the clinically use of PRP in implant dentistry.

# 9 Conclusion

In conclusion, the high heterogeneity among these studies, made it difficult to give a clear conclusion. Some of the studies had more than one parameter, part of it had a significant result, and another part had no significant results. Further human studies evaluating the use of PRP on bone and soft tissue formation and implant stability thus remain necessary.

# 10 List of Abbreviations

| | |
|---|---|
| PRP | Platelet rich plasma |
| L-PRF | Leucocyte- and platelet-rich fibrin |
| RBC | Red blood cells |
| WBC | Whole blood Cells |
| L-PRP | Leucocyte rich PRP |
| P-PRP | Pure PRP |
| WB | Whole blood |
| ACD | Acid citrate dextrose |
| PPP | Platelet poor plasma |
| RCF | Relative centrifugal force |
| HHD | Horizontal depth of defects |
| DH | Depth height |
| USB | Unilab surgibone= bovine bone, hydroxyapatide |
| BP | Bisphosphonate |
| PRGF | Plasma rich in growth factor |
| CAL | Clinical attachments level |
| BOP | Bleeding of probing |
| MR | Mesial bone loss |
| DR | Distal bone loss |
| MMB | Mean marginal bone levels |
| VB | Vertical bone |
| BIC | Bone to implant contact |
| RC | Root coverage |
| CAL | Clinical attachment level |
| KMW | Keratinized mucosa width |
| BL | Bone level |
| MGL | Marginal gingival level |
| GR | Gingival recession |
| AL | Attachment level |
| PPD | Probing pocket depth |

| | |
|---|---|
| BP | Bleeding on probing |
| AO | Alveolar osteitis |
| RCT | Randomized clinical studies |
| RFA | Resonance frequency analysis |
| ISQ | Implant stability quotient |

# 11 Contents of tables and figures

# 12 References


Agrawal AA: Evolution, current status and advances in application of platelet concentrate in periodontics and implantology. World journal of clinical cases 5:159-171, 2017.

Aimetti M, Romano F, Dellavia C, De Paoli S: Sinus grafting using autogenous bone and platelet-rich plasma: histologic outcomes in humans. The International journal of periodontics & restorative dentistry 28:585-591, 2008.

Al-Hamed FS, Tawfik MA, Abdelfadil E, Al-Saleh MAQ: Efficacy of Platelet-Rich Fibrin After Mandibular Third Molar Extraction: A Systematic Review and Meta-Analysis. Journal of oral and maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons 75:1124-1135, 2017.

Al-Jetaily S, Al-Dosari AA: Assessment of Osstell and Periotest(R) systems in measuring dental implant stability (in vitro study). The Saudi dental journal 23:17-21, 2011.

Amable PR, Carias RB, Teixeira MV, da Cruz Pacheco I, Correa do Amaral RJ, Granjeiro JM, Borojevic R: Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors. Stem cell research & therapy 4:67, 2013.

ArRejaie A, Al-Harbi F, Alagl AS, Hassan KS: Platelet-Rich Plasma Gel Combined with Bovine-Derived Xenograft for the Treatment of Dehiscence Around Immediately Placed Conventionally Loaded Dental Implants in Humans: Cone Beam Computed Tomography and Three-Dimensional Image Evaluation. The International journal of oral & maxillofacial implants 31:431-438, 2016.

Badr M, Coulthard P, Alissa R, Oliver R: The efficacy of platelet-rich plasma in grafted maxillae. A randomised clinical trial. European journal of oral implantology 3:233-244, 2010.

Cabbar F, Guler N, Kurkcu M, Iseri U, Sencift K: The effect of bovine bone graft with or without platelet-rich plasma on maxillary sinus floor augmentation. Journal of oral and

maxillofacial surgery: official journal of the American Association of Oral and Maxillofacial Surgeons 69:2537-2547, 2011.

Castro AB, Meschi N, Temmerman A, Pinto N, Lambrechts P, Teughels W, Quirynen M: Regenerative potential of leucocyte- and platelet-rich fibrin. Part A: intra-bony defects, furcation defects and periodontal plastic surgery. A systematic review and meta-analysis. Journal of clinical periodontology 44:67-82, 2017a.

Castro AB, Meschi N, Temmerman A, Pinto N, Lambrechts P, Teughels W, Quirynen M: Regenerative potential of leucocyte- and platelet-rich fibrin. Part B: sinus floor elevation, alveolar ridge preservation and implant therapy. A systematic review. Journal of clinical periodontology 44:225-234, 2017b.

Choukroun J AF, Schoeffler C Vervelle A  Une opportunite en paro- implantologie:. le PRF Implantodontie

Consolo U, Zaffe D, Bertoldi C, Ceccherelli G: Platelet-rich plasma activity on maxillary sinus floor augmentation by autologous bone. Clinical oral implants research 18:252-262, 2007.

Cooper LF, Raes F, Reside GJ, Garriga JS, Tarrida LG, Wiltfang J, Kern M, de Bruyn H: Comparison of radiographic and clinical outcomes following immediate provisionalization of single-tooth dental implants placed in healed alveolar ridges and extraction sockets. The International journal of oral & maxillofacial implants 25:1222-1232, 2010.

Cordaro L: Bilateral simultaneous augmentation of the maxillary sinus floor with particulated mandible. Report of a technique and preliminary results. Clinical oral implants research 14:201-206, 2003.

Dasmah A, Thor A, Ekestubbe A, Sennerby L, Rasmusson L: Marginal bone-level alterations at implants installed in block versus particulate onlay bone grafts mixed with platelet-rich plasma in atrophic maxilla. a prospective 5-year follow-up study of 15 patients. Clinical implant dentistry and related research 15:7-14, 2013.

Dhurat R, Sukesh M: Principles and Methods of Preparation of Platelet-Rich Plasma: A Review and Author's Perspective. Journal of cutaneous and aesthetic surgery 7:189-197, 2014.

Dohan Ehrenfest DM, Rasmusson L, Albrektsson T: Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends in biotechnology 27:158-167, 2009.

Gassling V, Purcz N, Braesen JH, Will M, Gierloff M, Behrens E, Acil Y, Wiltfang J: Comparison of two different absorbable membranes for the coverage of lateral osteotomy sites in maxillary sinus augmentation: a preliminary study. Journal of cranio-maxillo-facial surgery: official publication of the European Association for Cranio-Maxillo-Facial Surgery 41:76-82, 2013.

Hamzacebi B, Oduncuoglu B, Alaaddinoglu EE: Treatment of Peri-implant Bone Defects with Platelet-Rich Fibrin. The International journal of periodontics & restorative dentistry 35:415-422, 2015.

Harrison P, Cramer EM: Platelet alpha-granules. Blood reviews 7:52-62, 1993.

Huang Y, Bornstein MM, Lambrichts I, Yu HY, Politis C, Jacobs R: Platelet-rich plasma for regeneration of neural feedback pathways around dental implants: a concise review and outlook on future possibilities. International journal of oral science 9:1-9, 2017.

Kobayashi E, Fluckiger L, Fujioka-Kobayashi M, Sawada K, Sculean A, Schaller B, Miron RJ: Comparative release of growth factors from PRP, PRF, and advanced-PRF. Clinical oral investigations 20:2353-2360, 2016.

Kutkut A, Andreana S, Kim HL, Monaco E, Jr.: Extraction socket preservation graft before implant placement with calcium sulfate hemihydrate and platelet-rich plasma: a clinical and histomorphometric study in humans. Journal of periodontology 83:401-409, 2012.

Kutkut A, Andreana S, Monaco E, Jr.: Clinical and radiographic evaluation of single-tooth dental implants placed in grafted extraction sites: a one-year report. Journal of the International Academy of Periodontology 15:113-124, 2013.

Langer B, Langer L: Overlapped flap: a surgical modification for implant fixture installation. The International journal of periodontics & restorative dentistry 10:208-215, 1990.

Lekholm UZ, G.A.: Patient selection and preparation. In: Branemark, P.I., Zarb, G.A. & Albrektsson, T., eds. Tissue-Integrated Proth-eses: Osseointegration in Clinical Dentistry. Quintessence Publishing Co 199–209

Lemos CA, Mello CC, dos Santos DM, Verri FR, Goiato MC, Pellizzer EP: Effects of platelet-rich plasma in association with bone grafts in maxillary sinus augmentation: a systematic review and meta-analysis. International journal of oral and maxillofacial surgery 45:517-525, 2016.

Mihaylova Z, Mitev V, Stanimirov P, Isaeva A, Gateva N, Ishkitiev N: Use of platelet concentrates in oral and maxillofacial surgery: an overview. Acta odontologica Scandinavica 75:1-11, 2017.

Miron RJ, Fujioka-Kobayashi M, Bishara M, Zhang Y, Hernandez M, Choukroun J: Platelet-Rich Fibrin and Soft Tissue Wound Healing: A Systematic Review. Tissue engineering Part B, Reviews 23:83-99, 2017a.

Miron RJ, Zucchelli G, Pikos MA, Salama M, Lee S, Guillemette V, Fujioka-Kobayashi M, Bishara M, Zhang Y, Wang HL, Chandad F, Nacopoulos C, Simonpieri A, Aalam AA, Felice P, Sammartino G, Ghanaati S, Hernandez MA, Choukroun J: Use of platelet-rich fibrin in regenerative dentistry: a systematic review. Clinical oral investigations 21:1913-1927, 2017b.

Monov G, Fuerst G, Tepper G, Watzak G, Zechner W, Watzek G: The effect of platelet-rich plasma upon implant stability measured by resonance frequency analysis in the lower anterior mandibles. Clinical oral implants research 16:461-465, 2005.

Moraschini V, Barboza Edos S: Use of Platelet-Rich Fibrin Membrane in the Treatment of Gingival Recession: A Systematic Review and Meta-Analysis. Journal of periodontology 87:281-290, 2016.

Nevins M, Camelo M, De Paoli S, Friedland B, Schenk RK, Parma-Benfenati S, Simion M, Tinti C, Wagenberg B: A study of the fate of the buccal wall of extraction sockets of teeth with prominent roots. The International journal of periodontics & restorative dentistry 26:19-29, 2006.

Nystrom E, Ahlqvist J, Kahnberg KE, Rosenquist JB: Autogenous onlay bone grafts fixed with screw implants for the treatment of severely resorbed maxillae. Radiographic evaluation of preoperative bone dimensions, postoperative bone loss, and changes in soft-tissue profile. International journal of oral and maxillofacial surgery 25:351-359, 1996.

Oncu E, Alaaddinoglu EE: The effect of platelet-rich fibrin on implant stability. The International journal of oral & maxillofacial implants 30:578-582, 2015.

Pal US, Sharma NK, Singh RK, Mahammad S, Mehrotra D, Singh N, Mandhyan D: Direct vs. indirect sinus lift procedure: A comparison. National journal of maxillofacial surgery 3:31-37, 2012.

Panda S, Doraiswamy J, Malaiappan S, Varghese SS, Del Fabbro M: Additive effect of autologous platelet concentrates in treatment of intrabony defects: a systematic review and meta-analysis. Journal of investigative and clinical dentistry 7:13-26, 2016.

Patterson et al. AD, Adam WR, De Castro RA Phlladelphla Harber & Row: Considerations and indicationfor endodontic surgery Endodontic surgery 4-5

Pocaterra A, Caruso S, Bernardi S, Scagnoli L, Continenza MA, Gatto R: Effectiveness of platelet-rich plasma as an adjunctive material to bone graft: a systematic review and meta-analysis of randomized controlled clinical trials. International journal of oral and maxillofacial surgery 45:1027-1034, 2016.

Raghoebar GM, Schortinghuis J, Liem RS, Ruben JL, van der Wal JE, Vissink A: Does platelet-rich plasma promote remodeling of autologous bone grafts used for augmentation of the maxillary sinus floor? Clinical oral implants research 16:349-356, 2005.

Rose L MB, Genco R.: Periodontitics: Medicine, surgery and implants. 1 st edStlouis: Mosby.

Rosello-Camps A, Monje A, Lin GH, Khoshkam V, Chavez-Gatty M, Wang HL, Gargallo-Albiol J, Hernandez-Alfaro F: Platelet-rich plasma for periodontal regeneration in the treatment of intrabony defects: a meta-analysis on prospective clinical trials. Oral surgery, oral medicine, oral pathology and oral radiology 120:562-574, 2015.

Scherer SS, Tobalem M, Vigato E, Heit Y, Modarressi A, Hinz B, Pittet B, Pietramaggiori G: Nonactivated versus thrombin-activated platelets on wound healing and fibroblast-to-myofibroblast differentiation in vivo and in vitro. Plastic and reconstructive surgery 129:46e-54e, 2012.

Schilephake H: Bone growth factors in maxillofacial skeletal reconstruction. International journal of oral and maxillofacial surgery 31:469-484, 2002.

Schwarz F, Bieling K, Latz T, Nuesry E, Becker J: Healing of intrabony peri-implantitis defects following application of a nanocrystalline hydroxyapatite (Ostim) or a bovine-derived xenograft (Bio-Oss) in combination with a collagen membrane (Bio-Gide). A case series. Journal of clinical periodontology 33:491-499, 2006.

Simonpieri A, Del Corso M, Vervelle A, Jimbo R, Inchingolo F, Sammartino G, Dohan Ehrenfest DM: Current knowledge and perspectives for the use of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial surgery part 2: Bone graft, implant and reconstructive surgery. Current pharmaceutical biotechnology 13:1231-1256, 2012.

Tatum H, Jr.: Maxillary and sinus implant reconstructions. Dental clinics of North America 30:207-229, 1986.

Thoma DS, Buranawat B, Hammerle CH, Held U, Jung RE: Efficacy of soft tissue augmentation around dental implants and in partially edentulous areas: a systematic review. Journal of clinical periodontology 41 Suppl 15:S77-91, 2014.

Thoma DS, Nanni N, Benic GI, Weber FE, Hammerle CH, Jung RE: Effect of platelet-derived growth factor-BB on tissue integration of cross-linked and non-cross-linked collagen matrices in a rat ectopic model. Clinical oral implants research 26:263-270, 2015.

Thor A, Wannfors K, Sennerby L, Rasmusson L: Reconstruction of the severely resorbed maxilla with autogenous bone, platelet-rich plasma, and implants: 1-year results of a controlled prospective 5-year study. Clinical implant dentistry and related research 7:209-220, 2005.

Torres J, Tamimi F, Martinez PP, Alkhraisat MH, Linares R, Hernandez G, Torres-Macho J, Lopez-Cabarcos E: Effect of platelet-rich plasma on sinus lifting: a randomized-controlled clinical trial. Journal of clinical periodontology 36:677-687, 2009.

Weine FS BM: Periapical surgery. Weine FS, ed Endodontictherapy, 5th ed, St, Louis:Mosby 536_539, 1976.

Zinner ID, Small SA: Sinus-lift graft: using the maxillary sinuses to support implants. Journal of the American Dental Association (1939) 127:51-57, 1996.