Thesis

The role of autologous platelet concentrates (APCs) in the surgical treatment of medication-related osteonecrosis of the jaw (MRONJ)

A literature review

submitted by

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Graz, 31.05.2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 31.05.2023 *David Hamann m.p.*

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Abbreviations

AAOMS – American Association of Oral and Maxillofacial Surgeons

APC – Autologous platelet concentrate

AR – Antiresorptive agents / medication

AWMF - Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

BMP - Bone morphogenetic proteins

BPs - Bisphosphonates

BRONJ – Bisphosphonate-related osteonecrosis of the jaw

DNO – Denosumab

L-PRF - Leucocyte and platelet-rich fibrin

MRONJ – Medication-related osteonecrosis of the jaw

nm - Nanometer

PBM - Photobiomodulation

RANKL - Receptor Activator of NF-κB Ligand

SVF - stromal vascular fraction

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Zusammenfassung

Einleitung: Autologe Thrombozytenkonzentrate (engl.: APCs) werden eingesetzt um eine erhöhte lokale Konzentration von Wachstumsfaktoren zu erzielen, um die Gewebeheilung zu verbessern und/oder zu beschleunigen. Die derzeit gültigen Leitlinien geben keine klare Empfehlung bezüglich der Verwendung von APCs in der chirurgischen Behandlung von medikamenteninduzierten Kieferknochennekrosen (engl.: MRONJ). Da die Therapie von MRONJ in der klinischen Routine oftmals herausfordernd ist, wären Verbesserungen in der Behandlung hilfreich. Daher war das Ziel dieser Diplomarbeit den derzeitigen Wissensstand bezüglich der Verwendung von APCs in der chirurgischen Behandlung von MRONJ zu erheben.

Material und Methoden: Eine Literatursuche in den gängigen Datenbanken (Medline/Pubmed, Web of Science) wurde durchgeführt. Folgende Schlagwörter wurden verwenden: autologous platelet concentrate, PRP, PRF, PRGF, osteonecrosis, ONJ, BRONJ, MRONJ, ARONJ. Die so gefunden Literatur wurde von zwei Personen kontrolliert und ausgewählt. Die eingeschlossenen Artikel wurden gemäß der Klassifikation des Oxford Center of EBM dem jeweiligen Evidenzlevel zugeordnet.

Ergebnisse: 44 wissenschaftliche Artikel, welche die medizinischen Behandlungssequenzen von über 700 Personen im Zusammenhang mit MRONJ und APCs repräsentieren, wurden eingeschlossen: 14 Fallberichte, 22 Fallserien, 2 Fall-Kontroll-Studien, 4 Kohortenstudien und 2 randomisierte kontrolliert Studien.

Konklusion: Der Großteil der Literatur (n=36) wurde den unteren Evidenzlevel zugeordnet (4/5). Diese Fallberichte und Fallserien zeigen insgesamt gute Ergebnisse bei der Verwendung von APCs. Die Literatur mit höheren Evidenzlevel (n=6; Fall-Kontroll-Studien, Kohortenstudien, randomisiert kontrollierte Studien) zeigten insgesamt verbesserte Ergebnisse bei der Verwendung von APCs in der chirurgischen Behandlung von MRONJ. Eine Studie konnte keinen signifikanten Unterschied zwischen den Behandlungsgruppen erheben. Negative Effekte bei der Verwendung von APCs wurden nicht berichtet.

Auf Grundlage der im Rahmen dieser Diplomarbeit gesichteten Literatur empfiehlt sich die Verwendung von APCs vor allem bei Personen die an MRONJ erkrankt sind und zusätzliche Risikofaktoren aufweisen (z.B.: lange Behandlungsdauer mit Bisphosphonaten, mehrmaliges Auftreten von Kieferknochennekrosen, höhere AAOMS Klassifikation der

Erkrankung) und somit mit verringerten Erfolgsaussichten der konventionellen Therapie gerechnet werden muss.

Abstract

Purpose: Autologous platelet concentrates (APCs) are used with the intent to provide an increased local concentration of growth factors to improve and/or accelerate tissue healing. So far existing guidelines do not give a clear recommendation if or if not or when, APCs should be used in the treatment of medication related osteonecrosis of the jaw (MRONJ). Since MRONJ remains often a challenging disease to manage in clinical practice, improvements in the surgical therapy are important. Therefore, the aim of this thesis was to perform a literature review in order to evaluate the current status of knowledge regarding the use of APCs in the surgical treatment of MRONJ.

Material and methods: A literature search was performed using electronic databases (Medline/PubMed, Web of Science) until 31.05.2022 by using the following search terms: autologous platelet concentrate, PRP, PRF, PRGF, osteonecrosis, ONJ, BRONJ, MRONJ, ARONJ. Two persons screened, reviewed and selected the literature. Articles included were classified using the Oxford center for EBM – Levels of evidence and conclusion was drawn from the found articles.

Results: 44 Articles were included in this thesis, representing the medical history of more than 700 persons surgically treated for MRONJ in connection with use of APCs: 14 case reports, 22 case series, 2 case-control studies, 4 cohort studies and 2 randomized controlled trails (RCTs).

Conclusion: Most of the literature (n=36) included was assigned to evidence level 4 or 5. These articles, case reports and case series, overall showed favorable outcomes when APCs were used. Literature with a higher level of evidence (cohort studies, low quality RCT, case-control series, RCT; n=6) mostly showed benefits when using APCs in MRONJ treatment. One study however could not show significant difference between treatment groups with or without APCs used. No negative adverse effects of APCs were reported in the literature.

On the background of this literature search, it can be stated that the beneficial use of APCs is most likely given in patients with additional risk factors (e.g. long treatment periods with bisphosphonates, disease recurrence or higher disease grading) and when conventional surgical techniques are likely to produce poor outcome. However, more randomized controlled trails on this topic are needed.

1 Introduction

1.1 Medication-related osteonecrosis of the jaw (MRONJ)

1.1.1 Definition

The currently valid definition of MRONJ was established by the AAOMS in 2014 and got accepted by the AWMF. There are two conditions need to be fulfilled and one condition which must not be fulfilled to meet the diagnostic criteria of MRONJ:

1. Current or previous treatment with antiresorptive or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws (Ruggiero et al., 2014, Schiegnitz et al., 2018)

1.1.2 Incidence and occurrence rate

In literature you may find quite different information about incidence and prevalence of MRONJ. These numbers depend on many variables like the quality of studies and the true frequency of disease occurrence.

Furthermore, in clinical practice it is essential to divide patients receiving antiresorptive agents into separate risk groups. There are different approaches dividing these groups with no real consensus in literature. Most authors agree that indication (osteoporosis vs. oncologic), type of agent (BP vs antibody), duration of therapy and other risk factors (smoking, co-medication, oral hygiene) are factors that influence the likelihood of developing MRONJ. (Schiegnitz et al., 2018, Nicolatou-Galitis et al., 2019)

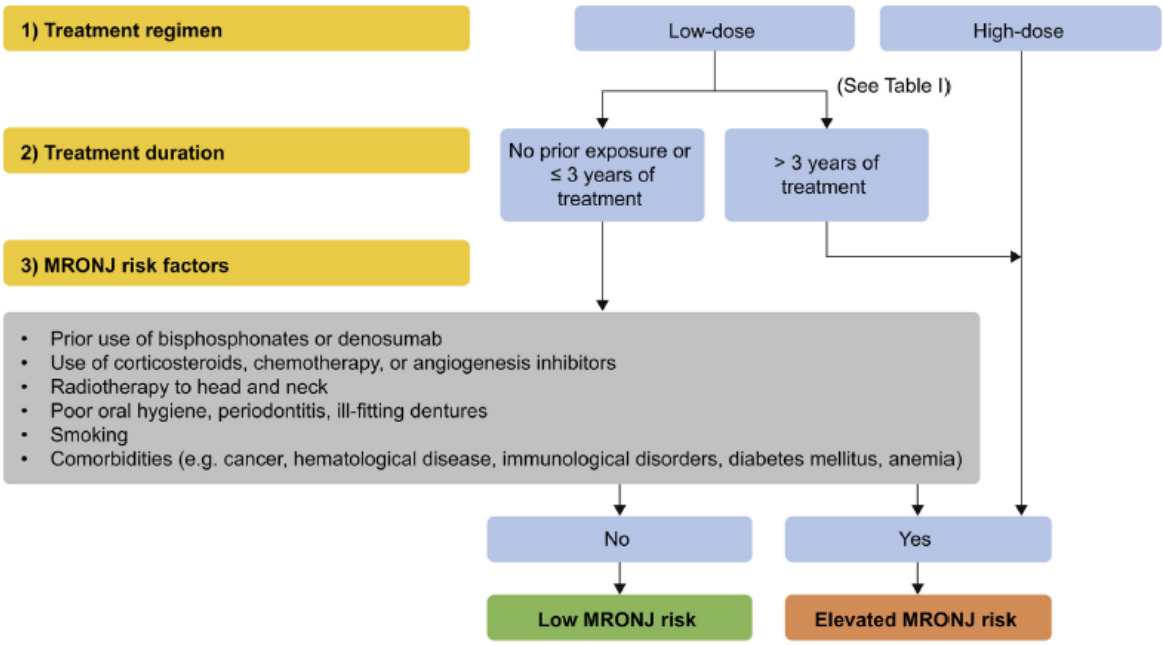
In the following, two different risk models are presented, existing alongside several others.

Table 1 - MRONJ Risk Profiles defined by the AMWF

Group	*Medication*	*Indication*	*Co-factors*	*Prevalence*
Low risk	BP	Primary osteoporosis	-	0,0 – 0,5%
Low risk	Denosumab	Primary osteoporosis	-	0,1 – 0,2%
Medium risk	BP/Denosumab	Iatrogenic/ secondary osteoporosis	Co-medication (e.g. MTX) / wound healing disorder (e.g. diabetes)	1%
High risk	BP	Oncologic	Co-medication (e.g. VEGF-Antibody)	1-21%
High risk	Denosumab	Oncologic	Co-medication (e.g. VEGF-Antibody)	2-5%

(Schiegnitz et al., 2018)

Table 2 – MRONJ Risk Profiles defined by Nicolatou-Galitis et al.



(Nicolatou-Galitis et al., 2019)

Nicolatou-Galitis et al. defined low-dose therapy by 60mg Denosumab every 6 month, high-dose by 120mg Denosumab every 4 weeks. Low MRONJ risk is defined as only slightly elevated risk compared to general population (<0.01%), elevated MRONJ risk starts at around 1% (high dose Denosumab, 1 year treatment) and goes up to 4.6% (high dose Denosumab, >3 years treatment). (Nicolatou-Galitis et al., 2019)

1.1.3 Pathogenesis and pathophysiology

Up to now there is no final agreement regarding the pathophysiology of MRONJ. Most likely synergistic effects of local, bacterial infection (dental and periodontal), microtrauma and changes in bone turnover after exposure to antiresorptive agents are responsible for a multifactorial pathogenesis, ultimately leading to osteonecrosis. Furthermore, factors like immunosuppression, vitamin D deficiency, soft tissue toxicity of bisphosphonates and reduced angiogenesis were investigated and might play a role. (Ruggiero et al., 2014, Nicolatou-Galitis et al., 2019, Alsalih et al., 2021)

Retrospective if MRONJ appears, in many cases a local trigger event can be found. Possible trigger factors are pressure sores, endodontic treatment and – most common – tooth extraction. All of these mentioned can be summarized as a local infection in the jaws. This might represent the onset event of MRONJ in bone altered by antiresorptive therapy. (Otto et al., 2012, Otto et al., 2021)

1.1.3.1 Localization

A distinctive feature of the disease is the exclusive occurrence in the jawbone, although systemic antiresorptive therapy affects the whole body. More precisely, two thirds of MRONJ occur in the lower jaw while the upper jaw is affected in only one third of the cases. In both jaws MRONJ shows a predilection for the premolar and molar region. (Otto et al., 2021, Otto et al., 2012)

The predilection for the mandible is linked to its end-arterial blood supply and its higher ratio of cortical to cancellous bone. It is generally believed that the same factors make the mandible more susceptible to infection e.g., in osteomyelitis, which mostly occurs in the mandible. (Otto et al., 2012, Aljohani et al., 2019)

1.1.4 Stages

The staging of MRONJ was suggested by the AAOMS in 2009, in 2014 “Stage 0” was added, although it contradicts the diagnostic criteria mentioned above due to the fact that

patients at stage 0 do not have exposed bone. (see: 1.1.1 Pathogenesis and pathophysiology) The AAOMS justified this discrepancy because literature showed that patients at stage 0 have a risk up to 50% of disease progression to stages 1, 2 or 3. Same as the definition also the staging was accepted by the AWMF. (Ruggiero et al., 2014, Schiegnitz et al., 2018)

Table 3 - AAOMS staging of MRONJ lesions

Stage 0	non-specific clinical findings like pain or radiographic changes without clinical evidence of exposed or necrotic bone
Stage 1	exposed necrotic bone / fistula, no signs of infection, asymptomatic patient
Stage 2	exposed necrotic bone / fistula with infection (pain, erythema) +/- purulent drainage
Stage 3	same as stage 2 + ≥1 of following: bone exposure beyond alveolar bone; pathologic fractur, extraoral fistula; oral-antral communication

(Ruggiero et al., 2014)

1.1.5 Antiresorptive agents

Antiresorptive medications are used in different diseases with intention to stop or reduce bone resorption. The most common indication is osteoporosis and osteopenia to reduce the risk of bone fractures. Second most common is the use in solid malignancies with bone metastasis (e.g. breast, prostate and lung cancer) or non-solid malignancies, primarily multiple myeloma. It is not clear if this treatment improves cancer-related survival, but there is a significant benefit regarding the quality of life of this group of patients. (Ruggiero et al., 2014)

To be mentioned the use is recommended in treatment of Morbus Paget and osteogenesis imperfecta. (Ralston et al., 2019, Rossi et al., 2019) Because these are relatively rare disease they will not be discussed further in this thesis.

Additionally, 2014 the AAOMS changed the previous used term “bisphosphonate-related osteonecrosis of the jaw” (BRONJ) to MRONJ to take growing numbers of MRONJ caused by denosumab into account. (Ruggiero et al., 2014) Since then other medications like antiangiogenic medications (e.g. tyrosine kinase inhibitor), radiopharmaceuticals, selective estrogen receptor modulators and immunosuppressants, have been documented to cause MRONJ. (Alsalih et al., 2021) Nevertheless, in clinical practice antiresorptive agents are linked to the vast majority of patients suffering from MRONJ. Because of this, the thesis will focus on antiresorptive drugs, which can be divided into two groups:

1.1.5.1 Bisphosphonates (BPs)

BPs are inorganic pyrophosphate analogues with extremely high affinity to the mineral component of bone (hydroxyapatite) resulting in high local concentration in the skeleton, then trough endocytosis by osteoclasts it leads to osteoclast apoptosis. This mechanism ultimately results in less bone resorption and a positive bone balance. Today commonly used are second- and third-generation BPs. (alendronate, risedronate, ibandronate and zoledronate) (Drake et al., 2015)

BPs can be administered orally or intravenously. Because of the hydrophilic character of the BP the intestinal resorption results in less than 1% bioavailability, whereas intravenous application shows 100% bioavailability. Up to now we do not know the exact biologic half-life of BPs, but data shows that they are remaining in the bones at least for >5 years after administration, Barron et al. estimated the biological half-life at 10 to 12 years. (Drake et al., 2015, Baron et al., 2011)

1.1.5.2 Human antibodies

Denosumab (Prolia®, Xgeva®) is a fully human monoclonal antibody which specifically binds RANKL (Receptor Activator of NF-κB Ligand) and consecutive prevents RANKL from activating its cognate receptor RANK. RANK is located on the preosteoclastic membrane and – when activated trough RANKL – induces osteoclastogenesis, furthermore it is found on mature osteoclasts inducing their activity (bone resorption). When RANK is not activated through blocking of RANKL through denosumab, differentiation of preosteoclastic cells and the activity of mature osteoclasts is inhibited resulting in decreased bone resorption. (Drake et al., 2015)

Denosumab is administered by subcutaneous injection. A big difference compared to BPs is the biologic half-life of denosumab, approximately at 25 to 30 days. After the last dose of denosumab serum levels are decreasing over a period of 4 to 5 month. (Gibiansky et al., 2012, Baron et al., 2011)

1.1.6 Therapy of MRONJ

So far, there is no consent in international guidelines and literature about the therapy of MRONJ. Multiple factors make it hard to give a general suggestion for treatment:

1. Since Denosumab was approved by the FDA (Food and Drug Administration) and the EMA (European Medicines Agency) in 2010, but e.g. alendronat was approved by the FDA in 1995 the overwhelming part of literature investigated MRONJ

caused by BP, less data is available for MRONJ caused by Denosumab. (Balkhi et al., 2018)

2. Due to the fact that antiresorptive medications are used with different purposes (oncologic – improve quality of life vs. osteoporosis – prevent skeletal related events like bone fractures), there is no exact consent about the goals of MRONJ treatment and how to define treatment success. (Schiegnitz et al., 2018)

The AWMF defined successful treatment of MRONJ as completed soft tissue healing in patients without symptoms. (Schiegnitz et al., 2018) In contrast to this the AAOMS recommends to focus on the preservation of quality of life through pain control, prevention of extension of the lesion and preventing secondary infection. (Ruggiero et al., 2014)

In general, two treatment strategies are distinguished:

1.1.6.1 Non-surgical treatment of MRONJ

Main parts of this strategy are long term systemic use of antibiotics, disinfection through local lavage or mouth rinse and often combined with drug holiday. Non-surgical treatment leads to improvement of symptoms (pain, signs of infection) in up to 80%. But on the other hand, it shows very poor outcomes if complete mucosal healing is defined as treatment goal. Success rates vary between 0% to 23% in literature. (Schiegnitz et al., 2018)

1.1.6.2 Surgical treatment of MRONJ

Surgical approach in MRONJ treatment usually includes removal of all necrotic parts of the jaws and mucosal closure of the soft tissue lesion. This requires systemic antibiotics and sufficient anesthesia, in many cases general anesthetic. Literature shows mucosal healing in 78% to 94% of patients who underwent surgery. (Schiegnitz et al., 2018)

1.2 Autologous Platelet Concentrates (APCs)

1.2.1 Historical aspects

The starting point of the use of platelets in oral and maxillofacial surgery was the article by Matras on the use of fibrin sealant in 1982. (Matras, 1982) The fibrin used was donated by a third person resulting in the risk of disease transmission. At least one case of HIV infection was described in literature. (O'Sullivan and Ni Riordain, 2022)

1997 Whitman et al. introduced a method where autologous blood (450mL) is collected and transformed into “platelet gel” trough a relatively complex protocol including 2-stage centrifugation process, separating the blood components and the use of bovine thrombin for activation of the gel immediately before use. (Whitman et al., 1997) Nowadays the publication by Whitman et al. is considered as the starting point of the era of APCs.
Since 1997 many improved protocols were published. In 2001 Leucocyte and platelet-rich fibrin (L-PRF) was presented and remarked as a second generation of APC. This new generation is different from the previous ones because it is a single-step preparation protocol without need for manual fractionation and activation. (Dohan et al., 2006)

1) First platelet concentrates used in oral and maxillofacial surgery
    a) 1982: Fibrin Glue - Matras
2) First generation APCs
    a) 1997: Platelet Gel – Whitman
    b) 1998: Platelet-rich Plasma (PRP) – Marx
    c) 1999: Plasma rich in growth factors (PRGF) – Anitua
3) Second generation APCs
    a) 2001: Leucocyte and platelet-rich fibrin (L-PRF) – Choukroun

(O'Sullivan and Ni Riordain, 2022)

1.2.2 Platelets

Platelets, the smallest blood cells, play an important role in hemostasis. Around 1880 Bizzozero discovered their main role in thrombosis by the ability to form aggregates. (de Gaetano and Cerletti, 2002) Since then scientists recognized them as players in many other physiological and pathophysiological processes like antimicrobial defense, inflammation, atherosclerosis or tumor growth. (Gremmel et al., 2016)
Platelets are formed by cleavage of megakaryocytes, in consequence they do not contain a nucleus. In healthy persons they measure a diameter of 2 - 5 µm and a thickness of 0.5 µm. (Gremmel et al., 2016)

1.2.2.1 Platelet Activation

Many of the cytoplasmic organelles common to most eukaryotic cells also exist in platelets. Additionally, two platelet-specific of secretory organelles are present: most frequent (50 – 80 per platelet) are α-granules, followed by less frequent (3 – 8 per platelet) dense granules. (Gremmel et al., 2016)

If the platelet surface comes in contact with exposed collagen of injured tissue the activation of platelets is initiated. Consequently, a complex process is triggered including fibrinogen release, thrombin production and growth factor secretion resulting in the formation of a stable fibrin clot. To be mentioned, more than 300 different proteins, released out of α-granules alone, have been identified – this is mentioned to illustrate the complexity of platelet activation. (Gremmel et al., 2016, O'Sullivan and Ni Riordain, 2022)

1.2.2.2 Growth factors

Growth factors are a fundamental part in regenerative medical interventions, like the treatment of MRONJ. The use of APCs is intended to stimulate and accelerate tissue healing and bone regeneration. (Anitua et al., 2007) In **Table 4** a selection of the most important growth factors released during platelet activation are presented, also an overview about their physiologic function is given.

Table 4 – Selection of growth factors and their physiologic function

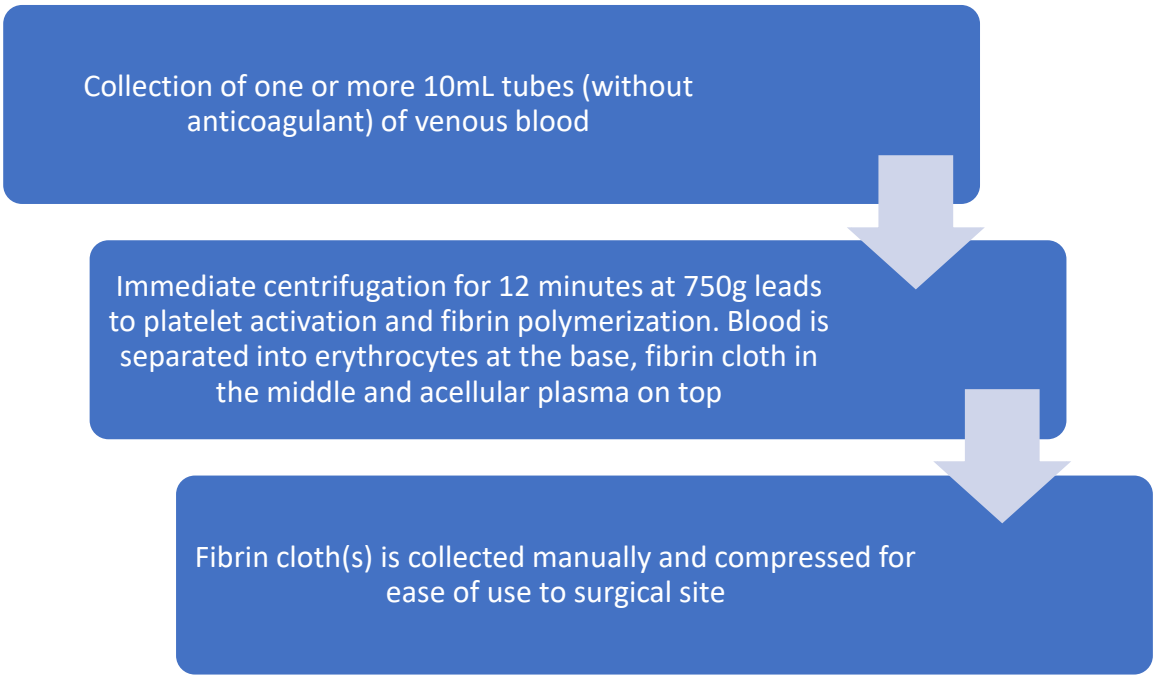
PDGF platelet-derived growth factor	Initiates connective tissue healing, Macrophage activation
VEGF vascular endothelial growth factor	Promotes angiogenesis through endothelial cell proliferation and migration
EGF epidermal growth factor	Promotes chemotaxis and angiogenesis of endothelial cells
IGF insulin-like growth factor	Regulates late-stage differentiation and activity of osteoblasts, regulates apoptosis
TGF- β transforming growth factor β	Chemotaxis and mitogenesis of osteoprogenitor cells, stimulates collagen deposition by osteoblasts, inhibits osteoclast formation and bone deposition

(O'Sullivan and Ni Riordain, 2022)

1.2.3 Manufacturing Protocol of L-PRF

As mentioned above there exist many different protocols for manufacturing of different forms of APCs. To provide an example the preparation of L-PRF, the currently most simplified and clinically used form, is presented:

Figure 1 - Manufacturing Protocol for APCs



(Dohan et al., 2006)

1.3 Relevance and goal of this thesis

As stated previously up to now there is no universally agreed protocol for the treatment of MRONJ. If mucosal healing and freedom from symptoms is defined as treatment goal, surgical intervention shows by far the best success rates compared to conservative therapy. APCs are not mentioned as an adjuvant treatment option for surgical treatment of MRONJ in current guidelines. (Ruggiero et al., 2014, Schiegnitz et al., 2018)

Although the necrotic bone is removed during surgery, it must be assumed that the remaining jawbone also has been exposed to the antiresorptive drugs in the same way and thus the physiologic bone metabolism is impaired. This circumstance increases the risk of disease recurrence or poor surgical treatment results. (Marx, 2003)

APCs promise to accelerate biological repair mechanisms and increase regenerative potential through growth factors. This could compensate for the negative side effects of antiresorptive therapy and improve the results of surgical therapy. Currently, there are already many commercial and easy-to-use solutions for PRF on the market. From the author's point of view, it would be possible to integrate this therapy into the standard therapy scheme without major problems.

In this regard, multiple already existing reports have tried to describe the role and efficacy of APCs in the surgical treatment of MRONJ. However, although several reviews exist

concerning this topic, none of these published articles provide a concrete recommendation ore guideline for the clinical use of APCs in the treatment of MRONJ. (Lopez-Jornet et al., 2016, Govaerts et al., 2020)
Therefore, the goal of this thesis is to assess the current status of knowledge regarding the use of APCs in the surgical treatment of MRONJ and to especially create a recommendation for the use of APCs as an adjuvant therapy, in general or specific cases of persons surgically treated for MRONJ.

2 Material and Methods

2.1 Search method

For this thesis an electronic literature search was performed using scientific databases (Medline via PubMed; Web of Science). Articles published up to 31.05.2022 were included. The keywords used are listed below. The search in Pubmed was performed trough a specific query to consider the different types of APCs and older or different nomenclature of MRONJ.

2.2 Key words

The following keywords were used in this work:
autologous platelet concentrates / autologous platelet concentrate / platelet concentrates / platelet concentrate / platelet-rich plasma / PRP / platelet-rich fibrin / PRF / plasma rich in growth factors / PRGF
AND
Osteonecrosis / osteonecrosis of the jaw / jaw necrosis / ONJ / BRONJ / MRONJ / ARONJ

2.3 Inclusion criteria

- Original publication in german or english language
- Study conducted in patients with diagnosed MRONJ according to AAOMS definition
- Use of APCs in surgical treatment

2.4 Exclusion criteria

- In vitro / animal study

- Patients with osteoradionecrosis
- Other medical discipline than head and neck surgery or oral surgery
- Non-surgical treatment protocol
- Prevention of MRONJ
- Literature review, letters or editorials

2.5 Level of Evidence

All studies included in this work were classified according to the level of evidence updated by March JH in 2009 (Oxford Center for Evidence-Based Medicine).

Table 5 - Definition: Oxford Center of EBM - level of evidence

Level of evidence	Typ of study
1a	Systematic review (SR) with homogenity of randomized controlled trails (RCT)
1b	Individual RCT with narrow confidence interval
1c	All or none study
2a	SR with homogeneity of cohort studies
2b	Individual cohort study / low quality RCT
2c	"Outcomes Research"
3a	SR with homogeneity of case-control studies
3b	Individual case-control study
4	Case-series / poor quality cohort and case-control studies
5	Expert opinion without explicit critical appraisal

(March, 2009)

3 Results

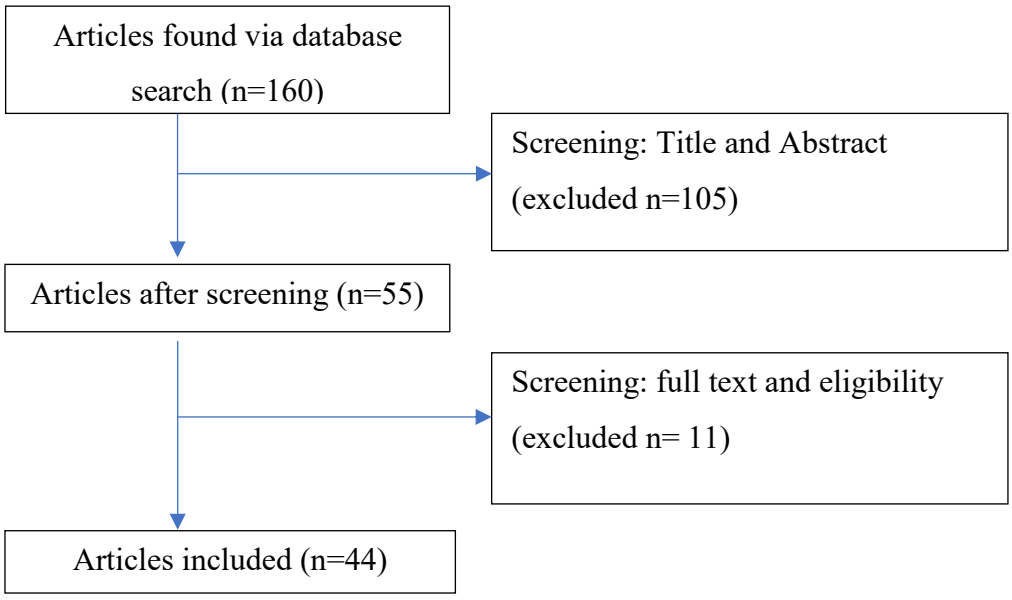
3.1 Data Search, Screening and Selection

A flow-diagram giving an overview on the selection process can be found at headline 3.2. Through the described search strategy (see: 2.1 Search method) 160 articles could be found in the electronic databases. At first the title and the abstract were screened; 105 articles were excluded and 55 articles were included for detailed full text screening. At this point another 11 articles that did not meet the inclusion criteria were excluded, resulting in 44 articles included for further analysis.

3.2 Selection of studies

The screening of the literature was conducted by the author of this thesis (DH) and the assigned supervisor (JW) separately. In case of differences, a third person was consulted (MS).

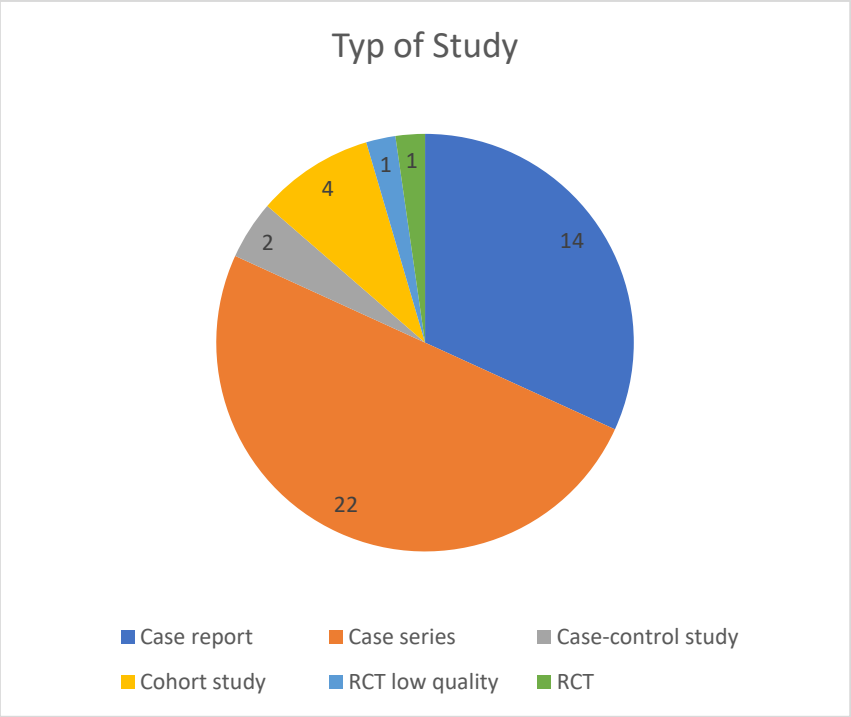
Figure 2 - Flowchart of study selection process



3.3 Study characteristics

Out of 44 articles 14 are case reports (1-2 patients), 22 case series (3 or more patients), 2 case-control studies, 4 cohort studies, 1 low quality randomized controlled trails (RCT) and 1 RCT.

Table 6 – Analysis: Type of study – design in included literature



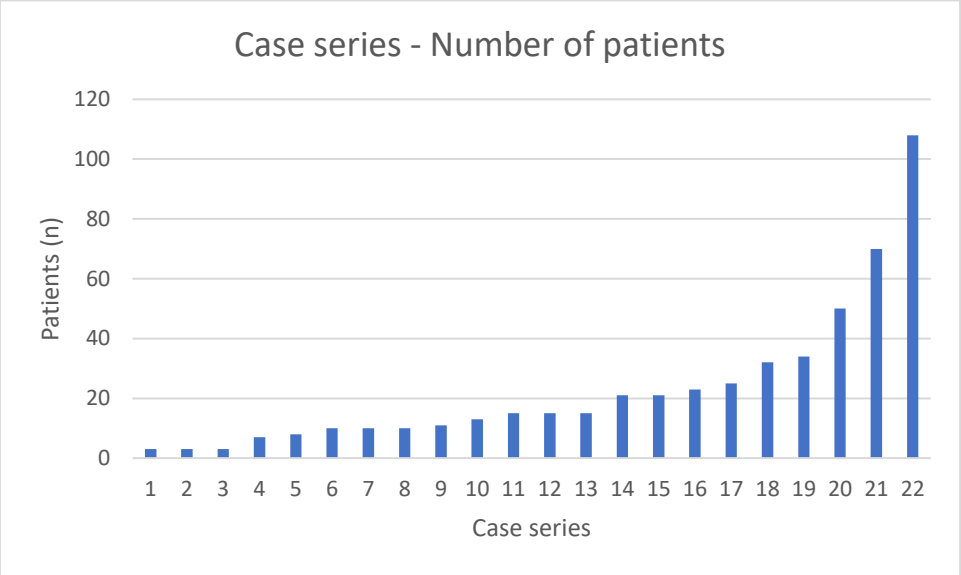
The majority of articles assigned to evidence level 4 (50%) and level 5 (32%). Two articles (9%) assigned to evidence level 3b, 5 articles (7%) assigned to evidence level 2b. Only one article (2%) fulfilled the criteria for evidence level 1b.

Table 7 – Analysis: Distribution of level of evidence in included literature

Level of evidence	Articles (n)	%
1a	0	0 %
1b	1	2 %
1c	0	0 %
2a	0	0 %
2b	5	11 %
2c	0	0 %
3a	0	0 %
3b	2	5 %
4	22	50 %
5	14	32 %
Total	**44**	**100 %**

Case series must include 3 or more patients. Three case series included 3 patients, the largest included 108 patients. (Pardo-Zamora et al., 2021, Curi et al., 2007, Hao et al., 2022, Nica et al., 2021) The mean number of patients included was 23. In total 507 patients were included in 22 case series.

Table 8 – Analysis: Case series - number of patients included



The oldest article included in this review was published in February 2007 (Curi et al., 2007), the two latest articles in May 2022. (Gurav et al., 2022, Hao et al., 2022).

Table 9 - List of included articles

Titel	Author	Typ	Level of evidence	date
The Effect of Platelet-Rich Fibrin Membrane in Surgical Therapy of Medication-Related Osteonecrosis of the Jaw.	Szentpeteri et al.	cohort study	2b	05 / 2020
Usefulness of advanced-platelet rich fibrin (A-PRF) and injectable-platelet rich fibrin (i-PRF) in the management of a massive medication-related osteonecrosis of the jaw (MRONJ): A 5-years follow-up case report.	Giudice et al.	case report	5	09 / 2020
Management of Medication-Related Osteonecrosis of the Jaw (MRONJ) Using Leukocyte- and Platelet-Rich Fibrin (L-PRF) and Photobiomodulation: A Retrospective Study	Tenore et al.	Cohort study	2b	10 / 2020
Combined Approach to Treat Medication-Related Osteonecrosis of the Jaws	Merigo et al.	case series	4	03 / 2018
Medication-Related Osteonecrosis of the Jaw: The Use of Leukocyte-Platelet-Rich Fibrin as an Adjunct in the Treatment.	Valente et al.	case series	4	06 / 2019
Medication related osteonecrosis of the jaws (MRONJ): Factors related to recurrence after treatment with surgery and platelet rich plasma (PRP) placement	Sánchez-Gallego et al.	case series	4	11 / 2021
Platelet rich fibrin in the management of medication-related osteonecrosis of the jaw: a clinical and histopathological evaluation	Inchingolo et al.	case series	4	07 / 2017
The use of platelet-rich fibrin in the surgical treatment of medication-related osteonecrosis of the jaw: 40 patients prospective study	Zelinka et al.	case series	4	09 / 2021
Case reports of medication-related osteonecrosis of the jaw (MRONJ) treated with uncultured stromal vascular fraction and L-PRF.	Bouland et al.	case report	5	09 / 2017
Bisphosphonate-related osteonecrosis of the jaws: analysis of a case series at a dental school	Mathias Duarte et al.	case series	4	03 / 2014
Platelet-rich plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients	Coviello et al.	case-control study	3b	01 / 2012
Laser and Platelet-Rich Plasma to treat Medication-Related Osteonecrosis of the Jaws (MRONJ): a case report.	Fornaini et al.	case report	5	09 / 2017
Complementarity of Photo-Biomodulation, Surgical Treatment, and Antibiotherapy for Medication-Related Osteonecrosis of the Jaws (MRONJ	Nica et al.	case series	4	02 / 2021
Use of platelet-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw	Bocanegra-Pérez et al.	case series	4	11 / 2012

Combined approach to treatment of advanced stages of medication-related osteonecrosis of the jaw patients.	Şahin et al.	case series	4	05 / 2021
Treatment of Stage 2 Medication-Induced Osteonecrosis of the Jaw: A Case Series	Pardo-Zamora et al.	case series	4	01 / 2021
Treatment of Refractory Medicine Related Osteonecrosis of Jaw With Piezosurgical Debridement and Autologous Platelet Rich Fibrin: Feasibility Study	Gurav et al.	case series	4	05 / 2022
The use of Platelet-rich Fibrin in the management of medication-related osteonecrosis of the jaw: A case series	Fernando de Almeida Barros Mourão et al.	case series	4	02 / 2020
Conservative Surgical Treatment of Bisphosphonate-Related Osteonecrosis of the Jaw with Er,Cr:YSGG Laser and Platelet-Rich Plasma: A Longitudinal Study.	Mauceri et al.	case series	4	08 / 2018
Epi-Mucosa Fixation and Autologous Platelet-Rich Fibrin Treatment in Medication-Related Osteonecrosis of the Jaw.	Cortese et al.	case report	5	04 / 2021
Can platelet-rich fibrin improve healing after surgical treatment of medication-related osteonecrosis of the jaw? A pilot study.	Giudice et al.	RCT	1b	11 / 2018
Surgical treatment of osteonecrosis of the jaw with the use of platelet-rich fibrin: a prospective study of 15 patients.	Nørholt et al.	case series	4	10 / 2016
Use of Leukocyte- and Platelet-Rich Fibrin in the Treatment of Medication-Related Osteonecrosis of the Jaws.	Maluf et al.	case report	5	01 / 2018
Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study.	Kim et al.	case series	4	11 / 2014
Report of a jaw osteonecrosis possibly caused by denosumab.	Saad et al.	case report	5	10 / 2017
Treatment of hemimandibular paresthesia in a patient with bisphosphonate-related osteonecrosis of the jaw (BRONJ) by combining surgical resection and PRGF-Endoret	Anitua et al.	case report	5	12 / 2013
Promising results of surgical management of advanced medication related osteonecrosis of the jaws using adjunctive leukocyte and platelet rich fibrin.	Özalp et al.	case series	4	12 / 2021
Management of Large Oroantral Fistulas Caused by Medication-Related Osteonecrosis with the Combined Sequestrectomy, Buccal Fat Pad Flap and Platelet-Rich Fibrin.	Esen et al.	case series	4	03 / 2021
Platelet-rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: a report of 32 cases.	Mozzati et al.	case series	4	05 / 2012
Does the Addition of Bone Morphogenetic Protein 2 to Platelet-Rich Fibrin Improve Healing After Treatment for Medication-Related Osteonecrosis of the Jaw?	Park et al.	RCT low quality	2b	06 / 2017
Treatment of Bisphosphonate-Related Osteonecrosis of the Jaw With Plasma Rich in	Gil et al.	case report	5	08 / 2019

Growth Factors After Dental Implant Surgery: A Case Report.				
Surgery Combined with LPRF in Denosumab Osteonecrosis of the Jaw: Case Report.	Maluf et al.	case report	5	05 / 2016
Alternative treatments for oral bisphosphonate-related osteonecrosis of the jaws: a pilot study comparing fibrin rich in growth factors and teriparatide.	Pelaz et al.	cohort study	2b	07 / 2014
Bisphosphonate-related osteonecrosis of the jaws--an initial case series report of treatment combining partial bone resection and autologous platelet-rich plasma.	Curi et al.	case series	4	09 / 2011
Treatment of bisphosphonate-related osteonecrosis of the jaw with platelet-rich fibrin.	Tsai et al.	case report	5	07 / 2016
Ultrasonic Piezoelectric Bone Surgery Combined With Leukocyte and Platelet-Rich Fibrin and Pedicled Buccal Fat Pad Flap in Denosumab-Related Osteonecrosis of the Jaw.	Şahin et al.	case report	5	07 / 2019
Association of laser phototherapy with PRP improves healing of bisphosphonate-related osteonecrosis of the jaws in cancer patients: a preliminary study.	Martins et al.	case-control study	3b	01 / 2012
Management of osteonecrosis of the jaws in patients with history of bisphosphonates therapy.	Antonini et al.	case report	5	11 / 2010
Management of bisphosphonate-related osteonecrosis of the jaw with a platelet-rich fibrin membrane: technical report.	Soydan et al.	case report	5	02 / 2014
Clinical and histopathological studies using fibrin-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw.	Dincă et al.	case series	4	07 / 2014
Simultaneous Application of Bone Morphogenetic Protein-2 and Platelet-Rich Fibrin for the Treatment of Bisphosphonate-Related Osteonecrosis of Jaw.	Kim et al.	case report	5	04 / 2016
Non-Interventional Prospective Observational Study of Platelet Rich Fibrin as a Therapy Adjunctive in Patients with Medication-Related Osteonecrosis of the Jaw.	Blatt et al.	cohort study	2b	01 / 2022
Treatment of avascular osteonecrosis of the mandible in cancer patients with a history of bisphosphonate therapy by combining bone resection and autologous platelet-rich plasma: Report of 3 cases.	Curi et al.	case series	4	02 / 2007
Osteonecrosis of the jaw induced by bisphosphonates therapy in bone metastases patient: Case report and literature review.	Hao et al.	case series	4	05 / 2022

4 Discussion

The following chapter is organized by the type of included articles. (case reports, case series, RCT, etc.) To improve the comparability of the articles, they are organized according to the level of evidence, starting with the lowest and ending with the highest level of evidence that was found.

4.1 Case reports (level of evidence: 5)

Case reports are one of the oldest methods of reporting in medical science, the oldest can be found in Egyptian sources written around 1500 BC. (Ghalioungui, 1987) They are often used when new treatments or unknown diseases appear, as is the case with MRONJ and APCs. Although case reports are and have been important in the history of medicine for groundbreaking findings, they must also be viewed critically.

Not the only problem, but probably the biggest one, is that valid conclusions for the entire population cannot necessarily be drawn from individual cases. Especially in medicine, where unknown, multifactorial processes often take place, this results in a limited level of evidence.

For the above reasons, case reports are assigned to the lowest level of evidence in the classification of the Oxford Center for Evidence-Based Medicine. (see: Table 5 - Definition: Oxford Center of EBM - level of evidence)

4.1.1 Case reports - overview

In this literature review a total of 14 case reports was included, representing the medical history of 16 patients. The oldest was published in November 2010 (Antonini et al., 2010) the latest in April 2021. (Cortese et al., 2021) (see: Table 9 - List of included articles)

In summary, all case reports describe a successful outcome in the context of surgical treatment of MRONJ with PRF. Treatment success was defined as complete mucosal healing and freedom from symptoms. Only Maluf et al. reported a case where two patients developed MRONJ after dental implantation surgery and did not show complete mucosal healing, but at least they became asymptomatic after surgical treatment with use of APCs. (Maluf et al., 2016)

4.1.2 Special case reports – a selection

As previously mentioned, case reports often present novel treatments or special cases. In the following, some important case reports are presented in more detail.

Bouland et al. combined the APC (L-PRF) with uncultured stromal vascular fraction (SVF) isolated out of fat tissue and claims a synergistic effect of these two components in the treatment of MRONJ. (Bouland et al., 2021)
Fornaini et al. additionally used a diode laser (808 nm) to biostimulate the surgical site. (Fornaini et al., 2017)
Cortese et al. published a new epi-mucosal fixation technique together with PRF to prevent or treat mandibular fracture in two patients suffering from MRONJ. (Cortese et al., 2021)
Kim et al. described a case of a women suffering from refractory MRONJ with multiple risk factors (4 years of BP therapy, diabetes type 2, 2 years of glucocorticoid therapy). No cure could be achieved with conventional conservative therapy or surgery. By using PRF and bone morphogenetic proteins (BMP) the authors achieved complete healing of the MRONJ lesion. (Kim et al., 2016)

4.1.3 Case reports – summary

Considering all the structural shortcomings of case reports, it can be summarized that the treatment of MRONJ in combination with APC is a promising option that has proven its efficacy in many cases, including severe ones. However, it must be mentioned that, e.g. due to the lack of a control group, no superiority or inferiority of this particular treatment method compared to others can be proven.
A particular strength of case reports, that should be mentioned separately, is to present new and progressive initiatives in medicine. In the course of this, reference is once again made to the articles listed under headline 4.1.2.

4.2 Case series (level of evidence: 4)

A major weakness of case reports, namely the influence of individual factors, can be largely compensated in the context of case series. These describe at least three patient histories and thus make the acquired knowledge more generalizable. Therefore, they are assigned to level 4 out of 5 in the classification of the Oxford Center for Evidence-Based Medicine. (see: Table 5 - Definition: Oxford Center of EBM - level of evidence)
Like case reports, case series are descriptive studies and therefore do not involve hypothesis testing.

4.2.1 Case series – overview

22 case series where considered in this review, summarizing the medical history of – in total – 507 patients. In average 23,0 patients where included per case series. The oldest one was published in February 2007 (Curi et al., 2007) while the latest on in May 2022 (Gurav et al., 2022). (see: Table 8 – Analysis: Case series - number of patients included)

4.2.2 Case series – a closer look

A comment must be made about the article published by Nica et al, since they also included patients who had not been operated on (AAOMS stage 0 / "at risk"). Therefore, only data from 108 patients – which had surgical intervention - were included in this review. They reported a total healing rate of 91.66%, when considering the downscaling MRONJ lesions to stage 1 (AAOMS) as a treatment success, success rate goes up to 99,59%. Only one failure was reported. (Nica et al., 2021)

Curi et al. reported complete mucosal healing in 20 out of 25 patients (success rate = 80%) their treatment protocol included surgical resection and use of APCs (PRP). (Curi et al., 2011) Ozalp et al. published a case series where incomplete mucosal healing occurred in 4 out of 13 patients (success rate = 69%). (Ozalp et al., 2021)

Kim et al. stated that the risk for delayed or incomplete healing of MRONJ after surgical intervention rises the higher the disease is classified in the AAOMS stage. (see: Table 3 - AAOMS staging) Delayed resolution occurred in 6 out of 34 patients (18%), 2 patients (6%) showed no resolution. The other 26 patients showed complete mucosal healing. (Kim et al., 2014)
Zelinka et al. showed a significant association between size of necrotic bone and treatment response. (Zelinka et al., 2021)
Gurav et. al published a series of 15 patients with 16 MRONJ lesions sites. (one patient suffered from 2 lesions) Eight lesions (50%) showed complete healing at the end of 1 month. After 4 months 13 lesions (81.50%) were completely healed, 2 lesions (12.5%) were downgrades, and 1 lesion (6.25%) did not respond to treatment. Number of doses of bone modifying agent was only factor found associated with nonhealing of in their study. (Gurav et al., 2022)
Considering the article by Kim. et al. and Zelinka et al., it shows that delayed healing processes might occur in patients treated for MRONJ. Especially higher AAOMS stage

(size of necrotic bone) and number of doses administered of antiresorptive agents should be considered as risk factors for delayed or troubled healing. (Gurav et al., 2022, Kim et al., 2014, Zelinka et al., 2021)
Albertos et al. showed that smoking and zoledronic acid (compared to other types of BPs) significantly increases risk of MRONJ recurrence. They performed one of the larger case series with 70 patients included, 18.6% of them showed MRONJ recurrence. (Sanchez-Gallego Albertos et al., 2021)

Mauceri er al. used a Er,Cr:YSGG laser to remove necrotic bone and then applied PRP to the surgical site. They reported complete wound healing in only 3 out of 10 patients treated, improvement of symptoms in 8 out of 10. (Mauceri et al., 2018)
Also Duarte et al. reported a relatively low success rate with only 4 out of 10 patients who showed complete healing. (Mathias Duarte et al., 2014)

4.2.3 Case series – summary

Due to the large number of patients included, a more realistic view is likely to be obtained in comparison with case reports. Case series showed a wider range in terms of the success rate of the treatment. A few papers described quite low success rates of 40% or even lower, they usually included around 10 patients. (Mauceri et al., 2018, Mathias Duarte et al., 2014) Most case series – especially the ones with more patients included - described success rates of around 80% and above. (Sanchez-Gallego Albertos et al., 2021, Zelinka et al., 2021, Nica et al., 2021)
These data appear realistic in the context of clinical treatment and also match with the previously known data from the surgical treatment of MRONJ published e.g. in the European guidelines. (Schiegnitz et al., 2018)

Another interesting point is that due to the larger collective, individual factors (such as smoking) can be evaluated. It seems logical that smoking and a higher AAOMS grade are risk factors for poor or slowed healing. Furthermore, zoledronic acid might be a risk factor for delayed mucosal healing. (Sanchez-Gallego Albertos et al., 2021, Zelinka et al., 2021, Kim et al., 2014)
Although they have a higher level of evidence than case reports, case series must also be viewed critically. Thus, it is not possible to judge whether the surgical procedure in combination with APC is superior or inferior compared to other treatment options.

Nevertheless, with many cases documented, it is proven that surgical resection of necrotic bone with additional use of APCs in MRONJ is performed frequently and - in most cases – a high success rate can be expected.

4.3 Studies at medium level of evidence (3b)

4.3.1 Comparison of treatment protocols with and without APCs

In 2012 Martins et al. released an article where they retrospectively analyzed 22 cases treated for MRONJ. According to the AAOMS stage the patients were assigned to one of the following groups, the higher the grading was, the more likely they were allocated in Group 2 or 3. 95% of the patients included did receive chemotherapy for oncological reasons. Photobiomodulation (PBM) was performed with a low intensity Laser (660nm).

- G1 (n=3) Protocol: Antibiotics only
- G2 (n=5) Protocol: Antibiotics + surgery
- G3 (n=14) Protocol: Antibiotics + surgery + PRP + PBM

In G3 12 out of 14 patients (86%) were cured, in G2 2 out of 5 patients (40%) showed complete healing. In G1 only 1 out of 3 patients was cured. (Martins et al., 2012)
As limitations following must be mentioned: retrospective study design with a relatively small sample size, especially in G1 and G2 and vaguely defined group allocation. Keeping these in mind we still can conclude that this study offers a direct comparison between usual surgical procedure and surgical procedure combined with APCs (PRP). Additionally, in G3 PBM was performed, so PBM and PRP cannot be evaluated separately from each other. Although almost all patients received chemotherapy, which tends to worsen the chances of cure, G3 showed a very good outcome, especially in direct comparison to G2 (healing rate: 86% (G3) vs. 40%(G2)).
In summary, this suggests that APCs tend to have an important positive influence.

Also in 2012 Coviello et al. published a paper where they compared 4 patients with standard surgical treatment versus 3 patients with additional use of APCs (PRP), they also showed a favorable outcome for the group treated with surgery and PRP, due to the small sample size the results must be viewed critically. (Coviello et al., 2012)

4.3.2 Summary

The two papers discussed above were assigned to evidence level 3b. Unlike case reports and case series, they allow direct comparison between groups of patients treated with or without APC. Of course, these works also have limitations, they were mentioned above in detail. Nevertheless, these studies consistently point to the positive influence of APCs in the surgical treatment of MRONJ.

4.4 Higher level of evidence (2b)

In 2014 Pelaz et al. investigated a group of patients suffering from MRONJ where the standardized treatment recommended by the AAOMS has failed. (see: 1.1.6 Therapy of MRONJ) If possible, depending on the general health condition, another surgery with additional use of APCs (PRGF) was performed (G1, n=5), if not they only applied teriparatide subcutaneous (G2, n=4). They reported good outcomes in G1 with 5 out of 5 persons reached complete mucosal healing, whereas in G2 only 1 out of 4 persons reached this goal. (Pelaz et al., 2014)

Although various limitations existing (small sample size, non-randomized) this might be an interesting article. Pelaz et al. showed good results after surgical resection combined with APCs in patients with recurrent MRONJ where “traditional” treatment protocols (without APCs) had failed before.

Tenore et al. published a retrospective study in 2020 where they analyzed 3 different groups with in total 34 patients. They included only MRONJ with AAOMS stages 1 or 2, stage 3 was excluded.

- Group 1 (G1) n=13 Protocol: Antibiotics + surgery + PRF + PBM (4 weeks)
- Group 2 (G2) n=8 Protocol: Antibiotics + surgery
- Group 3 (G3) n=13 Protocol: Antibiotics + PBM (4 weeks)

They showed a significant better outcome for G1 (100% healing rate) than G2 and G3, G3 was the group with the lowest outcome (46% healing after 3 month / 54% improvement of stage or recurrence). Their analysis did not show association between outcome and e.g. smoking habits or the AAOMS stage. They stated that G1 had a higher rate of smokers than G2 and G3. (Tenore et al., 2020)

This study showed a clear superiority of surgical procedure when treating MRONJ, especially if its combined with PRF. The overrepresentation of smokers in G1 may

potentially accentuate the strength of the treatment modality, as smoking has been shown in other studies tending to worsen the outcome. (Sanchez-Gallego Albertos et al., 2021)
It must be mentioned that the group allocation of the patients was not clearly defined, and that the cohorts in the retrospective analysis were relatively small, which limits the validity of the results. Furthermore, higher AAOMS disease stages where excluded.

Also, in 2020 Szentpeteri et al. published a retrospective cohort study where they compared two groups, one treated with and one without PRF. Patients were divided into two groups based on the time of treatment. Both groups received “minimal invasive surgery” and an antibiotic therapy.

- G1 (2009-2014) n=73 Protocol: antibiotics +minimal invasive surgery
- G2 (2015 – 2017) n=28 Protocol: antibiotics +minimal invasive surgery+ PRF

In G1 (without PRF) they observed a recovery rate of 58,5% by comparison, a rate of 82% was observed in G2 (with PRF). (Szentpeteri et al., 2020)
In addition to the unavoidable structural weaknesses of a cohort study, the following points must also be critically examined in this work:
Obviously, a few patients were not evaluated for outcome, as they are missing from the outcome results – without explanation by the author. These discrepancies in the patient numbers negatively affected the reliability of the statistical analysis. Furthermore, there was no definition given for “minimal invasive surgery”, with which the reproducibility of the work is limited. These concerns were also raised in two published "letters to the editor" and have not yet been dispelled. (Myoken et al., 2020, Giudice et al., 2020)

4.4.1 Results without significant difference

In January 2022 an article by Blatt et. al was published. They compared a group of 20 patients (study arm 1, n=20) treated with surgical resection of necrotic bone to another group (study arm 2, n=25) where PRF was used additionally. The patients mostly showed MRONJ in stage I (78.8%), followed by stage II (19.2%), and one patient in stage III (1.9%). In 25 cases (48%), MRONJ had already been treated before, with 12 patients (48%) having had more than one previous surgery.
The overall dehiscence rate was 30% after surgery (no differences between study arms). The authors themselves stated various limitations, most important that the majority of the patients presented with early (stage I) disease, consequently the results should be

interpreted with caution for higher stages. Furthermore, the patients were assigned to one of the study arms chosen by attending physician (no randomization). (Blatt et al., 2022) This presents one of the few works where the use of APCs showed no benefit in terms of mucosal healing or Quality of life. It should be mentioned that both study arms performed equally and - potentially - patients with worse conditions were more likely to receive treatment with APCs as the physician might assume that this is a “better” treatment.

4.4.2 APCs and new approaches

Mentioned in 4.1.2 Special case reports – a selection Kim et. al published a case they treated with PRF and additional BMP with good results. (Kim et al., 2016) They continued research on this and just one year later they were able to show in a cohort study that the addition of BMP to PRF showed an improvement in wound healing in the surgical treatment of MRONJ. (Park et al., 2017) It should be noted that - as stated several times before – up to now there is no clear evidence on the treatment with PRF, so it is difficult to interpret the results with regard to the research question of this paper as they did not compare their method to a group treated without PRF.
Nevertheless, it shows the progress in research on this topic and that new approaches or supplements in the treatment of MRONJ are being invented.

4.4.3 Summary

The five papers discussed above were assigned to evidence level 2b, involving four cohort studies (Pelaz et al., 2014, Tenore et al., 2020, Szentpeteri et al., 2020, Blatt et al., 2022) and one low quality RCT. (Park et al., 2017)
Three of the five works analyzed showed favorable results when APCs were used. (Pelaz et al., 2014, Tenore et al., 2020, Szentpeteri et al., 2020) Interestingly, Blatt et al. could not demonstrate any advantage in the treatment with PRF, here it must be noted that methodologically it is a very good study. The exact limitations were discussed above, both study arms performed in the same way. (Blatt et al., 2022)
As the level of evidence increases, so do the technical requirements for scientific work. As a result, there are more theoretically possible methodological errors. Thus, it must be noted that - although the results very clearly point to a superiority of surgical treatments with PRF - the work of Szentpeteri et al. is viewed very critically. (Szentpeteri et al., 2020, Myoken et al., 2020, Giudice et al., 2020)

4.5 Highest level of evidence (1b)

Giudice et al. performed a prospective randomized, single-blind, monocentric clinical trial assigned to evidence level 1b, the highest score found within this literature search. They investigated two groups of patients suffering from MRONJ at stage 2 or 3:
"PRF group" - included 24 patients treated with PRF in addition, the other – "non-PRF group" included 23 patients who were treated with surgical removal of the necrotic bone only. Then they evaluated treatment success after 1, 6 and 12 months:
1 month: PRF group 87.5% vs. 60,9% non-PRF group
6 months: PRF group 95,8% vs. 82,6% non-PRF group
12 months: PRF group 95,8% vs 91,3% non-PRF group
In the statistical analysis of this work only the difference in the first month after surgery was significantly in favor of the PRF group. (Giudice et al., 2018)
Although a statistically significant difference was found one month after treatment, the PRF-group had better outcomes at all times Giudice et al. did a follow-up.
In the opinion of the author of this literature review the timing of the healing process could be explained by the way how APCs work. When PRF is applied to the surgical site it contains lots of growth factors and so accelerating and improving soft tissue healing. At some point the growth factors are processed and thus the concentration slowly decreases. Consequently, it seems logical that the effect of APCs is temporary and wears off over time.
Summarizing this, the fact that the difference in the healing success in the work of Giudice et al. was only significant after one month appears like a confirmation of the assumption that APCs are a well-functioning adjunct to the conventional surgical approach.
Furthermore, it should be mentioned that this work is, to the best of the author's knowledge, the only prospective, randomized controlled trail investigating this topic. As it is often the case, a larger group of patients and a multi-center design would further improve the power of this study.

5 Conclusion and clinical recommendations

In this thesis a review of literature was conducted to assess the current status of knowledge according the use of APCs in the surgical treatment of MRONJ. Furthermore, an evidence-based recommendation for the use of APCs in the treatment of MRONJ will be made based on the current literature.

The treatment of MRONJ remains often challenging in clinical practice, especially if soft tissue healing might be troubled, which can be followed by local infection, pain and/or disease recurrence. It must be assumed that these wound healing troubles are caused by antiresorptive agents, such as bisphosphonates due to their long-time retention in the tissues. From a theoretical point of view APCs promise an improvement in mucosal healing after surgical resection through a higher local concentration of growth factors – which is assumed to be the major weakness in "conventional" surgical MRONJ treatment due to the fact that the healing process is disturbed by the antiresorptive agents. (see: 1.2.2.2 Growth factors)

Up until now the so far existing official guidelines do not give a clear recommendation if or if not, APCs should be used in the treatment of MRONJ. (Schiegnitz et al., 2018, Ruggiero et al., 2014) The literature included in this work was used to clarify the beneficial use of APCs in the surgical treatment of MRONJ. However, most of the analyzed literature were found to be case reports or case series (n=36) that were assigned to a low level of evidence (4 or 5). In total these studies represent the medical history of 523 patients treated for MRONJ. (see: Table 6 – Analysis: Type of study). With few exceptions (Mauceri et al., 2018, Mathias Duarte et al., 2014) these studies describe very good treatment outcomes (>80% success rate) when using APCs. This group of articles proof that surgical resection and APCs can potentially reach good outcomes and have already been used multiple times in clinical practice. Furthermore, no bad effects or adverse events have been reported when APCs were used. (see: 4.1 Case reports and 4.2 Case series)

Beside the numerous case reports and case series two case control studies were found and assigned to evidence level 3b. (Martins et al., 2012, Coviello et al., 2012) In total they compared 29 patients treated with and without additional APCs. Both studies showed favorable outcomes when APCs were used.

Five articles were assigned to evidence level 2b (in total 254 patients). Three of them demonstrate clear superiority in terms of an APC-use. (Pelaz et al., 2014, Tenore et al., 2020, Szentpeteri et al., 2020) Methodically weakness in the article of Szentpeteri et al.

was discussed at headline 4.4. Blatt et al. could not show a benefit in mucosal healing or in the quality of live when APCs were used compared to the conventional surgical therapy alone. (Blatt et al., 2022)
One article by Giudice et al. was classified as evidence level 1b, the highest found in this literature review. Giudice et al. were able to demonstrate improved soft tissue healing when APCs were used, especially in the first month after surgical intervention. (Giudice et al., 2018)

In summary, APCs seem to be a promising support in the surgical treatment outcome of MRONJ. Although there is no clear recommendation regarding the beneficial use of APCs in the literature so far, the overwhelming majority of scientific works report good results and show high healing success rates in the therapy of MRONJ when APCs are used. If investigated (e.g. case-control-studies, RCTs), cases where APCs were used often showed superior outcomes compared to “surgery alone” cases. Furthermore, there were no bad effects or adverse events observed when APCs were used.
After reviewing the literature of this work, the beneficial use of APCs is most likely given in patients with additional risk factors are present and when conventional surgical techniques are likely to produce poor outcome.
In more detail, long periods of bisphosphonate treatments (especially zolendronic acid), the presence of additional medications or diseases that can potentially disrupt normal wound healing (chemotherapy, long term steroid therapy, diabetes, etc.) should especially be considered as such risk factors. Also, the extend or expansion of bone necrotic lesions (high AAOMS stages) and the medical history of the patient (recurrent MRONJ lesions) should indicate the additional use of APCs when surgical therapies are performed.
Overall, the use of APCs can broadly be indicated, since no negative effects are known. In parallel if no additional risk factors are present (e.g. short term therapy with denosumab, small MRONJ lesions, low AAOMS stages, missing further medication or diseases that affect normal wound healing) the use of APCs added to the conventional surgical therapy does not seem to significantly increase the treatment success. In these cases, the higher technical effort and the time needed to get APCs ready to use might rather be a disadvantage.
On that background, the following table gives an overview about the clinical recommendations for a beneficial use of APCs in the surgical treatment of MRONJ.

Table 10 – Recommendations for APC usage in surgical MRONJ treatment

Conventional surgical techniques	Additionally APCs recommended
Low AAOMS stage	High AAOMS stage
Short term medication with denosumab	Long term medication of AR, especially zolendronic acid
No additional medication at risk (chemotherapy, steroids, etc.)	All medication that might affect soft tissue healing
No additional disease at risk (diabetes mellitus, peripheral artery disease, etc.)	All additional disease that might affect vascular growth / tissue healing
First time of MRONJ occurrence	Recurrence of MRONJ

Beside these recommendations, it must be mentioned that regarding this topic studies with a high level of evidence are still rare. Therefore, more high-level evidence studies are needed to support the recommendations of this work.

Until official guidelines provide a clear recommendation regarding the use of APCs in the surgical treatment of MRONJ, the suggested procedure (see: Table 10 – Recommendations for APC usage in surgical MRONJ treatment) should serve as a template. It is based on the currently available literature on the subject.

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