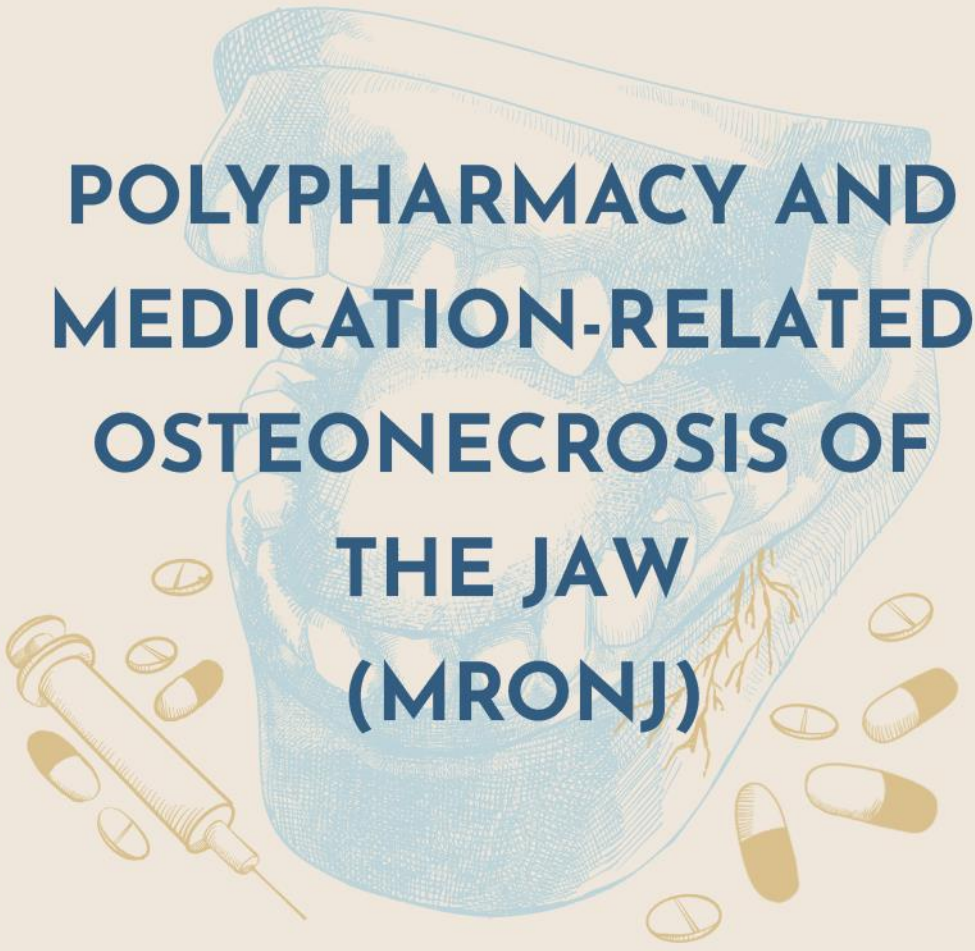
Isti Rahayu Suryani



POLYPHARMACY AND MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)

Identifying Patients at Risk

KU Leuven
Biomedical Sciences Group
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KU LEUVEN

DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

POLYPHARMACY AND MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ): IDENTIFYING PATIENTS AT RISK

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Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

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June 2024

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POLYFARMACIE EN MEDICATIE-GERELATEERDE OSTEONECROSE VAN DE KAAK (MRONJ):
IDENTIFICATIE VAN RISICOPATIËNTEN

Isti Rahayu SURYANI

Proefschrift voorgedragen tot
het behalen van de graad van
Doctor in de Biomediche
Wetenschappen

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Juni 2024

Preface

This doctoral thesis consists of 5 research articles, preceded with a general introduction, and concluded with a general discussion. The general introduction is partly based on 1 published systematic review of which parts and discussion have been used. Furthermore, the research articles followed the standard scientific IMRAD structure (Introduction, Materials and Methods, Results and Discussion) and were based on the following peer-reviewed publications:

General introduction

Article 1

Suryani IR, Ahmadzai I, Shujaat S, Ma H, Jacobs R. Non-antiresorptive drugs associated with the development of medication-related osteonecrosis of the jaw: a systematic review and meta-analysis. Clin Oral Investig. 2022 Mar;26(3):2269-2279. doi: 10.1007/s00784-021-04331-7. Epub 2022 Jan 11. PMID: 35013781.

Risk factors of healing impairment following tooth extraction.

Chapter 1: Systemic factors

Article 2

Suryani IR, Shujaat S, Ivković U, Coucke W, Coropciuc R, Jacobs R. Risk of healing impairment following tooth extraction in patients administered with antiresorptive and non-antiresorptive polypharmacy. J Stomatol Oral Maxillofac Surg. 2023 Sep 23;125(2):101645. doi: 10.1016/j.jormas.2023.101645. Epub ahead of print. PMID: 37748709.

Article 3

Suryani IR, Shujaat S, That MT, Coucke W, Jacobs R. Prediction of wound healing status following dental extraction using Adapted-University of Connecticut Osteonecrosis Numerical Scale, Health Science Reports (Accepted on 23 May 2024).

Chapter 2: Local factors

Article 4

Suryani IR, Ahmadzai I, That MT, Shujaat S, Jacobs R. Are medication-induced salivary changes the culprit of osteonecrosis of the jaw? A systematic review. Front Med (Lausanne). 2023 Aug 31; 10:1164051. doi: 10.3389/fmed.2023.1164051. PMID: 37720502; PMCID: PMC10501800.

Article 5

Gracea RS, Suryani IR, Fontenele RC, Araujo HG, Radi S, Elgarba BM, Shujaat S, Coropciuc R, Jacobs R. Alveolar socket surface as local risk factor from MRONJ development in polypharmacy patients. Oral Disease (Under review).

Personal acknowledgements

“Be grateful for whoever comes, because each has sent as guide from beyond”

-Rumi-

Finally, the day has arrived marking the end of long road filled of challenges, criticism and invaluable lessons. Alhamdulillah, “All the praises and thanks be to God who is the Lord of the universe”. I am here. On the long journey to completing this PhD, I am grateful for the excellent support I received from various institutions and individuals.

My deepest gratitude goes to my supervisor, **Professor Reinhilde Jacobs**, for granting me the opportunity to embark on this remarkable journey. I vividly recall an advertisement video of KU-Leuven few years ago, which claimed that every professor in KUL will force you to give the best part of you, and I have proven this statement on you. Thank you for never leaving me behind, always supporting me, and facilitating my academic growth from the first moment I stepped into the international academia. It is an honour for me to have you as my mentor and to be one of your students among those top scholars around the world. If it takes 10.000 hours to achieve mastery, then it takes at least 10.000 books to catch up with your intellectual level.

Professor Sohaib Shujaat, thank you for accepting my request to be the co-supervisor immediately upon my 2nd year PhD program. Your expertise, attention to details, and suggestion from the moment I started my international publication have pushed me to refine my writing skills. Outside research, I am glad to have you as a mentor and at the same time as a friend to talk some problems related to PhD.

I would also thank to my internal jury members, **Professor Carine Wouters** and **Professor Simon (Mariano N) Pedano de Piero** for the valuable insights on my PhD projects. Moreover, I would thank to my examiners in the public defense, **Professor Suryono** and **Dr Faris Younes** for taking your time to read my dissertation and give me insightful questions and feedback.

I would also like to express my gratitude to all OMFS-IMPATH team and especially Rudra´s members. How lucky I am to be part of this outstanding research group. Thank you for the good laugh and beautiful friendship. Please do remember, you have one Indonesian sister, keep in touch!

Personally, I want to thank to **Rocharles Cavalcante Fontenele** and my little sister, **Rellyca Sola Gracea**, for helping me out with the last article, you guys are the best! And thank to **Nele Vanloocke** for your assistance in administrative matters and sometimes bothered you with personal letters that needed Dutch translation, it means a lot during life in Leuven.

Thank you for **BPPLN-Dikti Scholarship** and all the staff members. With the funding and supportive management, I could finish the task and will give back to Indonesia as well,

I am intellectually and mentally indebted to my university, **Universitas Gadjah Mada**, **the Deans and colleagues in Faculty of Dentistry** and the sisters from different parents in **Department of Dentomaxillofacial Radiology** and **Manis-Manja Group**. Thank you for consistently be my side through my ups and downs of my educational journey.

Thank you for the administrative and life support for our family from **Indonesian Embassy in Belgium and European Union**. For the friendship and generosity from **Indonesian Student Association (PPI)**, **their families,** and **Indonesian community in Belgium and Netherlands**. You make us feel home when far away from home.

Through many things I earned, family is a given. I am blessed to be born as the daughter of **M. Ichsan** and **Pudji Astuti**, the daughter in law of **Fathonah** and the sister of **Yuni-Agung** and **Yudi-Fifin**. Thank you for continuous supports and prayers for me.

Lastly, the greatest gratitude goes to my super team, my husband, **Mohammad Masrur**, and our sons, **Nandra** and **Reza**. You are the force behind anything good that I have in life. Thank you for being the reliable source and strength, and for loving me unconditionally, even when I must juggle the roles between being a mother, wife, and PhD student abroad. I can not wait to have new adventures with you!

I would like to extend my heartfelt gratitude to those whose names I can not mentioned individually. Thank you for being an integral part of these outstanding milestones in my life. I am truly grateful with your help, kindness, and beautiful moments we have shared.

Isti Rahayu Suryani

Leuven, June 2024

Table of contents

List of abbreviations

AAOMS	American Association of Oral and Maxillofacial Surgeons
ADRs	Adverse Drug Reactions
AR	Anti-Resorptive
A-UCONNS	Adapted-University of Connecticut Osteonecrosis Numerical Scale
BMAs	Bone Modifying Agents
BMI	Body Mass Index
BPs	Bisphosphonates
BRONJ	Bisphosphonates-Related ONJ
CBCT	Cone-Beam Computed Tomography
CI	Confidence Interval
CPS	Comorbidity–Polypharmacy Score
DICOM	Digital Imaging and Communication In Medicine
DM	Diabetes Mellitus
DRONJ	Denosumab-Related ONJ
ES	Effect Size
HIV	Human Immunodeficiency Virus
ICC	Inter-Class Correlation Coefficient
IL	Interleukin
IL-IRA	Interleukin-1 Receptor Antagonist
IM	Intramuscular
IV	Intravenous
MAB	Monoclonal Antibody
MIP	Macrophage Inflammatory Protein
MMP8	Matrix Metallopeptidase 8

MMP9	Matrix Metallopeptidase 9
MMPs	Matrix Metalloproteinases
MRONJ	Medication-Related Osteonecrosis of the Jaw
mTOR	Mammalian Target of Rapamycin
NOS	Newcastle–Ottawa Scale
ONJ	Osteonecrosis of the Jaw
OPG	Osteoprotegerin
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RA	Rheumatoid Arthritis
RANK	Receptor Activator of Nuclear Factor-Kappa
RANKL	Receptor Activator of Nuclear Factor-Kappa-Ligand
RMBS3	Ribonucleic Acid Binding Motif Single Stranded Interacting Protein 3
RoB	Risk Of Bias
RWS	Resting Whole Saliva
SD	Standard Deviation
SS	Sjogren's Syndrome
STL	Standardized Tessellation Language
SWS	Stimulated Whole Saliva
TKIs	Tyrosine Kinase Inhibitors
TNF	Tumor Necrosis Factor
VEGF	Vascular Endothelial Growth Factor

GENERAL INTRODUCTION, AIMS AND HYPOTHESIS

Polypharmacy and Medication-Related Osteonecrosis of the Jaw (MRONJ): Identifying Patients at Risk

General Introduction, Aims and Hypothesis

This chapter was partly based on the following systematic review:

Suryani IR, Ahmadzai I, Shujaat S, Ma H, Jacobs R. Non-antiresorptive drugs associated with the development of medication-related osteonecrosis of the jaw: a systematic review and meta-analysis. Clin Oral Investig. 2022 Mar;26(3):2269-2279. doi: 10.1007/s00784-021-04331-7. Epub 2022 Jan 11. PMID: 35013781.

General Introduction

1. Definition of polypharmacy

From recent literature reviews, the concept of polypharmacy can be classified into four distinct categories. These include definitions solely based on numbers, numerical definitions incorporating duration of therapy, numerical definitions considering the healthcare setting, and descriptive definitions [1]. Within numerical definitions alone, the range of medications varies widely, starting from two or more up to 11 or more [2]. To gauge the severity of polypharmacy, numerical polypharmacy is categorized into four groups: minor-polypharmacy (2 to 4 medications), moderate-polypharmacy (4 to 5 medications), major-polypharmacy (5 to 9 medications), and hyper-polypharmacy (10 or more medications) [3].

Meanwhile, the term polypharmacy including the duration of therapy has different variations. Additionally, polypharmacy with consideration to duration of therapy shows diverse ranges, spanning from 2 to 9 medications used for 90 days or more [4,5], over 240 days [6], within the same quarter of a year [7], and or within the same month [8]. Hospital settings introduce further variations in polypharmacy definitions, such as the presence of 5 or more medications after hospital discharge [9], 5 to 9, or more than 10 medications during the hospital stay. Lastly, descriptive definitions of polypharmacy refer to the necessity, lack of necessity, or unclear benefit of medication use [10].

2. Epidemiology

The occurrence of polypharmacy, which refers to the simultaneous use of multiple medications, varies significantly among studies, attributable to a range of factors including geographic locations, age distribution, and healthcare environments [1]. As an illustration, a cross-sectional examination carried out in Europe unveiled a prevalence that varied between 26.3% and 39.9% among the elderly residing in the community [11]. A cross-sectional analysis of electronic primary healthcare records for individuals in Scotland revealed that the incidence of polypharmacy (the use of four to nine medications) was 28.6% among those aged 60–69 and 51.8% among those aged 80 and older. Furthermore, among those aged 60–69 years, 7.4% of patients were found to be taking ten or more medications, compared to 18.6% among those aged 80 years and older [12].

Differences in these results may be notably influenced by variations in methodologies and definitions, as well as self-reported medication use. Furthermore, notable discrepancies can be observed in the prevalence of polypharmacy among European nations, where rates vary from 26.3% in Switzerland to 39.9% in the Czech Republic. The overall prevalence of polypharmacy was almost identical for women (32.1%; 95% CI 31.3–32.9) and men (32.2%; 95% CI 31.4–33.0) [11]. The prevalence of polypharmacy is significantly influenced by socioeconomic factors, as evidenced by the higher rates of polypharmacy observed in more impoverished populations. This highlights the intricate relationship that exists between demographics, healthcare access, and medication management practices [13].

3. Polypharmacy in oral health

Polypharmacy in elderly patients mostly related exhibit poor oral health even after adjusting age, sex, BMI (Body Mass Index), chronic disease, cognitive and motor function [14]. The most common medication-induced oral manifestation is summarized in Figure 1.1. [14-16].

From the figure, it is a known that one of the oral manifestations of the medications is xerostomia. The coexistence of acid reflux and inadequate salivary flow may contribute to a low oral pH, which stimulates the proliferation of acidophilic bacteria. Consequently, this can result in the deterioration of mucosa and tooth structure [17]. A significant incidence of xerostomia and medication-related osteonecrosis of the jaw (MRONJ) was identified among patients who were prescribed five or more medications (71%), with xerostomia being identified as a side effect in approximately 80%-100% of these patients. In case-control studies, the incidence of xerostomia and MRONJ was approximately three times greater in patients who received medication as opposed to those who did not [18].

4. Medication-related Osteonecrosis of the Jaw (MRONJ)

Osteonecrosis of the jaw (ONJ) is a well-known condition where the exposure of jawbone occurs secondarily to the intraosseous vascular supply disruption or avascular necrosis. The main causes of ONJ include radiation therapy, long-term or high dose administration of corticosteroids, chronic use of recreational drugs, and treatment with antiresorptive and/or antiangiogenic agents [19]. Out of all the types of ONJ, medication related osteonecrosis of the jaw (MRONJ) is the most recent addition to the ONJ classification which was first described in 2003 in patients who received nitrogen-containing bisphosphonate therapy [20].

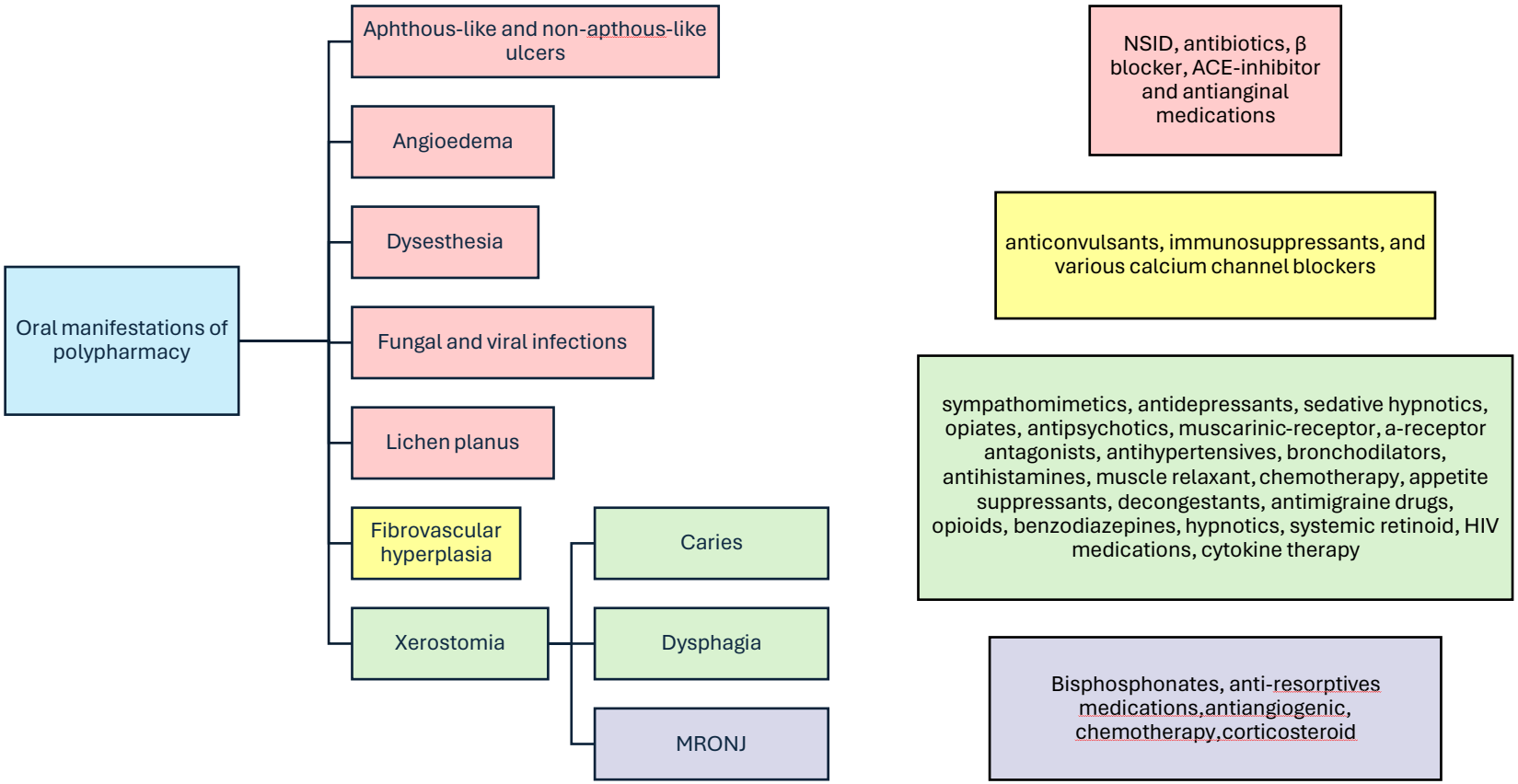

Figure 1.1. Drugs-induced oral reactions[14]–[16].

Until now, MRONJ has been estimated to have a prevalence of approximately 0.001-0.01% in osteoporotic patients and 1-15% in oncology patients [21]. It is mainly characterized by non-healing exposed bone especially in patients with a history of antiresorptive or antiangiogenic drug therapy. Even though it is a rare disease, the potential of MRONJ to profoundly impact the patients' quality of life due to the progressive maxillofacial bone destruction cannot be ignored. Clinical manifestations might vary depending on the course of the disease and might include, exposed or non-exposed bony lesion, pain, infection, intra- or extra-oral fistulae, pathological fracture, or alteration of regional nerve function [22]. In 2006, Ruggiero et al. developed a MRONJ staging system and diagnostic criteria which was later on adapted in 2014 by American Association of Oral and Maxillofacial Surgeons (AAOMS) based on pharmacological history and clinical and radiographic features. According to AAOMS, MRONJ is diagnosed in a patient if the following two criteria are met: history of antiresorptive or antiangiogenic drug therapy; exposed/non-healing bone prevailing for a period of 8 weeks or more, with no prior history of metastatic disease of the jaws or radiation therapy in the head and neck region [23].

The MRONJ lesions are staged (stage 0 – stage 3) based on clinical and radiological features as proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS). Stage 0: no exposed bone + non-specific signs/symptoms, stage 1: asymptomatic exposed bone, stage 2: symptomatic exposed bone + infection/pain, stage 3: symptomatic exposed bone + infection + pathological fracture/extraoral fistula/ oro-antral or oro-nasal communication/ osteolysis extending to inferior mandibular border or sinus floor [24].

5. Drugs related to the development of MRONJ

a. Anti-resorptive medications

Bisphosphonates

Bisphosphonates (BPs) are a class of anti-resorptive (AR) drugs that have demonstrated efficacy in the treatment of various cancer-related complications. These include spinal cord compression, pathologic fractures [skeletal-related events (SREs)] caused by bone metastases in solid tumors (e.g., breast, prostate, and lung cancers), and multiple myeloma [24]. BPs are administered intravenously to patients with solid tumor bone metastases, including breast, prostate, bladder, lung, and kidney cancers, as well as certain conditions involving abnormal growth of lymphocytes [25, 26]. Additionally, BPs are used in patients with osteoporosis and osteopenia to prevent fragility fractures. These medications include alendronate (Fosamax®), risedronate (Actonel®) or parenterally (zoledronic acid [Reclast®]), and ibandronate (Boniva®) [27].

Notwithstanding the considerable advantages associated with bisphosphonates and other antiresorptive drugs, a notable drawback is the occurrence of ONJ due to the medication's effects when a local risk factor is present [28]. Although the precise mechanism by which bisphosphonates function remains unknown, several studies have indicated that they bind with great affinity to hydroxyapatite crystals that are present in bone. This binding subsequently hinders the resorptive capability of osteoclasts through the induction of apoptosis [29, 30]. Furthermore, the absence of cytokines secreted by osteoclasts may impede differentiation of osteoblasts, thereby impeding the ability of bone to regenerate; this further elucidates the notion of Bisphosphonates-ONJ (BRONJ). Bisphosphonate therapy may consist of nitrogen-containing bisphosphonates (pamidronate, alendronate, ibandronate, risedronate, zoledronic acid) or non-nitrogen-containing bisphosphonates (etidronate, clodronate, tiludronate) [31]. Although 95% of the substance is eliminated from the body within six hours, its potent affinity for the bone may cause its half-life to exceed ten years [29]. The inhibition of the bone remodelling process is additionally accomplished through the equilibrium between osteoblast-produced receptor activator of nuclear factor-kappa-B (RANK) ligand (RANKL) cytokine, which stimulates bone resorption, and osteoprotegerin (OPG), which impedes bone resorption by impeding the binding of RANK/RANKL [32].

Denosumab

Denosumab, is a recently developed, anti-resorptive medication [33]. It is a human monoclonal IgG2 antibody that mimics the biological effect of osteoprotegerin (OPG) by selectively binding to the ligand of the Receptor Activator of Nuclear Factor κβ (anti-RANKL), which disrupts the system that regulates bone metabolism (RANKL/RANK/OPG) [34]. It reduces bone resorption by interfering with the formation, differentiation, and survival of osteoclasts through the inhibition of RANKL/RANK interaction [31].

Denosumab is a therapeutic agent employed to address osteoporosis and various malignant bone disorders [32]. The incidence of denosumab-related ONJ (DRONJ) is estimated to be 0.01-3.03 percent in patients with osteoporosis and 1.2 percent in patients with malignancy [21]. In contrast to bisphosphonate, denosumab possesses a brief half-life due to the fact that RANKL-inhibitors do not attach to the bone. Consequently, the impact of denosumab on the bone is transient and largely diminishes within six months following the discontinuation of treatment [23].

The duration of occurrence is the primary distinction between Bisphosphonates-ONJ (BRONJ) and Denosumab-ONJ (DRONJ); BRONJ can manifest between 33 months (when administered orally) and 48 months (when administered

intravenously) [31]. On the contrary, DRONJ manifests shortly after administration [8]. Furthermore, BRONJ is extremely susceptible to variation in dosage, duration, and route of administration [26].

b. Non-antiresorptive medications

To fill the knowledge gap of the non-anti resorptive drugs that related to development of MRONJ, we conducted a systematic review with the aim to provide evidence related to the association between non-antiresorptive medications and MRONJ as well as to perform a meta-analysis on the available outcome data [35].

The result of this study showed a significant association existed between MRONJ and non-antiresorptive drugs. However, due to the availability of limited evidence, the findings should be interpreted with caution. The risk of developing MRONJ should be assessed for each drug individually to allow an improved prediction of MRONJ occurrence. Dentists should be aware of these drugs and proper management guidelines should be established. Unlike bisphosphonates, majority of the non-antiresorptive drugs mentioned in the review have a shorter half-life which might allow the dentist to apply the principle of "drug holiday" following concurrence from the drug prescribing clinician.

The quantitative synthesis showed a higher association between MRONJ and chemotherapeutic agents and corticosteroids. The chemotherapeutic agents suppress the immune system and inhibit the formation of osteoclasts. Additionally, the cytotoxic effects of these drugs on bone metabolism and vascularization also further increase the risk of MRONJ development. Zhou et al. found chemotherapy-related osteonecrosis to be more common in patients with multiple myeloma, which could be attributed to the fact the treatment regimens included both chemotherapeutic and antiangiogenic agents [36]. According to DeSesa et al., a higher risk of MRONJ was observed in patients undergoing chemotherapy with gemcitabine, which might have resulted due to the anti-angiogenic effect of the drug as it inhibits the formation of vascular endothelial growth factor (VEGF) [37]. Apart from chemotherapeutic agents, corticosteroids were also linked with a higher number of MRONJ cases, however these drugs have a complex pathway, and the mechanism appears to be multifactorial. The findings suggested that corticosteroids therapy for an extended period of time also increased the risk of developing osteonecrosis or avascular necrosis. The main reasons might include impairment of wound healing due to either suppression of VEGF production or decreased recruitment and volume of osteoclastic and osteoblastic precursors, which not only has the ability to cause early apoptosis, but it also impacts the born turnover [38].

Aims and Hypothesis

Dentoalveolar surgery in oncology patients who receive anti-resorptive drugs are prone to delayed wound healing and MRONJ occurrence. The risk of healing impairment following tooth extraction is also significantly associated with the administration of vitamin A, corticosteroids, and chemotherapeutic agents alone or in combination with anti-resorptive agents such as bisphosphonates and denosumab. Currently, there is a lack of scientific evidence on the contribution of polypharmaceutical administration on wound healing impairment and development of ONJ. It is also not clear if the administration of AR drugs within a polypharmaceutical cocktail predominantly responsible for the development of jawbone osteonecrosis or whether polypharmacy as such, even when no AR drugs are administered, can lead to the development of wound healing impairment and eventually MRONJ.

The overall aim of this Ph.D. project is to evaluate the impact of polypharmacy and to predict some risk factors on wound healing impairment following tooth extraction and thus prevent or anticipate problematic tooth extractions. It is hypothesized that polypharmacy may have a negative correlation with wound healing after dental extraction. Individuals taking a higher number of medications may experience delayed or impaired wound healing due to potential drug interactions, side effects, or compromised physiological processes caused by the multidrug administration.

The main objectives dealt within the different parts of this thesis are:

Chapter 1. Systemic Risk Factors of healing impairment following tooth extraction.

Subobjectives: (1) To primarily investigate the impact of polypharmacy (with or without AR drugs) on wound healing and occurrence of MRONJ following tooth extraction. (2) to identify patient-related risk factors which might influence the healing status. (3) to validate Adapted-University of Connecticut Osteonecrosis Numerical Scale (A-UCONNS) as a potential predictor of patient's risk of wound healing impairment.

The hypothesis was that wound healing in patients administered with AR+ non-AR polypharmacy was significantly impaired following tooth extraction. In addition, the A-UCONNS could act as a promising tool for predicting wound healing outcomes. It can provide clinicians the ability to pinpoint patients at high risk and allow tailoring

of patient-specific strategies for improving healing outcomes following tooth extraction.

Article 2: Risk of healing impairment following tooth extraction in patients administered with antiresorptive and non-antiresorptive polypharmacy.

Suryani IR, Shujaat S, Ivković U, Coucke W, Coropciuc R, Jacobs R. Risk of healing impairment following tooth extraction in patients administered with antiresorptive and non-antiresorptive polypharmacy. J Stomatol Oral Maxillofac Surg. 2023 Sep 23;125(2):101645. doi: 10.1016/j.jormas.2023.101645. Epub ahead of print. PMID: 37748709.

Article 3: Evaluation of wound healing outcomes in polypharmacy patients with A-UCONNS (Adapted-University of Connecticut Osteonecrosis Numerical Scale)

Suryani IR, Shujaat S, That MT, Coucke W, Jacobs R. Prediction of wound healing status following dental extraction using Adapted-University of Connecticut Osteonecrosis Numerical Scale, Health Science Reports (accepted).

Chapter 2. Local Risk Factors of healing impairment following tooth extraction.

Subobjectives: (1) to systematically assess the potential influence of medication-induced salivary changes on development of MRONJ. (2) to evaluate the relationship between extraction sites developing MRONJ following multiple tooth extractions in polypharmacy patients and the total alveolar socket surface area exposed by multiple extractions. The secondary aim involved assessing the number of tooth root extractions resulting in MRONJ development of the related extraction sockets.

The hypothesis was that the reduction in salivary flow and changes in the concentration of salivary proteins were associated with the development of MRONJ. Furthermore, patients with polypharmacy undergoing multiple tooth extractions are at higher risk to develop MRONJ in multiple extraction sites.

Article 4: Are medication-induced salivary changes the culprit of osteonecrosis of the jaw? A systematic review

Suryani IR, Ahmadzai I, That MT, Shujaat S, Jacobs R. Are medication-induced salivary changes the culprit of osteonecrosis of the jaw? A systematic review. Front Med (Lausanne). 2023 Aug 31; 10:1164051. doi: 10.3389/fmed.2023.1164051. PMID: 37720502; PMCID: PMC10501800.

Article 5. Alveolar socket surface as local risk factor from MRONJ development in polypharmacy patients

Gracea RS, Suryani IR, Fontenele RC, Araujo HG, Radi S, Elgarba BM, Shujaat S, Coropciuc R, Jacobs R. Oral Diseases (submitted).

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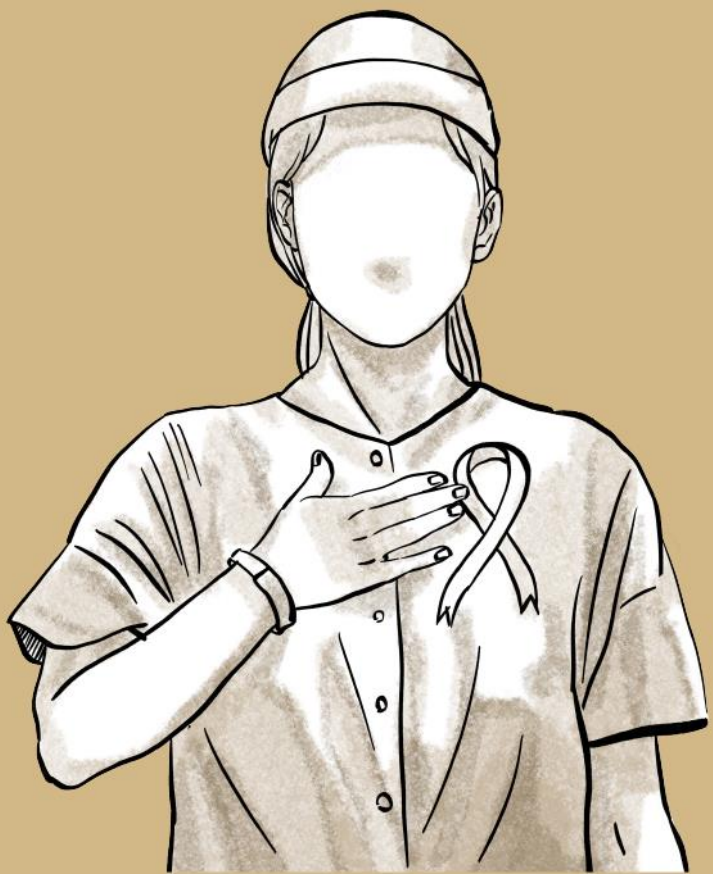
CHAPTER

01

SYSTEMIC RISK FACTORS OF HEALING IMPAIRMENT FOLLOWING TOOTH EXTRACTION



Polypharmacy and Medication-Related Osteonecrosis of the Jaw (MRONJ): Identifying Patients at Risk

Chapter 1
Systemic risk factors of healing impairment following tooth extraction

Article 2

Suryani IR, Shujaat S, Ivković U, Coucke W, Coropciuc R, Jacobs R. Risk of healing impairment following tooth extraction in patients administered with antiresorptive and non-antiresorptive polypharmacy. J Stomatol Oral Maxillofac Surg. 2023 Sep 23;125(2):101645. doi: 10.1016/j.jormas.2023.101645. Epub ahead of print. PMID: 37748709.

Article 3

Suryani IR, Shujaat S, That MT, Coucke W, Jacobs R. Prediction of wound healing status following dental extraction using Adapted-University of Connecticut Osteonecrosis Numerical Scale, Health Science Reports (accepted).

Article 2

Risk of healing impairment following tooth extraction in patients administered with antiresorptive and non-antiresorptive polypharmacy

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Published in Journal Stomatology Oral Maxillofacial Surgery. 2023 Sep 23

Abstract

Introduction: Lack of evidence existed related to the essential role by which anticancer medications alone or in combination with other polypharmacy would be accountable for wound healing impairment post-dental extraction. The following study was conducted to assess the influence of antiresorptive (AR) and non-antiresorptive (non-AR) drugs and other patient-related risk factors on wound healing status following tooth extraction.

Material and methods: A total of 353 patients (age range: 40-90 years, average age: 67.4 years, clinical and radiological follow-up) were recruited. All the patients were divided into three groups, which included, patients used polypharmacy with non-AR drugs, polypharmacy with a combination of AR + non-AR drugs, and the control group. Based on time of healing, the outcome was defined as, normal healing, delayed healing, and Medication-related osteonecrosis of the jaw (MRONJ). The polypharmacy score was categorized depending on the sum of the number of administered medications.

Results: The odds of delayed healing were significantly higher in 80+ years old patients (OR=6.98, 95%CI:2.45-19.88, p=<0.001) administered with AR+ non-AR drugs (OR=14.68, 95%CI:4.67-46.14, p=<0.001), having a major polypharmacy score (OR= 15.37, 95%CI:4.83-48.91, p=<0.001). On the contrary, patient administered with non-AR drugs (OR=11.52, 95%CI: 4.45-29.83, p=<0.001) with hyper polypharmacy (OR=58.86, 95%CI:25.03-138.40, p=<0.001) were significantly more likely to develop MRONJ. Smoking and extraction sites showed no significant impact on wound healing impairment.

Discussion: Wound healing status in patients administered with both non-AR and AR+ non-AR polypharmacy was significantly impaired following tooth extraction. Other risk factors, such as increased age and high polypharmacy scoring, also significantly contributed towards the occurrence of delayed healing and MRONJ.

Keywords: Tooth extraction, Polypharmacy, Wound healing, Osteonecrosis of the jaw, Delayed healing

Introduction

Polypharmacy refers to the simultaneous administration of different medications for multiple indications [1]. Over the past few years, it has become an area of global public health concern due to a high risk of adverse drug reactions (ADRs) and drug-drug interactions. The spectrum of these negative outcomes is an issue for any population group; however, it is more expanded in a geriatric population due to the presence of various comorbidities, altered drug's pharmacokinetic and pharmacodynamic parameters and age-related deterioration of renal and hepatic functions for drug clearance. A recent survey suggested that approximately half of the geriatric population is susceptible to polypharmacy [2]. This combination of multiple drug administration and patient-related factors such as age, gender, and physiological functions, could also have a deleterious effect on a patient's overall health with an increased risk of hospitalization and higher healthcare costs.

Amongst oncology patients, polypharmacy has a noticeable consequence with a steady increase in its incidence rate. These patients are typically prescribed anticancer agents such as antiresorptive (AR) and/or non-AR medications for control of the primary disease, preventing skeleton-related adverse events and supportive care. Bisphosphonate and denosumab are well-established AR bone modifying agents (BMAs). While non-AR drugs commonly include, non-AR angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) inhibitors, chemotherapy, and corticosteroids. One of the most common ADRs shared by both AR and non-AR drugs is delayed wound healing which might result in medication-related osteonecrosis of the jaw (MRONJ). The impact of a drug on the wound healing process might vary depending on its mechanism of action, dosage, and route of administration. Numerous growth factors and cytokines are involved in the healing mechanism, where each phase of healing is susceptible to disruption due to certain medications[3].

Medication-related osteonecrosis of the jaw (MRONJ) is one of the types of non-healing wounds in the maxillofacial area [4,5]. The latest definition of MRONJ by the American Association of Oral and Maxillofacial Surgeons (AAOMS) includes the following elements; current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications, exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks, no history of radiation therapy to the jaws or metastatic disease to the jaws [6]. MRONJ can also be detected through radiographic imaging. Radiographic predictors of MRONJ include certain alterations to the appearance of the bone in affected areas, particularly the absence and incomplete endodontic fillings with caries, widened

periodontal ligament space and/or periapical lesions, and sclerotic and heterogeneous bone patterns [7].

Dentoalveolar surgery, particularly tooth extraction in oncology patients receiving anticancer agents, are prone to delayed wound healing and considered as a major triggering factor for developing MRONJ. The risk of delayed healing following tooth extraction has been found to be significantly associated with the administration of different drugs, such as vitamin A, corticosteroids, bisphosphonates, denosumab, and chemotherapy. However, lack of evidence existed related to the essential role by which anticancer medications alone or in combination with other polypharmacy would be accountable for wound healing impairment.

Therefore, the primary aim of the following study was to investigate the impact of AR and non-AR polypharmacy on time of healing following tooth extraction. The secondary aim was to identify patient-related risk factors which might influence the healing outcomes.

Material and methods

Study design and setting participants

This retrospective study was conducted in compliance with the World Medical Association Declaration of Helsinki on medical research. Ethical approval was obtained from the Ethical Review Board of the University Hospitals Leuven (reference number: S57824). Informed consent was not required as patient-specific information was anonymized.

Digital medical records of patients were reviewed who underwent tooth extraction during a period of six years (September 2015-April 2021) at the Department of Oral and Maxillofacial Surgery, UZ Leuven, Belgium. The inclusion criteria consisted of patients aged ≥40 years with a radiological follow-up. Patients with a history of craniofacial radiotherapy and malignant and metastatic diseases of the jaw were excluded.

All the patients were divided into different groups depending on the type of BMA polypharmacy administered, which included, polypharmacy with non-AR drugs (non-AR group) and polypharmacy with a combination of AR + non-AR drugs (AR+ non-AR group). The control group consisted of age and gender-matched medically fit patients who underwent tooth extraction without any drug administration in the last 12 months.

Outcome of interest and assessment of exposure

The recorded parameters included patient demographics (age, gender), site of extraction, time of healing status and administered medications. Time of healing status of a patient was categorized as either normal healing (<14 days, clinically normal healing, no symptoms), delayed healing (14 days to 8 weeks, bleeding, pain, redness, open socket then heal), or MRONJ (>8 weeks, bone sequester, pain, no signs of healing or no-epithelization) was recorded based on the clinical criteria proposed by American Association of Oral and Maxillofacial Surgeons (AAOMS) and also confirmed radiologically with panoramic radiography.

Polypharmacy score was assessed using a modified version of a validated tool known as comorbidity–polypharmacy score (CPS). Due to the variability of underlying comorbid conditions, the tool was modified to only assess the polypharmacy score. This criterion was applied to evaluate the association between accumulation of polypharmacy administered in the past 12 months and wound healing status. It was defined as the sum of the number of polypharmacy medications, where each medication was assigned with one point. The polypharmacy score was categorized as either minor (0-2 points), moderate (3-5 points), major (6-9 points) or hyper (>10 points).

Statistical methods

The sample size was in accordance with the previous studies and was also calculated using a priori power analysis in G*power software (G*Power, Version 3.1.9.2, Düsseldorf, Germany), at a power of 80% and 0.05 level of significance.

Data were analysed with IBM SPSS Statistics, version 22 (IBM Corporation 2017 ©, Armonk, NY, USA). Chi-square test was used to evaluate the association between the potential risk factors and healing status. Fisher's exact test was applied when cells had expected frequencies of less than 5. Multivariate logistic regression analysis was conducted for risk factors showing significant values in univariate analyses. Stepwise logistic regression was applied to assess the association between different drugs and healing status. Odds ratio (OR) and 95% confidence interval (CI) for each independent factor was calculated. Statistical significance was set at $p< 0.05$.

Results

The digital medical records of 3977 patients were reviewed, out of which 353 patients (age range: 40-90 years, average age: 67.4 years) were recruited following the eligibility criteria, all of whom were coincidentally male. Table 2.1. summarizes the distribution of demographic and study characteristics. The majority of extraction

sites were located in the posterior region of both maxilla and mandible (37.4%) and 16.1% of the subjects were active smokers. Based on polypharmacy classification, 16.4% patients were included in the non-AR group, 22.4% in AR + non-AR group and 61.2% in control group. Minor polypharmacy scoring was observed in 70.3% of the patients. Amongst the risk factors, age (p=<0.0001), polypharmacy type (p=<0.0001) and polypharmacy score (p=<0.0001) observed a statistically significant association with the wound healing status. In addition, no significant association existed based on smoking status (p=0.088) and extraction site (p=0.187).

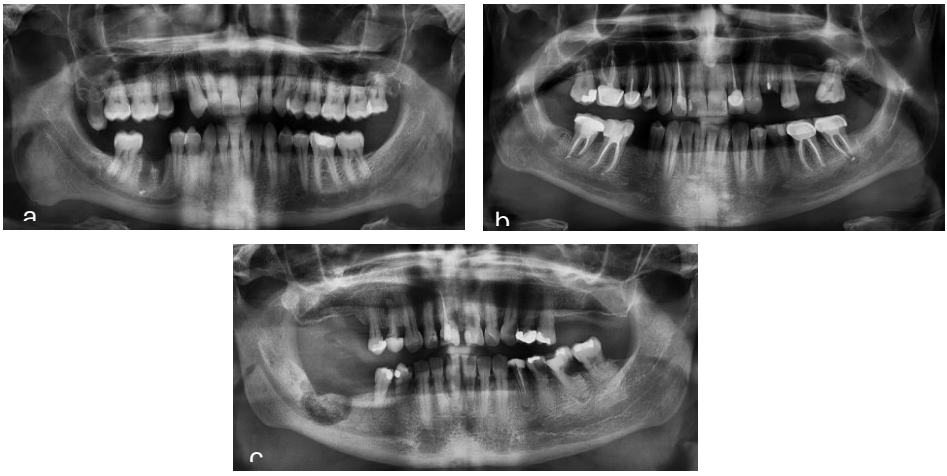

Figure 2.1. Panoramic radiograph of patient with normal healing (a), delayed healing (b), and MRONJ (c) in lower right mandible

Univariate analysis of the relationship between potential risk factors and wound healing status is presented in Table 2.2. The following risk factors obtained a statistically significant association with delayed healing: age categories of 40-59 and 60-79 years (p= 0.003), smokers (p=0.035), non-AR (p= 0.001) and AR+non-AR drug groups (p= 0.001), major (p= <0.001) and hyper (p= 0.001) polypharmacy score. On the other hand, MRONJ was significantly associated with all age categories (40-59 years, p=<0.001; 60-79 years, p= <0.001; 80+ years, p= 0.014), non-AR (p= 0.010) and AR+ non-AR drug groups (p= <0.001) and all polypharmacy score categories compared to minor scoring (p= <0.001).

According to the multivariable analysis (Table 2.3.), the odds of developing delayed healing were significantly higher in 80+ years old patients (OR=6.98, 95%CI:2.45-19.88, p=<0.001) administered with AR+ non-AR drugs (OR=14.68, 95%CI:4.67-46.14, p=<0.001), having a major polypharmacy score (OR= 15.37, 95%CI:4.83-

48.91, p=<0.001). Furthermore, patient administered with non-AR drugs (OR=11.52, 95%CI: 4.45-29.83, p=<0.001) having hyper polypharmacy (OR=58.86, 95%CI:25.03-138.40, p=<0.001) were significantly more likely to develop MRONJ.

Table 2.4. demonstrates the stepwise logistic regression between type of administered medication and healing status. The findings suggested that monoclonal antibodies, hormone therapy, and bisphosphonate were significantly associated with delayed healing, where bisphosphonates showed the highest OR of 3.12 (95% CI= 1.40-6.92, p= 0.005). In relation to MRONJ, methotrexate, immunosuppressant, chemotherapy, corticosteroid, hormone therapy, bisphosphonates, and denosumab were significantly associated with the development of MRONJ. Out of these, the odds of developing MRONJ was highest with corticosteroids (OR= 2.18, 95% CI: 1.22-3.89, p=0.008).

Discussion

In this study, the potential impact of bone modifying polypharmacy and other patient-related risk factors on wound healing status were analysed following tooth extraction. The findings of the present study suggested a significant impact of both AR and non-AR drugs on wound healing, which was consistent with previous reports. The effect of a medication on wound healing process may vary depending on its mechanism of action, dosage, and route of administration. Furthermore, numerous growth factors and cytokines are involved in the healing cascade, and each phase is susceptible to disruption by certain medications [3]. Antiresorptive medications have been found to impair vascular endothelial cell proliferation, migration, and differentiation, delaying vessel remodelling and soft tissue repair in the oral mucosa [8]. In addition, non-antiresorptive drugs have also been suggested as potential agents responsible for the development of delayed healing. Some investigations demonstrated histologic and volumetric abnormalities at tooth extraction site following vascular endothelial growth factor suppression therapy with bevacizumab as a non-AR agent, indicating that non-AR drug delayed the healing process [9,10].

Table 2.1. Descriptive characteristics of the patients and the wound healing status

Factors	Total	Wound healing outcome			*p*-value
	N (%)	Normal healing	Delayed healing	MRONJ	
Subjects					
Male	353 (100)	243	44	66	
Age					0.000ǂ
40-59	207 (58.6)	189	7	11	
60-79	124 (35.1)	47	30	47	
80+	22 (6.2)	7	7	8	
Smoking Status					0.088*
Yes	57 (16.1)	37	12	8	
No	296 (83.9)	206	32	58	
Site of extraction					0.187ǂ
Anterior maxilla	53 (18.4)	42	11		
Posterior maxilla	132 (37.4)	100	15		
Anterior mandible	24 (6.8)	13	4		
Posterior mandible	132 (37.4)	88	14		
Patient classification					0.000*
Polypharmacy non-AR	58 (16.4)	25	15	18	
Polypharmacy AR+ non-AR	79 (22.4)	12	19	48	
No-medication	216 (61.2)	206	10	0	

Factors	Total	Wound healing outcome			*p*-value
	N (%)	Normal healing	Delayed healing	MRONJ	
Polypharmacy category					0.000ǂ
Minor	248 (70.3)	219	19	10	
Moderate	75 (21.2)	16	16	43	
Major	24 (6.8)	6	8	10	
Hyper	6 (1.7)	2	1		

ǂ : Fisher's exact test
*: Chi-square

Table 2.2. Univariable association between risk factors and healing status

Factors	Delayed healing				MRONJ			
	OR	95% CI		*p*-value	OR	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Age								
40-59	2.652	1.380	5.094	0.003*	0.235	0.133	0.416	0.000*
60-79	2.652	1.380	5.094	0.003*	0.235	0.133	0.416	0.000*
80+	0.913	0.319	2.614	0.865	0.432	0.221	0.847	0.014*
Smoking Status (ref: no smoking)								
Yes	2.200	1.055	4.588	0.035*	0.670	0.301	1.492	0.327
Site of extraction								
Anterior maxilla	1.717	0.732	4.028	0.214	1.646	0.689	3.934	0.262
Posterior maxilla	1.081	0.499	2.338	0.844	0.943	0.431	2.062	0.883
Anterior mandible	1.686	0.504	5.642	0.397	1.934	0.552	6.781	0.303
Posterior mandible	0.582	0.248	1.367	0.214	0.714	0.271	1.884	0.496
Patient classification (ref: no-medications)								
Polypharmacy non-AR	3.200	1.586	6.454	0.001*	0.432	0.229	0.816	0.010*
Polypharmacy AR+ non-AR	3.154	1.631	6.101	0.001*	0.045	0.024	0.088	0.000*
Polypharmacy Score category (ref: minor)								
Moderate	0.415	0.046	3.734	0.433	23.800	4.258	133.022	0.000*
Major	0.166	0.063	0.437	0.000*	17.000	6.075	47.570	0.000*
Hyper	0.306	0.148	0.631	0.001*	31.981	14.648	69.823	0.000*

* Result is significant: $p<0.05$

Table 2.3. Multivariable association between risk factors and healing status

Factors	Delayed healing				MRONJ			
	OR	95% CI		*p*-value	OR	95% CI		*p-value*
		Lower	Upper			Lower	Upper	
Age								
40-59	0.070	0.021	0.230	0.000*	0.850	0.239	3.024	0.802
60-79	4.852	0.992	23.736	0.051	0.676	0.151	3.018	0.608
80+	6.984	2.453	19.887	0.000*	2.153	0.603	7.694	0.238
Smoking Status (ref: no smoking)								
Yes	2.385	0.827	6.878	0.108	0.944	0.259	3.441	0.931
Site of extraction								
Anterior maxilla	1.902	0.619	5.841	0.261	1.168	0.363	3.759	0.794
Posterior maxilla	1.853	0.696	4.931	0.217	1.105	0.410	2.979	0.843
Anterior mandible	2.498	0.493	12.652	0.269	2.322	0.393	13.710	0.352
Posterior mandible								
Patient classification (ref: no-medications)								
Polypharmacy non-AR	4.864	1.618	14.626	0.005*	11.517	4.446	29.831	0.000*
Polypharmacy AR+ non-AR	14.678	4.669	46.139	0.000*	7.669	7.669	7.669	0.000*
Polypharmacy Score category (ref: minor)								
Moderate	5.763	0.499	66.505	0.160	32.850	4.923	219.222	0.000*
Major	15.368	4.829	48.909	0.000*	36.500	11.058	120.482	0.000*
Hyper	11.526	4.993	26.609	0.000*	58.856	25.029	138.400	0.000*

* Result is significant: $p<0.05$

Table 2.4. Association between type of medication and healing status

Type of medications	Delayed healing OR (95% CI)	*p-value*
Monoclonal antibodies	1.66 (1.08, 2.54)	0.020
Hormone therapy	3.10 (1.51, 6.36)	0.002
Bisphosphonates	3.12 (1.40, 6.92)	0.005

Type of medications	MRONJ OR (95% CI)	*p-value*
Methotrexate	0.07 (0.01, 0.45)	0.006
Immunosuppressant	0.12 (0.03, 0.41)	0.001
Chemotherapy	0.58 (0.45, 0.77)	0.000
Corticosteroid	2.18 (1.23, 3.89)	0.008
Hormone therapy	0.27 (0.23, 3.89)	0.002
Bisphosphonates	0.05 (0.02, 0.13)	0.000
Denosumab	0.03 (0.01, 0.10)	0.000

The fact that AR drugs could cause delayed healing and MRONJ has been thoroughly investigated. Based on our findings, bisphosphonate was most likely to cause delayed healing amongst all the other drugs. The most probable reasoning could be the impact of the drug on the regional immune system suppression, principally due to its effect on monocytes and macrophages [11]. In addition, it is also the most widely used AR medication for treating patients with osteoporosis and bone events related to metastases [12,13]. Similarly, a biological AR medication known as denosumab was significantly associated with MRONJ occurrence. The impact of denosumab on MRONJ was slightly lower which might be due to the fact that it does not form a lasting bond with the bone matrix and its residual effect on the rebuilt bone is reduced compared to bisphosphonates. Although monoclonal antibodies and TKIs showed no significant association with the occurrence of MRONJ, previous studies have suggested a positive correlation between these drugs and MRONJ [14]. This contradictory evidence might be associated with the eligibility criteria of the patients which differed from those studies. Our findings suggested that a combination of AR and non-AR drugs was also significantly associated with impaired wound healing, which was consistent with a previous study where the authors demonstrated that the formation of MRONJ was more likely to occur when non-AR antiangiogenic medication was administered in combination with AR drugs [15].

The risk of developing MRONJ was highest in patients administered with corticosteroids. These drugs cause an increased apoptosis of osteoblasts and osteocytes, thereby inhibiting healing of both bone and soft tissue [16,17] According to the AAOMS guidelines and the International Taskforce on ONJ, the use of corticosteroids has been documented as a confounding variable which increases the risk of MRONJ. Several studies have reported the impact of these drugs on the osteonecrosis of femur and vertebrae, however, no comparable evidence on the induction of MRONJ following corticosteroid administration has been reported in literature. Hence, further standardized prospective studies should be conducted to assess the influence of corticosteroids with and without other polypharmacy on wound healing.

Moreover, a significant association existed between different age groups and impaired wound healing, where the risk of both delayed healing and MRONJ occurrence were higher in older patients. Our findings were in accordance with prior investigations which showed a reduction of inflammatory and proliferative responses in elderly patients, causing impaired wound healing compared to younger patients [18]. In oncology patients, a combination of increasing age, polypharmacy and disease-related changes in the microcellular environment results in the delay of the healing process, which might have further contributed towards the occurrence of healing impairment. Based on the polypharmacy scoring, the risk of delayed wound healing and MRONJ was higher in patients with an increased score. As the influence of polypharmacy score on wound healing status has not been previously investigated, hence, further studies are warranted to investigate whether the adjustment of drug type or dosage in patients administered with polypharmacy could allow avoidance of wound impairment complications.

The study had certain limitations. Firstly, the retrospective design with lack of drugs dosage information and other unknown patient-and disease-related confounding factors could have impacted our outcomes. Hence, the findings of the study should be interpreted with caution. Secondly, heterogeneity in comorbid conditions of the patients did not allow to verify the relationship between different diseases and polypharmacy. Despite these limitations, this study adds valuable information related to the impact of polypharmacy on wound healing. Furthermore, it lays a platform to conduct future well-designed studies to isolate specific risk factors and improve the standard of care.

Conclusions

Wound healing in patients administered with non-AR and AR+ non-AR polypharmacy was significantly impaired following tooth extraction. Amongst other risk factors, older patients and increased polypharmacy scoring further contributed

towards delayed healing and MRONJ occurrence. Prospective studies are required to further elucidate the factors contributing towards healing impairment in patients administered with bone modifying polypharmacy agents, to allow for a patient-specific delivery of care and drugs dosage adjustment if possible, for achieving a normal healing status.

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Article 3

Prediction of wound healing status following dental extraction using Adapted-University of Connecticut Osteonecrosis Numerical Scale: A retrospective study

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Accepted in Health Science Reports on 23 May 2024

Abstract

Background and Aims

There is a scarcity of evidence concerning the use of a prognostic instrument for predicting normal healing, delayed healing and medication-related osteonecrosis of the jaw (MRONJ) occurrence following tooth extraction in medically compromised patients. The present study aimed to predict healing outcomes following tooth extraction in medically compromised patients using an Adapted-University of Connecticut Osteonecrosis Numerical Scale (A-UCONNS).

Methods

The digital medical records of medically compromised patients were reviewed, who underwent tooth extraction. The A-UCONNS parameters included the initial pathological condition, dental procedures, comorbidities (smoking habits, type and duration of medication, and type of intervention), and administered antiresorptive (AR) medications. Each parameter was assigned a different weight, and the scores were then accumulated and classified into three categories: minimal risk (less than 10), moderate risk (10 to 15), and significant risk (16 or more). The patient's healing status was categorized as normal healing, delayed healing, or MRONJ.

Results

A total of 353 male patients (mean age: 67.4 years) were recruited from a pool of 3977 patients, where 12.46% of patients had delayed wound healing, and 18.69% developed MRONJ. The median A-UCONNS scores for MRONJ were higher based on initial pathology, comorbidity, and AR drugs compared to normal or delayed healing. In addition, a significant correlation existed between A-UCONNS and healing outcomes ($p<0.05$), with a unit increase in A-UCONNS associated with 1.347 times higher odds of experiencing MRONJ compared to normal healing. In contrast, a low scoring was linked to an increased likelihood of normal wound healing.

Conclusion

The A-UCONNS could act as a promising tool for predicting wound healing outcomes. It can provide clinicians the ability to pinpoint patients at high risk and allow tailoring of patient-specific strategies for improving healing outcomes following tooth extraction.

Keywords: Delayed healing, Osteonecrosis of the jaw, Prognosis, Polypharmacy, Wound healing.

Introduction

Tooth extraction is one of the most common dental procedures performed in a clinical practice [1]. Following extraction, the socket undergoes a healing process with four distinct stages i.e., hemostasis, inflammation, proliferation, and remodeling. Hemostasis occurs shortly after tooth extraction and involves blood clotting at the wound site [2]. Inflammation begins approximately 24 hours after the procedure and lasts up to 72 hours. During this stage, the immune system is activated to eliminate potential infections and debris [3]. Proliferation occurs on days 4-21 and involves the replacement of the provisional fibrin matrix with a new matrix [4]. The final stage, remodeling, can take up to a year and involves the formation of new epithelium and scar tissue [5].

The post-extraction healing process can be impaired, especially in osteoporotic and oncology patients who are administered polypharmacy and have comorbid conditions [6,7]. One type of non-healing wound following tooth extraction in such patients is medication-related osteonecrosis of the jaw (MRONJ) [8,9]. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has established a definition of MRONJ that includes the following criteria: current or previous treatment with antiresorptive (AR) agents alone or in combination with immune modulators or antiangiogenic drugs; exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks; and no history of radiation therapy to the jaw [10].

Some medications, such as glucocorticoid steroids, non-steroidal anti-inflammatory drugs, and chemotherapeutic drugs, can interfere with clot formation or platelet function [11]. Additionally, AR medications such as bisphosphonates, denosumab, calcitonin, estrogen, and raloxifene may delay repair due to impairment in the remodeling phase [12]. A positive correlation has been observed between the number of medications and the incidence of non-healing wounds [13]. Cancer patients receiving multiple medications and immunosuppression are at an increased risk for developing MRONJ, even in the absence of exposure to AR drugs. A variety of AR medications, including bisphosphonates and denosumab used to treat osteoporosis and malignancies, have a high risk of developing MRONJ. Additionally, non-AR drugs, such as antiangiogenic inhibitors, immunosuppressants, and chemotherapy agents, have recently gained attention for their association with MRONJ as well [14].

So far, numerous risk factors have been recognized as potential contributors to the development of delayed healing or MRONJ [15–20]. Despite this, the pathophysiology of MRONJ remains incompletely understood, and there is a scarcity of evidence regarding the precise prediction of patients who may experience delayed healing or develop MRONJ following tooth extraction. A tool referred to as University of Connecticut Osteonecrosis Numerical Scale (UCONNS) was previously developed to provide a prognostic score for predicting MRONJ surgical treatment outcomes [21,22]. Nevertheless, there is an existing gap in the evidence concerning the utilization of such a tool for predicting healing outcomes following tooth extraction. This is particularly relevant when attempting to assess and stratify the risk posed by medications and comorbidities in the onset of MRONJ. Therefore, the aim of the present study was to apply an Adapted-UCONNS (A-UCONNS) as a predictor of wound healing outcomes following tooth extraction.

Methods

Study design, setting participants, and outcomes

This retrospective study was conducted in compliance with the World Medical Association Declaration of Helsinki and received ethical approval from the University Hospitals Leuven Ethical Review Board (reference number: S57824). Patient-specific information was anonymized, eliminating the need for informed consent. A review of digital medical records from patients aged 40 years or older was conducted, who underwent tooth extraction at the Department of Oral and Maxillofacial Surgery, UZ Leuven, Belgium between September 2015 until April 2021. Patients with radiological follow-up and used multiple medications were included, while those with a history of craniofacial radiotherapy or malignant and metastatic diseases of the jaw were excluded. The sample size was determined using G*Power software (Version 3.1.9.2, Düsseldorf, Germany) and was based on previous studies, with a power of 80% and a significance level of 0.05.

The A-UCONNS parameters encompassed initial pathological condition, dental treatment, comorbidities (including smoking habits, medication type and duration, and intervention type), and administered AR medications. Each parameter's score was weighted differently, accumulated, and then categorized as follows: minimal risk (<10), moderate risk (10 to 15), and significant risk (16 or above) (Table 3.1.).

The healing status of a patient was classified based on the duration and symptoms of the healing process. The three categories were: normal healing, which occurred within 10 days and exhibited no symptoms; delayed healing, which took between 14

Table 3.1. Adapted-University of Connecticut Osteonecrosis Numerical Scale

Parameter	Criteria	Points
Initial pathology condition (max 10)	Healthy	0
	HIV	1
	DM/RA	2
	Other cancer	2
	Breast/prostate cancer	3
	Multiple Myeloma	5
Dental therapy (max 5)	Prophylaxis	0
	Restorative procedure	0
	Endodontic treatment	1
	Denture sore	1
	Periodontal surgery	3
	Tooth extraction	4
	Dental implant	5
Comorbid condition (max 10)	Non-smoker	0
	Former smoker >6 months	1
	Current smoker	2
	Oral steroid	2
	Steroid IV/IM	3
	Immunosuppressants, chemotherapy; 12 months	5
	Immunomodulation (rheumatoid disease, organ transplant; 12 months)	5
Anti-resorptive used	Bisphosphonate <3 years	1
	Bisphosphonate 3-5 years	2
	Bisphosphonate >5 years	3
	Denosumab <3 years	1
	Denosumab 3-5 years	2
	Denosumab >5 years	3
Risk assessment	Minimal risk (<10)	1
	Moderate risk (10 to 15)	2
	Significant risk (16 or above)	3

HIV: Human Immunodeficiency Virus; DM: Diabetes Mellitus; RA: Rheumatoid Arthritis; IV: Intravenous; IM: Intramuscular; Adapted from Reich et al, 2015[16].

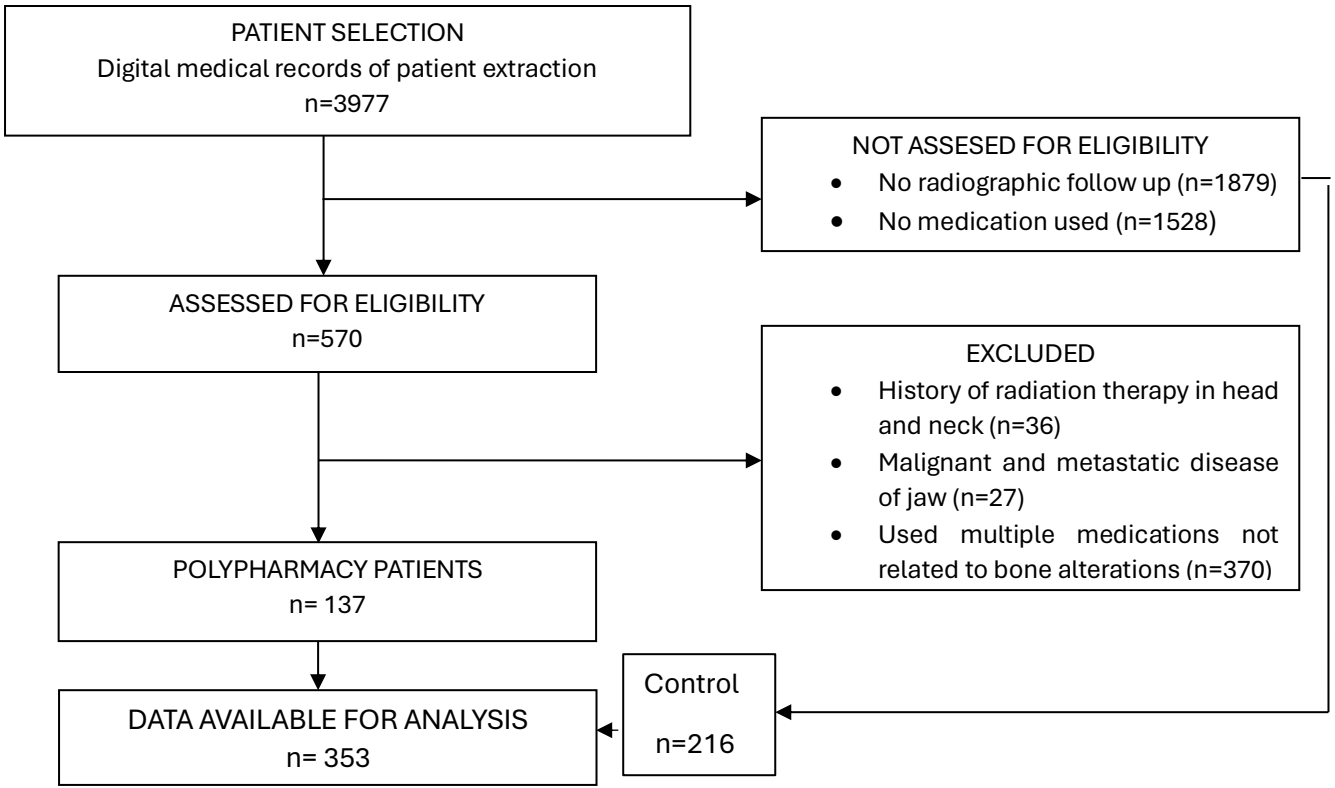


Figure 3.1. Flow chart of patient selection process

days to 8 weeks and was characterized by bleeding, pain, redness, and an open socket that eventually healed; and MRONJ, which persisted for more than 8 weeks and was marked by bone sequestration, pain, and an absence of healing or epithelization. This classification was based on the clinical criteria proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS) and was confirmed radiologically using panoramic radiography.

Statistical methods

Multinomial logistic regression was employed to assess the relationship between A-UCONNS criterion and healing outcome. In addition, survival regression was used to evaluate differences between different risk groups, with p-values adjusted using Tukey's correction. Statistical analysis was performed using S-Plus 8.0 for Linux (Tibco, Palo Alto, CA, USA). A p value < 0.05 was considered significant.

Results

The digital medical records of 3977 medically compromised patients were reviewed, who underwent tooth extraction. Of these, 353 male patients, aged between 40 and 90 years (average age: 67.4 years), were chosen based on specific eligibility criteria (Figure 3.1.). The patient characteristics, according to the A-UCONNS parameters are detailed in Table 3.2. The majority of the patients were diagnosed with prostate cancer (58 patients). Out of these, 35 patients developed MRONJ, and 9 patients experienced delayed healing post-extraction. In terms of healing outcomes, 18.6% of patients developed MRONJ, 12.4% experienced delayed healing, and 65% exhibited normal healing. In the context of comorbid conditions, 22% of patients were former smokers for more than 6 months and 16.4% had undergone chemotherapy treatment. Notably, 56% of the patients who received chemotherapy developed MRONJ. Regarding the use of AR medication, 23 patients were treated with Denosumab, and 17 patients had been using bisphosphonates for less than 3 years.

Figure 3.2. provides a visual representation of the score distribution for each criterion of A-UCONNS. It is noteworthy that the median scores for MRONJ outcomes were higher for the initial pathology score, comorbidity score, and AR score when compared to the scores of delayed and normal healing outcomes. Moreover, no significant differences were detected in the dental therapy scores. Based on the mean A-UCONNS risk assessment scores and healing outcomes (Figure 3.3.), scores of MRONJ and delayed healing were mainly associated with higher scores, while normal healing outcomes corresponded to lower scores.

The association between each parameter of A-UCONNS and healing outcomes is presented in Table 3.3. A multinomial logistic regression analysis was conducted to investigate the relationship between pathology score, dental therapy score, AR score, comorbidity score and healing outcomes. Overall, these variables were highly significant in the development of MRONJ, or delayed healing compared to normal healing. The dental therapy score (P=0.01, OR=2.8) and the use of AR medications demonstrated stronger relationship with MRONJ (P<.001, OR=4.6) compared to delayed healing (P<.001, OR=3.6).

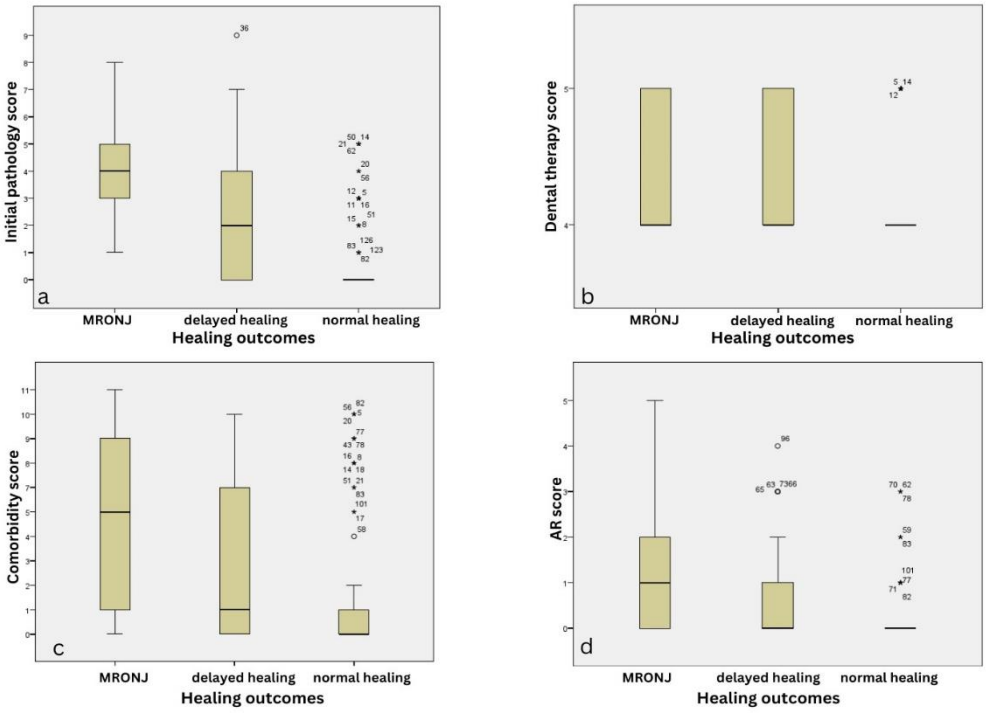


Figure 3.2. Patient distribution based on Adapted-University of Connecticut Osteonecrosis Numerical Scale parameters. (a) Initial pathology score and healing outcomes; (b) Dental therapy and healing outcomes; (c) Comorbidity score and healing outcomes; (d) anti-resorptive (AR) score and healing outcomes

Figure 3.4. presented a survival analysis correlating A-UCONNS risk assessment with healing time. The Kaplan-Meier survival analysis was used to compare the duration of healing across three different risk levels. These categorical variables showed statistically significant outcomes ($p<.001$), where the comparisons between minimal and moderate risk, minimal and significant risk, as well as moderate and significant risk, all exhibited negative direction. This suggested that individuals with higher risk assessment are more susceptible to experience delayed healing or MRONJ. On the other hand, individuals with lower risk assessment scores are more likely to exhibit a faster healing time.

Discussion

In this study, A-UCONNS was utilized to conduct an analysis of potential risk determinants for predicting the wound healing status subsequent to tooth extraction. The findings indicated that a higher A-UCONNS score had an increased likelihood of delayed wound healing and MRONJ. Conversely, lower scores were associated with a higher probability of normal wound healing. The findings were consistent with a previous study that used the 'comorbid polypharmacy score' (CPS) to quantify the cumulative severity of disease and medication accumulation [16]. However, it is important to note that the CPS does not account for dental risk factors, which are crucial in determining the likelihood of MRONJ development in a given patient [17]. As such, A-UCONNS was selected to predict wound healing impairment based on relevant risk factors.

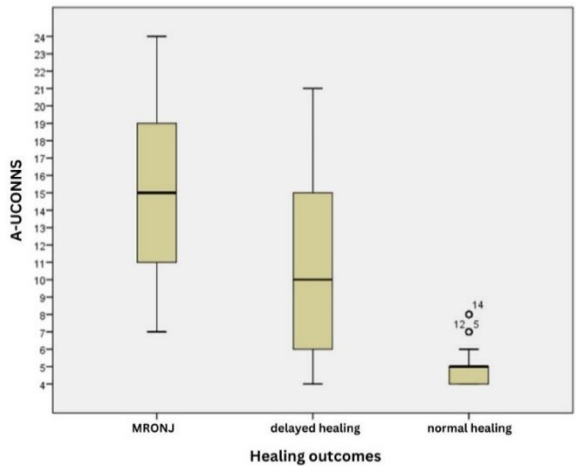


Figure 3.3. Mean and standard deviation of Adapted-University of Connecticut Osteonecrosis Numerical Scale (A-UCONNS) and healing outcomes

Table 3.2. Demographic data of the included subjects

Characteristic	TOTAL N(%)	MRONJ	Delayed healing	Healed
			n	
A-UCONN Parameter				
Initial pathology condition (n=183)				
Multiple myeloma	17 (4.8)	13	4	0
Prostate cancer	58 (16.4)	35	9	14
Other cancer	49 (13.9)	24	12	13
Osteoporosis	32 (9.1)	12	10	10
Rheumatoid arthritis	13 (3.6)	9	2	2
Diabetes Mellitus	24 (6.8)	12	8	4
HIV	3 (0.8)	2	0	1
Dental therapy				
Restorative procedure	10 (2.8)	0	0	10
Endodontic treatment	12 (3.3)	0	0	12
Tooth extraction	353 (100)	66	44	243
Dental implant	33 (9.3)	4	3	26
Denture sore	27 (7.6)	19	8	0
Periodontal surgery	40 (11.3)	14	8	18
Comorbidities condition				
Former smoker >6 months	78 (22)	14	10	54

Characteristic	TOTAL N(%)	MRONJ	Delayed healing	Healed
		n		
Smoker, current or last month	32 (9.1)	4	9	19
Steroid inhale/oral within 12 months	44 (12.5)	26	8	10
Steroid IV/IM within 12 months	36 (10.1)	22	6	8
Immunosuppressants, chemotherapy within 12 months	58 (16.4)	33	13	12
Immunomodulators (rheumatoid arthritis, organ transplant) within 12 months	22 (6.2)	8	5	9
Anti-resorptive used				
Bisphosphonate <3 years	17 (4.8)	11	4	2
Bisphosphonate 3-5 years	10 (2.8)	9	1	0
Bisphosphonate >5 years	14 (3.9)	6	5	3
Denosumab <3 years	23 (6.5)	11	7	5
Denosumab 3-5 years	18 (5)	13	3	2
Denosumab >5 years	5 (1.4)	5	0	0
Risk Assessment				
Minimal risk (<10)	261 (74.2)	14	22	225
Moderate risk (10 to 15)	45 (12.7)	21	12	12
Significant risk (16 or above)	47 (13.3)	31	10	6

IV: Intravenous; IM: Intramuscular, HIV: Human Immunodeficiency Virus

This research builds upon previous work that employed UCONNS to monitor and prevent MRONJ development [21], as well as other studies that used this tool to evaluate predisposing factors and prognosis in surgical treatment failure cases following bisphosphonates administration [22,23]. It is noteworthy that comparison with existing evidence was difficult due to a lack of research on the prediction of healing outcomes following dental extraction using UCONNS.

Table 3.3. Relation between each criterion of A-UCONNS and healing outcome

	MRONJ		**delayed healing**		**normal healing**
Comparison	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**	
A-UCONNS criteria[ǂ]					
Initial pathology condition	2.4 (1.8-3.1)	<.001	1.6 (1.3-2.1)	<.001	
Dental therapy	4.6 (1.8-11.7)	<.001	2.8 (1.3-6.3)	0.01	
Comorbidities condition	1.1 (1.0-1.3)	0.045	1.1 (0.1-1.2)	0.14	reference
Anti-resorptive used	3.6 (2.2-5.9)	<.001	2.4 (1.5-3.9)	<.001	

[ǂ] Multinomial logistic regression

Typically, wounds undergo a healing process that lasts between 4 to 6 weeks [24], [25]. Once the wound has closed, the remodeling phase commences. The primary objective of this final stage of wound healing is to restore normal tissue structure and maximize tensile strength through extracellular matrix reorganization, breakdown, and synthesis[4]. The administration of AR drugs might cause the failure of extraction socket to progress through the normal stages of healing within the expected timeframe, which can either lead to delayed healing or MRONJ occurrence [26].

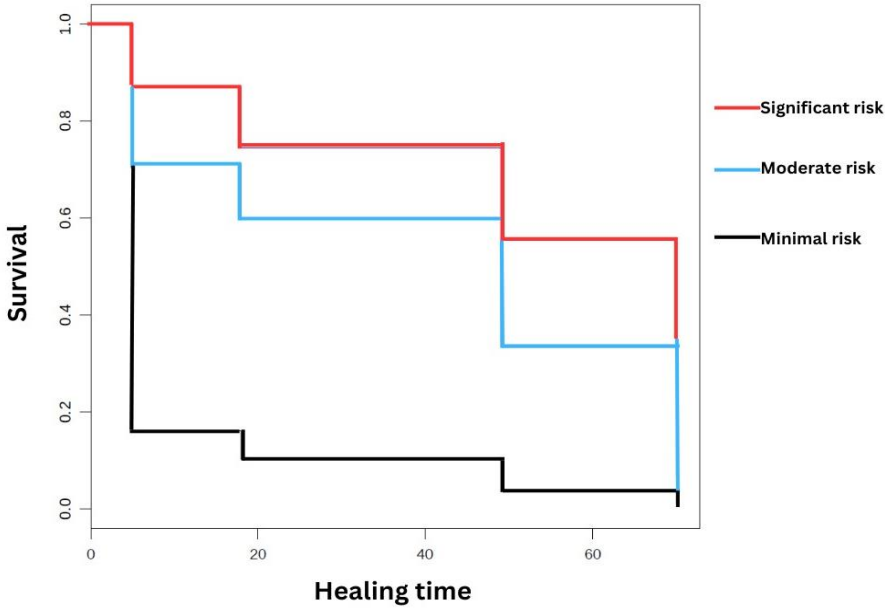
Wound healing can be inhibited by multiple variables. These factors can be classified as either local or systemic. Local factors have a direct impact on the characteristics of the wound, while systemic factors pertain to the individual's overall health or disease condition, which can affect their ability to heal [27]. Systemic factors influence wound healing through local effects, and many of these factors are interrelated. Oxygenation, infection, foreign body presence, and venous sufficiency are among the local factors that influence healing time [28]. Systemic risk factors such as immunocompromised conditions and immunosuppression

medications, including chemotherapy and steroids, have been reported to contribute towards healing failure [29,30]. Accordingly, the present study also showcased that both corticosteroids and chemotherapy were found to be used by medically compromised patients exhibiting delayed healing or MRONJ.

Corticosteroids directly inhibit the production and activity of osteoclasts, osteoblasts, and osteocytes. Specifically, osteonecrosis might have been caused by the induction of apoptosis in osteocytes [31]. Moreover, chemotherapeutic agents delay cell migration into wounds, reduce early wound matrix development, decrease collagen production, impair fibroblast proliferation, and inhibit wound contraction [32]. These medications also weaken the patients' immune system, slowing down the inflammatory phase of the healing process and increasing the likelihood of wound infection. Chemotherapy side effects such as neutropenia, anemia, and thrombocytopenia increase the susceptibility of wounds to infection, reduce oxygen delivery to the area, and increase the risk of excessive bleeding at the wound site [11,28].

The clinical scoring of the A-UCONSS based on administered AR medications showed a strong relationship between the use of AR medications and delayed healing or MRONJ following tooth extraction. However, a study found that the use of alendronate and zoledronic acid did not have a significant association with impaired bone and mucosal wound healing after dental extraction in women with osteoporosis who followed an appropriate surgical protocol and continued bisphosphonate therapy [33]. Hence, it is important to identify and stratify the risk factors and develop patient-specific protocols for improved surgical outcomes.

Within the clinical context, considering risk factors and healing duration, patients classified as low risk generally demonstrated enhanced healing compared to their counterparts in the moderate and high-risk categories. This data could be instrumental in guiding clinical decision-making processes. It is imperative for healthcare professionals to prioritize patient risk assessment. Patients falling under the moderate risk category may exhibit standard healing patterns, yet these individuals require more consistent monitoring, preventive measures, or targeted treatments. Simultaneously, for those classified as high risk, healthcare providers should consider personalized treatment strategies, intensive interventions, or more frequent follow-ups to improve their survival prospects, particularly in relation to MRONJ development.



Comparison	Difference	P-value
Minimal risk-Moderate risk	-29.3	0.001
Minimal risk-Significant risk	-41.8	0.001
Moderate risk-Significant risk	-12.5	0.008

Figure 3.4. Survival analysis of Adapted-University of Connecticut Osteonecrosis Numerical Scale (A-UCONNS) risk assessment and healing time

The study had certain limitations, which should be acknowledged when interpreting the results. Firstly, the retrospective approach employed may impede the establishment of a causal link between risk factors and wound healing outcomes. Secondly, the accessibility of data pertaining to the pharmacological protocol, previous medical history, and drug dosage was limited, thereby complicating the identification of potential confounding factors. Thirdly, the variability in follow-up durations among the patients included in the study could have increased the likelihood of selection bias. Future longitudinal studies with extended follow-up periods could offer valuable insights into the long-term effects of polypharmacy and other risk factors on wound healing. In order to enhance the reliability of the results, this study implemented multinomial logistic regression to adjust for potential confounding factors. Finally, the sample size was relatively small and lacked diversity, as it only included male patients. Thereby, a larger and more diverse

sample could enhance the applicability of the findings to a broader population. Moreover, future research is recommended to consider the aforementioned limitations in an attempt to improve the prediction capability of the A-UCONNS scale before it can be used in a clinical setting.

Conclusion

The A-UCONNS could act as a valuable tool for enhancing care in medically compromised patients, where it can enable a clinician to identify high-risk patients who are more prone to develop MRONJ and allow tailoring of patient-specific treatment planning and post-operative therapy to improve healing outcomes following tooth extraction. To elevate the existing standard of care and improve healing outcomes in medically compromised patients, it is recommended that additional research be conducted to develop risk reduction protocols and clinical practice guidelines based on the stratification of the risk factors.

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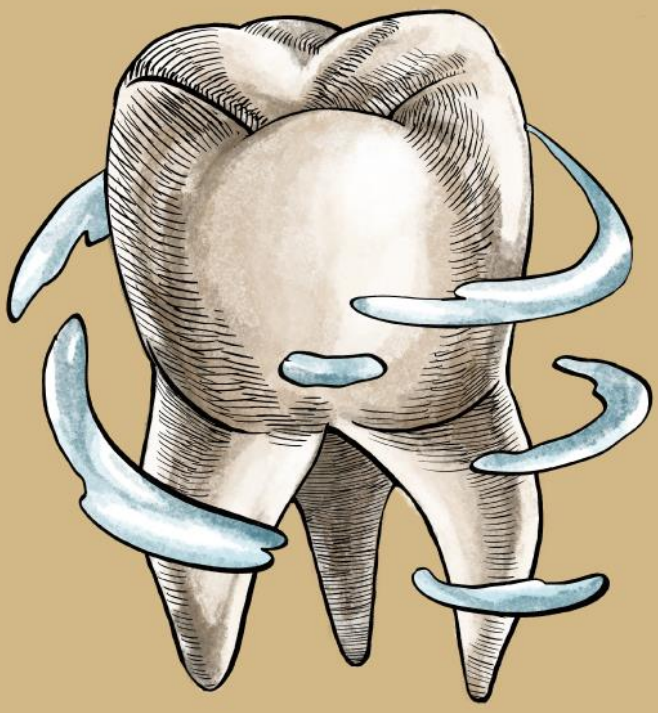
CHAPTER

02

LOCAL RISK FACTORS OF HEALING IMPAIRMENT FOLLOWING TOOTH EXTRACTION



Polypharmacy and Medication-Related Osteonecrosis of the Jaw (MRONJ): Identifying Patients at Risk

Chapter 2

Local risk factors of healing impairment following tooth extraction

Article 4

Suryani IR, Ahmadzai I, That MT, Shujaat S, Jacobs R. Are medication-induced salivary changes the culprit of osteonecrosis of the jaw? A systematic review. Front Med (Lausanne). 2023 Aug 31;10:1164051. doi: 10.3389/fmed.2023.1164051. PMID: 37720502; PMCID: PMC10501800.

Article 5

Gracea RS, Suryani IR, Fontenele RC, Araujo HG, Radi S, Elgarba BM, Shujaat S, Coropciuc R, Jacobs R. Alveolar socket surface as local risk factor from MRONJ development in polypharmacy patients. Oral Diseases (Submitted).

Article 4

Are medication-induced salivary changes the culprit of osteonecrosis of the jaw? A systematic review

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Published in Frontiers in Medicine. 2023 Aug 31

Abstract

Purpose: This systematic review was performed to assess the potential influence of medication-induced salivary changes on the development of medication-related osteonecrosis of the jaw (MRONJ).

Methods: An electronic search was conducted using PubMed, Web of Science, Cochrane and Embase for articles published up to June 2023. Risk of bias assessment was performed according to the modified Newcastle-Ottawa Scale (NOS). Due to heterogeneity of the selected studies in relation to type of medications and outcomes evaluated, a meta-analysis could not be performed.

Results: The initial search revealed 765 studies. Only 10 articles were found to be eligible based on the inclusion criteria that reported on the impact of salivary changes on MRONJ following administration of different medications. A total of 272 cases of MRONJ were included (35% female, 32% male, 32% no gender reported) with a mean age of 66 years at the time of diagnosis. Patients administered with bisphosphonates, steroids, chemotherapy, thalidomide, interferon and hormone therapy had a significantly higher association between decreased salivary flow and MRONJ occurrence. In addition, bisphosphonates, denosumab, and other bone modifying agents showed a significantly higher risk of developing MRONJ owing to the changes in salivary microbiome profile, cytokine profile, interleukin, hypotaurine, and binding proteins.

Conclusion: The reduction in salivary flow and changes in the concentration of salivary proteins were associated with the development of MRONJ. However, due to the availability of limited evidence, the findings of the review should be interpreted with caution.

Prospero registration number: CRD42022327645

Keywords: polypharmacy – saliva – xerostomia - adverse drug reactions – osteonecrosis of the jaw

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is an adverse drug reaction, described as an exposed necrotic bone or a bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region, that persists for more than eight weeks in patients without history of radiotherapy or disease metastasis to the jaws [1,2]. It commonly occurs in oncology patients receiving pharmacological agents, such as antiresorptive drugs, antiangiogenic drugs, immunomodulators and immunosuppressants [3,4]. The pathological mechanism of MRONJ varies depending on the administered drugs. However, the main mechanism of the majority of drugs involves impairment of bone remodelling via osteoclastic activity inhibition, induction of cell apoptosis and/or disruption of blood vessels formation through deterioration of vascular endothelial growth factor. The frequency of MRONJ is highest in patients with multiple myeloma and its occurrence rate is more in osteoporotic patients compared to general population [5,6].

The early imaging signs of MRONJ include bone sclerosis, lamina dura thickening, alveolar socket persistence following tooth extraction, periapical radiolucency, robust mandibular cortex, expanded periodontal ligament space, receding periodontal bone, and an expanded mandibular canal [7–9]. These patients often exhibit common symptoms such as pain, infection with purulent discharge, jaw discomfort, paraesthesia, malodour and non-healing extraction site [10]. The MRONJ lesions are staged (stage 0 – stage 3) based on clinical and radiological features as proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS). Stage 0: no exposed bone + non-specific signs/symptoms, stage 1: asymptomatic exposed bone, stage 2: symptomatic exposed bone + infection/pain, stage 3: symptomatic exposed bone + infection + pathological fracture/extraoral fistula/ oro-antral or oro-nasal communication/ osteolysis extending to inferior mandibular border or sinus floor [11]. Their management ranges from conservative therapy with antibiotics, antimicrobials, and analgesics to surgical debridement or sequestrectomy, depending on disease severity. In order to prevent MRONJ occurrence, it is important to appropriately maintain oral hygiene of the patient, treat oral infections and complete all dental surgical procedures before initiating osteonecrosis of the jaw-related medications. Moreover, during the drug therapy patients should undergo regular dental screening to prevent possible future occurrences [12].

Current evidence indicates that MRONJ is a multifactorial consequence arising from the direct periodontal tissue infection [13–15], distinctive oral microflora or biofilm [16], invasive oral surgical procedures [17,18], systemic risk comorbidities [19], and alteration of the local immune system [20]. Despite the availability of robust data

related to the risk factors for developing MRONJ, the pathogenesis of the disease in relation to changes in salivary mediators is still not well-understood.

Saliva plays a vital role in maintaining oral homeostasis due to its protective and functional properties. Some of these include teeth remineralization, buffering and neutralizing intrinsic and extrinsic acids, inhibiting harmful microorganisms' overgrowth, preventing xerostomia, and facilitating speech and swallowing. Any change in the salivary function would lead to a plethora of complications and result in a decreased quality of life [21,22]. It is a known fact that the medications responsible for MRONJ are also responsible for altering the salivary composition, levels and secretion. These salivary dysfunctions have significantly been associated with a higher incidence of dental caries. However, few studies have assessed the association between salivary changes and MRONJ occurrence. To the best of our knowledge, no previous systematic approach has been applied to investigate the relationship between salivary changes and MRONJ. Therefore, this review aimed to explore the link between medication-related salivary changes and development of MRONJ.

Material and Methods

Protocol and Registration

The study protocol was registered in the PROSPERO database under the number CRD42022327645. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23]. The review question was formulated according to the PICO (patient, intervention, comparison and outcomes) framework, as follows:

P: cancer and osteoporotic

I: medications that induce salivary changes

C: no comparators

O: MRONJ

"What is the association between the use of medications that induce salivary changes (I) and the occurrence of MRONJ (O) among cancer and osteoporotic patients (P)."

Search Strategy

An electronic literature search was conducted using PubMed (pubmed.ncbi.nlm.nih.gov), Web of Science (webofscience.com), Cochrane (cochranelibrary.com) and Embase (embase.com), from January 2013 to June 2023. The search was restricted to the past 10 years with a goal to include the most recent body of evidence related to drug administration in oncology and osteoporotic patients. Studies evaluating the possible association between salivary changes due to medications and MRONJ occurrence were identified. The search was conducted

using the following MeSH terms, topics, and keywords: "hyposalivation", "xerostomia", "dry mouth", "burning mouth syndrome", "mouth dryness", "osteonecrosis of the jaw", "osteonecrosis/drug therapy", "medication-related osteonecrosis of the jaw", "MRONJ", "BRONJ", "ARONJ", "human". No language restriction was applied. A grey literature search was performed on ProQuest, OpenGrey and Google Scholar, followed by manual search of cross-references within the selected studies.

Eligibility Criteria

The full text of relevant articles was acquired based on the inclusion and exclusion criteria. The inclusion study consisted of both children and adult human clinical studies that assessed medication-related salivary changes and osteonecrosis of the jaw occurrence. Exclusion criteria were animal studies, *in vitro* studies, case reports, systematic reviews, conference abstracts, letters, editorials and surveys. In addition, studies involving patients with a history of radiotherapy, disease metastasis to the jaws and surgical intervention of head and neck cancer impacting the salivary flow were also excluded.

Study selection

The identified articles were imported into Endnote X9 software (Thomson Reuters, Philadelphia, PA, USA). Following removal of duplicates, two independent reviewers (IA and MT) screened the articles based on the titles and abstracts. Subsequently, full text of the articles deemed eligible for inclusion were obtained. Reasons for exclusion were also recorded. Any disagreement between reviewers was resolved through discussion and a third expert (IS) was consulted if a consensus could not be reached. The Cohen kappa coefficient was employed to assess the agreement between the reviewers for the selection process.

Data Extraction

The extracted data included the following: title, author, year of publication, study design, number of patients, gender, age, underlying disease, pharmacological agents and type of salivary changes.

Risk of Bias Assessment

Risk of bias (RoB) was assessed with the Newcastle–Ottawa Scale (NOS)[24] by two independent reviewers (IA and MT). The NOS tool was adapted to assess the selection (maximum 4 stars), comparability (maximum 2 stars), and outcome (maximum 3 stars) parameters, with a total score of nine stars. The study quality was categorized as either good, fair, or poor, based on the modified NOS guidelines.

Results

Study Selection

Figure 4.1. illustrates the flowchart of the entire selection process based on PRISMA guidelines. The search strategy yielded a total of 765 articles. Following removal of duplicates, title and abstract screening, and full-text reading, 10 studies were found to be eligible based on the selection criteria to be included in the qualitative synthesis. A quantitative synthesis was not possible owing to the heterogeneity in assessment methodologies, pharmacological agents and reported outcomes.

Study Characteristics

Table 4.1. presents the summary of the patients and disease characteristics. A total of 272 cases of MRONJ were included (35% female, 32% male, 32% no gender reported) with a mean age of 66 years (range: 33-81 years) at the time of diagnosis. The predominant primary disease and comorbid condition reported were breast cancer (n=57) and hypertension (n=107), respectively. The most common salivary change was xerostomia (dry mouth) due to Sjogren's syndrome (SS=35) and the main pharmacological contributors for MRONJ occurrence were bisphosphonates (n=233), followed by chemotherapy (n=11) and corticosteroids (n=11).

Qualitative synthesis

The characteristics of the 10 included studies and significance of the association between salivary alterations by pharmacological agents and MRONJ occurrence are presented in Table 4.2. The included study designs were case-control (n=6), cohort (n=3) and retrospective (n=1) in nature.

Based on the qualitative synthesis, a reduction in salivary flow and changes in salivary protein levels led to the development of MRONJ. Two studies revealed a significant association between SS and MRONJ following administration of bisphosphonates, steroids, and chemotherapy [25],[26]. In 2 studies, patients with a history of bisphosphonates, steroids, chemotherapy, thalidomide, interferon, and hormone therapy showed a significantly higher association between salivary flow and MRONJ development [27],[28]. Moreover, bisphosphonates, denosumab, and other bone modifying agents were associated with a significantly higher risk of developing MRONJ owing to the changes in the microstructure of saliva in correlation to microbiome profile, cytokine profile, interleukin (IL), hypotaurine, and RNA-binding motif, single-stranded-interacting protein 3 (RMBS3) gene [29]–[34].

Risk of Bias Within Studies

Based on the modified NOS tool, all studies were rated as good, apart from one which had a poor-quality rating. Table 4.3. and Figure 4.2. describe the quality analysis of included studies per domain. The outcome assessment revealed significant shortcomings, however, overall, the studies had good (78%) and fair quality (22%).

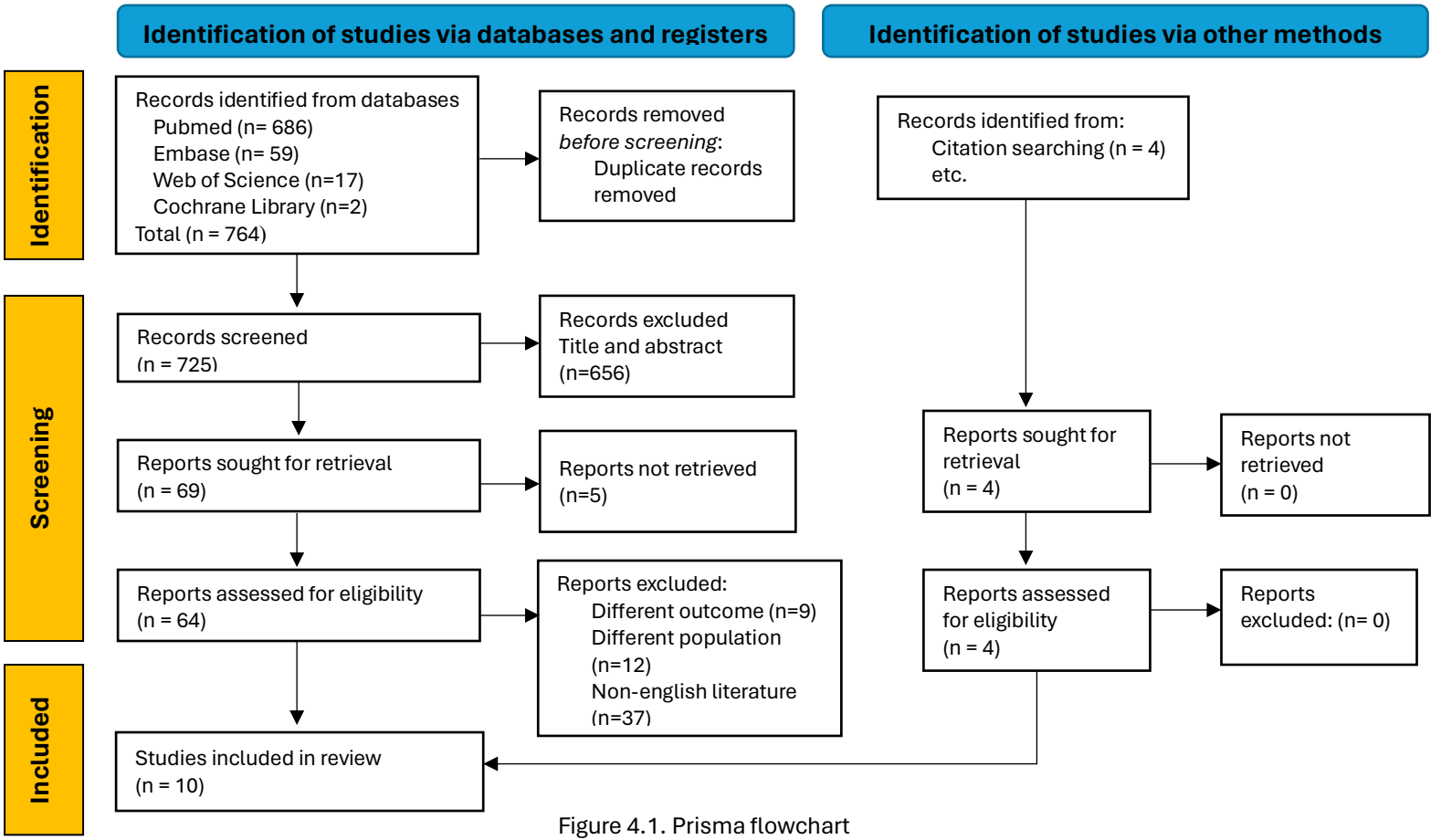

Figure 4.1. Prisma flowchart

Table 4.1. Summary of patients and disease characteristics

Reported cases MRONJ	n=272	100%
Gender		
Female	96	35.29
Male	88	32.35
Not reported	88	32.35
Age		
Mean	65.6	
Min	33	
Max	81	
Primary disease		
Multiple myeloma	55	20.22
Breast cancer	57	20.95
Prostate cancer	19	6.98
Renal cancer	8	2.94
Other Cancer	58	21.32
Osteoporosis	19	6.98
Comorbid conditions		
Diabetes Mellitus	30	11.02
Hypertension	107	37.5
Medications		
Bisphosphonate	233	85.76
Denosumab	4	0.65
Corticosteroids	11	1.78
Chemotherapy	11	1.78
Others	14	2.27

Discussion

In recent years, it has become evident that the changes in salivary properties and constituents are altered in response to various medications and diseases. With the recent advancements in salivaomics, a wide range of discriminatory and definitively validated salivary biomarkers have been established for diagnostic purposes. As a non-invasive and safe source, saliva could replace blood as a medium of choice for diagnostics and assessing disease prognosis [35], hence, the following review was conducted, which might enable the isolation of certain salivary factors for a better understanding of the pathophysiology of MRONJ.

Table 4.2. Characteristics of the included studies in correlation to MRONJ

Author	Location	Study design	Age (X)	n	MRONJ cases	Gender	Underlying conditions	Medications	Sialometric assessment	Saliva changes	P-value
Liao, et.al (2018)	Taiwan	Retro-specti-ve-cohort	57.4	13,398	11	nm	Malignancy DM Hypertension CKD Osteoporosis	BPs Steroids Chemotherapy	nm	Saliva flow↓	0.017*
Margaix-Muñoz, et.al (2013)	Spain	Case-control	63.7	156	67	39F,28M	MM BC PC LC KC BlC	BPs Steroids Thalidomide Interferon Hormones	RWS and SWS	Resting whole saliva↓ Stimulated whole saliva↓	>0.05 >0.05
Badros, et. al (2021)	USA	Observa-tional prospec-tive	60	110	14	5F,9M	MM DM Smoking	BPs Lenalidomide Carfilzomib Other	RWS every 3 months	MIP-1β↑ TNF-α↑ IL-6↑	0.01* 0.09 0.02*
Lorenzo-Pouso, et.al (2022)	Spain	Case-control	69.8	586	18	14F,4M	BC Osteoporosis MM PC Others	IV zoledronate Oral pamidronate Subcutaneous denosumab BMA	RWS	MMP9↑	<0.05*

Author	Location	Study design	Age (X)	n	MRONJ cases	Gender	Underlying conditions	Medications	Sialometric assessment	Saliva changes	P-value
Stockmann et.al (2020)	Germany	Case-control	70	60	20	9F, 11M	BC PC MM CC Osteoporosis	BPs	SWS	Saliva flow↓	0.039*
Bagan, et.al (2014)	Spain	Case-control	66.1	70	30	15F,15M	BC MM PC LC KC Sarcoma	IV BPs	RWS	IL-6↑	<0.01*
Bagan, et.al (2013)	Spain	Case-control	65.7	81	26	10F,16M	BC MM PC RC	BPs	RWS	IL-1α↑ IL-1β↑ IL-IRA↑	<0.05* <0.05* <0.05*
Yatsuoka, et.al (2019)	Japan	Cohort	70.8	35	9	4F,5M	SC	BMA	Metabolic analysis	Hypotauri-ne↑	0.017*
Nicoletti, et.al (2012)	USA	Case-control	62.8	67	53	nm	nm	BPs	Questionnaire and genotyping	RMBS3↑	$<7x10^{8}$*

F (female), M (male), nm (not mentioned), MRONJ (medication-related osteonecrosis of the jaw), IV (intravenous), BMAs (bone modifying agents), IL (interleukin), IL-IRA (Interleukin-1 receptor antagonist), MMP9 (matrix metallopeptidase 9), RMBS3 (ribonucleic acid binding motif single stranded interacting protein 3), MIP (macrophage inflammatory protein), TNF (tumour necrosis factor), α (alpha), β (beta), RWS (resting whole saliva), SWS (stimulated whole saliva), DM (Diabetes Mellitus), BC (Breast Cancer), PC (Prostate Cancer), MM (Mutiple-Myeloma, LC (Lung Cancer), KC (Kidney Cancer), CC (Cervic Cancer), SC (Solid Cancer), CKD (Chronic Kidney Disease). *Statistical significant

Table 4.3. Result from the Newcastle-Ottawa risk assessment for observational studies.

Author	Newcastle Ottawa Scale		
	Selection (max 4)	Comparability (max 2)	Outcome (max3)
Liao, et.al (2018)	***	**	***
Margaix-Muñoz, et.al (2013)	***	**	***
Kuo, et.al (2021)	***	**	**
Badros, et. al (2021)	***	**	***
Lorenzo-Pouse, et.al (2022)	***	**	**
Stockman, et.al (2020)	****	**	**
Bagan, et.al (2014)	***	**	**
Bagan, et.al (2013)	***	**	**
Yatsuoka, et.al (2019)	****	**	**
Nicoletti, et.al (2012)	***	**	**

, 2 stars; *, 3 stars; ****, 4 stars

The majority of included studies diagnosed changes in salivary flow by collecting samples of either resting or stimulated whole saliva, while others used metabolic analysis and genotyping. The lack of standardization in saliva collection techniques, targeted biomarkers, and analytical methods precluded direct comparison of data across studies. A higher percentage of patients with MRONJ were receiving chemotherapy at the time of saliva collection compared to non-MRONJ patients, which may partially explain the observed differences in oral health [36]. The prolonged use of bisphosphonates and concurrent chemotherapy in MRONJ patients might also contribute to oral disorders, not only through reduced salivary gland function but also through increased susceptibility to fungal and bacterial infections and changes in oral microflora [37,38]. Further research is needed to explore the link between these infections and the development of MRONJ [39].

Based on the findings of the review, a decreased production of saliva was considered to be a risk factor for the development of MRONJ, where xerostomia was mainly triggered by SS following administration of bone modifying drugs. In patients with SS, the prevalence of dental caries and early tooth loss is twice as higher and risk of infection due to candida albicans is 10 times more compared to a general population. All these factors increase the risk of MRONJ and the health-related quality of life of these patients is severely diminished. It should be noted that patients with SS were more susceptible to bisphosphonate-related osteonecrosis

of the jaw which might be due to the shared risk factors and molecular pathways [25,26]. Low salivary flow in combination with acid reflux might result in a low oral pH environment which promotes the growth of acidophilic bacteria, in turn leading to tooth destruction and mucosal degradation [40]. Even in low dosages, these drugs can exert a considerable influence on the expression of genes that play a role in the differentiation and growth of osteoblasts. Potent bisphosphonates, such as zoledronate, have the ability to limit ischemia-induced neovascularization by inhibiting the mobilization of endothelial progenitor cells and angiogenic activities. While, zoledronate can reduce bone mineralization within tooth extraction socket, which causes poor bone healing [25]. These outcomes imply that early detection of the changes in salivary flow could act as a diagnostic aid for avoiding MRONJ occurrence and formulating strategies to overcome the salivary flow dysfunction.

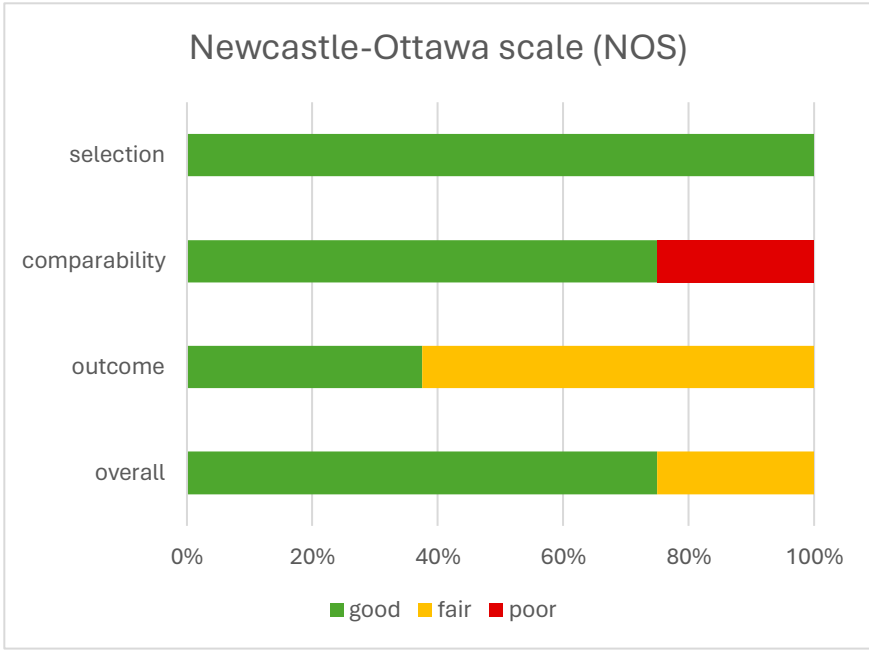

Figure 4.2. Rating Newcastle-Ottawa Scale (NOS)

Polypharmacy was found to be a significant predictor for xerostomia, regardless of the age or gender of the patient. The highest prevalence of xerostomia and MRONJ was observed in patients taking five or more drugs (71%) [41], where xerostomia was determined to be side-effect in around 80-100% of the patients. Based on case-control studies, xerostomia and MRONJ occurrence were nearly three times higher

compared to patients taking no medication. The mechanism of xerostomia varies depending on the administered drugs. For instance, cytotoxic drugs cause dry mouth by directly damaging the salivary gland, anticholinergic drugs act by interrupting the neural simulation of salivary secretions and diuretics promote dehydration and excretion of bodily fluids [42]. In addition, the majority of medications also decrease salivary flow by vasoconstriction in the glands [43]. Therefore, it is important to identify the dose and type of administered polypharmacy in an attempt to predict the impact of each drug separately as such preventive measures could be taken to lower the risk of oral manifestations and complications.

Recent research has indicated an association between diabetes and decreased saliva production. Chronic high blood sugar levels can negatively impact the salivary glands, where parasympathetic vasodilation and salivary secretion might get impaired. The incidence of hyposalivation has also been shown to be higher in diabetic patients compared to non-diabetic population. This decrease in salivary flow may further increase the risk of developing MRONJ. In a study examining hyperglycaemic patients, the risk of developing MRONJ was significantly higher compared to patients with normal glucose levels. This study analysed baseline characteristics such as age, gender, cancer type, presence of osteoporosis, and habits, in addition to the possible synergistic impact of hyperglycaemia and AR therapy that may result in hyposalivation and ischemia. Ischemia is a potential risk factor for mandibular necrosis following invasive dental or oral surgical procedures [44]. Additionally, several factors have been identified as playing a role in the pathogenesis of MRONJ in diabetic patients, including compromised bone microenvironment, altered immune cell function, increased infection and inflammation, inhibition of osteoclast function and induction of apoptosis, microvascular damage, and genetic predisposition [45]. Consequently, it is suggested that further research be conducted to accurately evaluate the coexisting medical conditions of patients and their impact on salivary changes, with the aim of developing potential preventative strategies to reduce the incidence of MRONJ.

In relation to bone modifying agents, the review also suggested a significant association existed between bisphosphonates, hyposalivation and MRONJ occurrence. It is unclear whether discontinuation of osteonecrosis of the jaw related medications would be effective in reducing or preventing MRONJ. The risk of MRONJ varies depending on type of drug, frequency of administration, dose and duration of treatment, where patients treated with high-dose drugs are at a greater risk. A study by Kim et al. proposed that a temporary cessation of bone-modifying drugs, known as a drug holiday, during tooth extraction may reduce the risk of

MRONJ [46], however, another study found no evidence to support an association between drug holiday and reduction is the risk of MRONJ[47]. An alternative solution is to lower the cumulative doses of medications as suggested by the American Dental Association Council on Scientific Affairs [48]. However, till now no detailed guidelines exist related to the impact of different drugs and alternative therapies to reduce the risk of MRONJ. Hence, future prospective studies are required to reach firmer conclusions.

The findings of the review also demonstrated that changes in salivary proteins acted as a risk factor for the development of MRONJ. Bone-modifying drugs, especially bisphosphonates, increased the production of IL-6 and osteoprotegerin while simultaneously reducing the production of receptor activator of nuclear factor kappa-B ligand (RANKL) [49]. This increasing ratio of RANKL to osteoprotegerin signifies that IL-6 is responsible for stimulating osteoclast activity. In addition, IL-6 release is also increased due to the decrease of the enzyme hydroxymethylglutaryl coenzyme A (HMG-CoA) following drug administration. All these changes in the salivary proteins result in a higher occurrence of MRONJ. Bagan et al. suggested that patients with high salivary IL-6 levels following bisphosphonate therapy had a 1.01 odds ratio of developing MRONJ, which increased with the severity of the disease [29,32]. On the other hand, Badros et al. proposed that cytokine response was the main culprit in the pathogenesis of MRONJ, since the tissue injury in MRONJ patients was associated with a pro-inflammatory cytokine profile indicative of macrophage activation [30].

Other cytokines, such as tumour necrosis factor-alpha (TNF-α) [50,51] and interleukin-1 beta (IL-1β) [52], might also cause osteonecrosis of the jaw by promoting inflammation and bone resorption. TNF-α together with RANKL are both members of the TNF superfamily which maintain immune homeostasis and contribute towards bone degradation. TNF-α is an osteoclast-stimulating molecule which stimulates osteoclastogenesis either by acting on osteoclast precursors or increasing the production of RANKL. As TNF-α influences bone metabolism similar to RANKL, its inhibition might result in a decrease in bone turnover following administration of bone modifying drugs and lead to the development of MRONJ [53]. In addition, IL-1β has also been regarded as a potent proinflammatory cytokines, for stimulating bone resorption by causing upregulation of RANKL, which ultimately leads to an imbalance in bone metabolism through osteoclastogenesis [54]. In relation to MRONJ, it acts a pro-inflammatory factor and causes delayed wound healing [55].

The findings also suggested that overexpression of matrix metalloproteinases (MMPs), specifically MMP8 and MMP9, were observed in patients with MRONJ when

compared to healthy patients. These salivary proteins are collagen-degrading zinc-dependent endopeptidases, primarily produced by macrophages and granulocytes [56], where MMP8 is associated with cancer and MMP9 is related to RANKL expression. In addition, hypotaurine, a cystamine analog and precursor for taurine synthesis, was also elevated in MRONJ patients. The concentration of taurine in saliva rises as a biological response to bacterial inflammation and infection during MRONJ development. Yatsuoka et al. suggested that its high concentration could enable detection of MRONJ at an early stage. In relation to genomic profiling, RBMS3 was also significantly associated with MRONJ occurrence. It binds to Prx1, a homeobox transcriptional factor that increases the expression of collagen type I in fibroblasts [57]. The changes in RBMS3 commonly occur following administration of bisphosphonates, which causes loss of bone mass and osteoporotic fractures. In relation to the diagnostic impact of saliva-based protein biomarkers for identifying patients who are at risk of developing MRONJ and monitoring the progression of the disease, further longitudinal and large-sample sized studies are required to determine the sensitivity and specificity of each biomarker and to establish their predictive value in MRONJ occurrence. The main strength of this systematic review was the inclusion of studies evaluating the association between salivary changes and MRONJ occurrence which has not been previously investigated. The introduction of a clear-cut diagnostic and prediction criteria of MRONJ based on polypharmacy, salivary flow and biomarkers could act as a step forward in devising patient-specific management guidelines. The review also had certain limitations. Firstly, a limited number of studies, mostly having a small sample size assessed salivary changes. Secondly, heterogeneity existed in relation to study design, type of administered drugs, primary disease, and outcome assessment methodologies. Hence, future standardized case-control studies involving larger cohort of patients are required to identify and confirm the potential association between MRONJ and salivary changes following administration of different drug categories.

Conclusion

The reduction in salivary flow and changes in the concentration of salivary proteins were associated with the development of MRONJ. However, due to the availability of limited evidence, the findings of the review should be interpreted with caution. It is recommended to assess salivary specimen in patients before and after the development of MRONJ, to provide a better understanding of the disease and validate biomarkers for early detection of the disease.

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Article 5

Alveolar socket surface area as local risk factor for MRONJ development in polypharmacy patients

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Under Review in Oral Diseases

Abstract

Objective: To determine the impact of alveolar socket surface area and number of root extractions for developing medication-related osteonecrosis of the jaw (MRONJ) in polypharmacy patients following multiple tooth extractions.

Methods: A retrospective follow-up study was conducted on 40 patients, including 20 polypharmacy patients (109 tooth extractions) matched to 20 controls (100 tooth extractions). Tooth-specific socket surface areas were assessed. Correlations between number of extracted teeth roots, alveolar socket surface area, and development of MRONJ were analysed.

Results: Forty % of tooth extractions in polypharmacy patient led to MRONJ development, with a higher prevalence in the mandible (46%). Half of the extracted mandibular tooth roots and 45% of the exposed alveolar socket surface area were susceptible to MRONJ. Both jaws exhibited an increased risk (20%) for MRONJ following molar extractions. A strong positive correlation was observed between extraction sites developing MRONJ, mandibular tooth roots extracted ($r = +0.861$; $p < 0.001$), and total alveolar socket surface exposed ($r = +0.757$; $p < 0.001$).

Conclusions: This study is the first to demonstrate that both mandibular alveolar socket surface area and number of extracted tooth roots are positively related to extraction sites developing MRONJ in polypharmacy patients undergoing multiple tooth extractions.

Keywords: Tooth extraction, Polypharmacy, Tooth socket, Wound healing, Jaw, Osteonecrosis

Introduction

Tooth extraction is a routine procedure in which the post-extraction healing outcome is vital to the overall health [1]. The alveolar socket, also known as a dental socket or alveolus, is a cavity in the jawbone that houses the tooth and plays a crucial role in the healing process [2]. The healing of the alveolar socket involves a series of internal and external processes aimed at wound closure and the establishment of tissue homeostasis [3].

In recent years, there has been a surge in studies investigating the intricate factors influencing healing post-extraction, especially in patients with polypharmacy, i.e., the concurrent use of multiple medications [4,5]. Indeed, the combination of medications can impact physiological processes, potentially affecting the body's recover ability from various medical treatments, such as dental extraction [6]. Patients on multiple medications, particularly bone-modifying agents, are at an elevated risk of delayed wound healing and developing medication-related osteonecrosis of the jaw (MRONJ) [7]. For instance, bisphosphonates (BPs) are renowned agents with potent inhibitory effects on osteoclastic activity [8,9]. In patients treated with these medications, tooth extraction can result in the alveolar bone's inability to form new bone. The overlying bone, deprived of blood supply from the underlying bone is prone to deterioration, leading to clinically exposed bone [10]. Additionally, non-antiresorptive agents such as chemotherapy, antiangiogenic tyrosine kinase inhibitors, and corticosteroids have also been associated with MRONJ cases [11,12].

MRONJ, defined as the presence of exposed bone for more than 8 weeks without a prior history of radiotherapy in the head and neck region [13], has been extensively researched in numerous studies in relation to clinical risk factors and early radiographic signs preceding its development. Clinical risk factors associated with MRONJ include medical comorbidities such as the stage of cancer, chemotherapy, antiresorptive use, targeted therapy, systemic inflammatory disease, and tobacco use. While dental comorbidities include tooth extraction, periodontal disease, dental implants, oral surgery, and trauma [14]. Radiographic signs such as bone sclerosis, osteolytic areas, thickening of the lamina dura, persistent alveolar socket, periapical radiolucency, thicker mandibular cortex, widening periodontal ligament space, periodontal bone loss and enlargement of the mandibular canal have also been identified as early indicators of MRONJ development [15].

Local risk factors for MRONJ development related to the defect size following multiple tooth extractions are seldom explored [16]. Large defects resulting from multiple tooth extractions, reconstructive surgery of congenital defects, trauma, or tumour, as well as pre-prosthetic reconstructive surgery, are among the local

factors influencing wound healing in the oral cavity [17]. Regarding tooth-specific type, from the literature, it is known that molars need a longer time to heal. Kim et al. in 2014 [18] reported that erratic socket healing was more commonly observed at molar sites compared to premolar sites, with a prevalence of 5% and 3%, respectively. Furthermore, underlying bony conditions (e.g., endodontic and periodontal disease) in the area where teeth are extracted increase the likelihood of developing MRONJ [16]. From this perspective, it is vital to gain insight into the increased risk of MRONJ development based on the wound size resulting from multiple tooth extractions. This study hypothesises that patients with polypharmacy undergoing multiple tooth extractions are at a higher risk of developing MRONJ in multiple extraction sites.

Therefore, the current study primarily aimed to evaluate the relationship between extraction sites developing MRONJ following multiple tooth extractions in polypharmacy patients and the total alveolar socket surface area exposed by multiple extractions. The secondary aim involved assessing the number of tooth root extractions resulting in MRONJ development of the related extraction sockets.

Methods

This retrospective follow-up study was conducted in compliance with the World Medical Association Declaration of Helsinki on medical research. Ethical approval was obtained from the Ethical Review Board of the University Hospitals Leuven (Reference number: S57824). Informed consent was deemed unnecessary, as patient-specific information was anonymised.

Medical records and dental reports of patients who underwent tooth extraction at the Department of Oral and Maxillofacial Surgery, UZ Leuven, Belgium were examined. Inclusion and exclusion criteria are listed in Table 5.1. A total of 40 patients with multiple tooth extractions were divided into two groups; 20 patients with polypharmacy matched for age and tooth extraction with 20 patients serving as controls. The polypharmacy group was composed of patients who used combined medications related to bone alterations such as bisphosphonates, denosumab, chemotherapy, corticosteroids, hormone therapy, and immunosuppressive drugs prior to tooth extraction. The control group consisted of healthy patients without any medications before extraction who demonstrated uneventful socket healing (i.e., no need for recall or reintervention). Figure 5.1 illustrates the pre- and post-extraction panoramic radiographs of patients belonging to control and polypharmacy group.

Table 5.1. Inclusion and exclusion criteria for patient in either polypharmacy or control groups

Criteria	Polypharmacy	Control
Inclusion		
1. Polypharmacy: concurrent use of multiple medications	✓	-
2. Panoramic radiograph prior to extraction	✓	✓
3. Panoramic radiograph 6 months post-extraction	✓	✓
4. Multiple extractions in at least two regions	✓	✓
5. Clinical diagnosis on extraction socket healing as either normal healing or MRONJ development	✓	✓
6. Normal or uneventful extraction socket healing	✓	✓
7. Extraction socket with MRONJ development	✓	-
8. CBCT present prior to extraction	-	✓
Exclusion		
1. Patients with previous history of head and neck radiotherapy	✓	✓
2. No panoramic radiograph prior to tooth extraction	✓	✓
3. Panoramic radiograph with low image quality	✓	✓

MRONJ = medication-related osteonecrosis of the jaw
(✓) = applicable
(-) = not applicable

Clinical characteristics of patients were obtained from medical records and dental reports, encompassing factors such as age, gender, and primary disease. The medication status of the patients, whether they were on multiple medications (polypharmacy) or not on any medications, was also noted. Details pertaining to extracted teeth were recorded, including the number of extracted teeth, their location in the upper or lower jaw, and the type of tooth (incisor, canine, premolar, molar). The post-extraction outcomes were categorised as either normal healing or MRONJ occurrence. Normal healing was determined based on the evaluation of mucosal healing within an 8-week period post-extraction. The diagnosis of MRONJ was based on clinical observations and panoramic radiographic data (Vistapano,

Dürr Dental, Bittingheim-Bissingen, Germany), collected 6 months after the extraction.

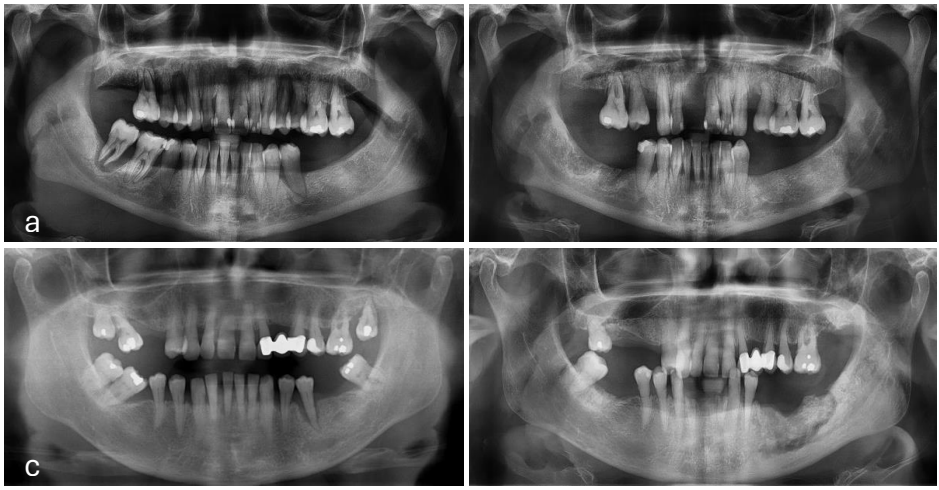


Figure 5.1. Panoramic radiograph of either a control patient (a-b) or a polypharmacy patient (c-d) undergoing multiple tooth extractions. (a) pre-extraction image of teeth 35, 46, 47; (b) normal healing of the alveolar socket of teeth 35, 46, 47. (c) pre-extraction of teeth 17, 28, 37, 35, 31, 41, 42, 47; (d) MRONJ observed at site of tooth 31, 41, 35, 37 and normal healing at sites of teeth 17, 28, 42, 47.

To establish a standard for the dimensions of alveolar sockets, a three-dimensional (3D) analysis was conducted on selected cone beam computed tomography (CBCT) images of all types of teeth. These images were captured using the Newtom VGI evo device (Cefla, Imola, Italy) prior to extraction. The CBCT images were saved in the Digital Imaging and Communication in Medicine (DICOM) format and then imported to an online cloud-based platform called 'Virtual Patient Creator' (creator.relu.eu, version 3.12, Relu BV, Leuven, Belgium). This platform was used to generate segmentations of the jawbone and teeth, which allowed for the creation of virtual 3D models in Standard Tessellation Language (STL) format. These STL 3D models were then imported into the Mimics Innovation Suite (version 24.0, Materialise N.V., Leuven, Belgium) to calculate the surface area of the alveolar socket. This calculation followed the method described by Regnstrand et al. [19]. Manual segmentation of the alveolar socket 3D digital models was performed at the crestal bone level, specifically 1.50 mm apical to the cementoenamel junction (CEJ) to the

Table 5.2a. Characteristics of patients and extracted teeth in the polypharmacy group

Characteristics of polypharmacy patients					
Number of patients, n			20		
Age, years (mean±SD)			67 ± 10.8		
Gender, n		Male	9		
		Female	11		
Primary cancer, n		Breast cancer	9		
		Prostate cancer	6		
		Multiple myeloma	3		
		Lung cancer	2		
Characteristics of extracted teeth					
Number of extracted teeth, n (%)			109 (100%)		
MRONJ development, n (%)			n	MRONJ+	MRONJ-
			109	43 (40)	66 (60)
Jaw position, n (%)		Upper jaw	109	19 (35)	35 (65)
		Lower jaw		24 (44)	31 (56)
Number root extracted, n (%)		Upper jaw	117	43 (37)	74 (63)
		Lower jaw	76	35 (46)	41 (54)
Tooth type, n (%)	Upper	Incisor	54	1 (2)	5 (9)
		Canine		3 (6)	4 (7)
		Premolar		4 (7)	7 (13)
		Molar		11 (20)	19 (35)
	Lower	Incisor	55	7 (13)	6 (11)
		Canine		2 (4)	4 (7)
		Premolar		4 (7)	11 (20)
		Molar		11 (20)	10(18)

Table 5.2b. Characteristics of patients and extracted teeth in the control group

Characteristics of control patients			
Number of patients, n			20
Age, years (mean ± SD)			62 ± 11.4
Gender, n		Male	14
		Female	6
Characteristics of extracted teeth			
Number of extracted teeth, n (%)			100 (100%)
Tooth type, n (%)	Upper	Incisor	13 (26)
		Canine	11 (22)
		Premolar	10 (20)
		Molar	16 (32)
	Lower	Incisor	14 (28)
		Canine	7 (14)
		Premolar	14 (28)
		Molar	15 (30)

lowest point of the root/s in the axial, coronal, and sagittal planes. Thereafter, the alveolar socket at the time of extraction was simulated, and the surface area of alveolar socket was automatically calculated in square millimeters (mm^2). For each specific type of tooth in either the upper or lower jaw, an average was calculated from 10 alveolar sockets to obtain reference values for the surface area of the alveolar socket. This resulted in a total of 80 measurements of alveolar socket surface area.

Reliability evaluations for surface area measurements were carried out on a subset comprising 10% of the total sample. Two maxillofacial radiologists (IRS and RSG), each with more than 5 years of experience, independently and blindly conducted the assessments twice. The observations were repeated at an interval of one week to compute both intra- and inter-observer reliability.

Statistical analysis

Statistical analysis was performed using R (version 4.4.0, R Core Team, Vienna, Austria) in conjunction with RStudio (2023.12.1+402). The intra- and inter-observer reliability for the measurement of alveolar socket surface area in the control group was evaluated using the intra-class correlation coefficient (ICC). Descriptive

statistics were reported for all the data. In the polypharmacy group, Pearson correlation analyses were performed to examine the correlation between the total number of extracted tooth roots and the number of extraction sites that developed MRONJ. This statistical method was also employed to evaluate the relationship between the total exposed alveolar socket surface area following multiple tooth extractions and the alveolar socket surface area of the extraction sites that developed MRONJ within the same jaw for each patient. A p-value of less than 0.05 was considered statistically significant.

Results

Table 5.2a. presents a summary of the patient characteristics and details of the teeth extracted in the polypharmacy group. The age of the patients varied from 47 to 85 years, with a majority being female. Out of the 109 teeth that were extracted, 44% from the lower jaw resulted in the development of MRONJ, primarily in the molar region. Additionally, a descriptive analysis of the number of tooth roots extracted revealed that approximately 37% of the total roots extracted from the upper jaw and nearly 46% from the lower jaw were susceptible to MRONJ.

Table 5.2b. delineates the characteristics of the control group. The ages of the patients ranged from 46 to 89 years with a female-to-male ratio of 1:2. A total of 100 extracted teeth were included, which were almost equally distributed across different types of teeth. All teeth extracted in the control group demonstrated normal healing of the extraction socket.

Table 5.3. with pictorial models list the measurements of the alveolar socket surface area for upper and lower incisors, canines, premolars, and molars. Both intra-rater and inter-rater reliability for these measurements were found to be high, with values of 0.9 (95% CI 0.9-1) and 0.9 (95% CI 0.8-0.9), respectively. Molar teeth had the largest average alveolar socket surface area. Specifically, the extraction of upper molars resulted in an exposed alveolar socket surface area averaging 350± 62 mm^2, while the extraction of lower molars averaged 359±84 mm^2.

Figure 5.2. displays scatter plots showing the distribution of extraction sites that developed MRONJ and the total number of tooth roots extracted within the polypharmacy group, categorized by upper and lower jaw. Pearson correlation analysis showed no significant correlation in the upper jaw, while a strong positive correlation ($r = +0.861$, $p < 0.001$) was observed in the lower jaw. Notably, a cutoff value of 4 roots was identified, suggesting that the extraction of 4 or more tooth roots significantly increased the risk of MRONJ development.

The evaluation of the alveolar socket surface area following multiple tooth extractions in the polypharmacy patients showed that MRONJ development occurred in 36% of the exposed alveolar surface area in the upper jaw and 45% in the lower jaw. Figure 5.3. illustrates the distribution of the alveolar socket surface area in the polypharmacy group. Pearson correlation analysis showed no significant correlation for multiple extractions in the upper jaw of polypharmacy patients. Interestingly, a strong positive correlation ($r = +0.757$, $p < 0.001$) was observed between the total exposed alveolar socket area and the alveolar socket area developing MRONJ after multiple tooth extractions in the lower jaw of these patients.

Discussion

The healing process of extraction sockets is influenced by a variety of factors, including local and systemic conditions, iatrogenic influences, and environmental elements [20,21]. The overall aim of this study was to assess the impact of multiple tooth extractions on the development of MRONJ in polypharmacy patients. Analysis of MRONJ development in polypharmacy patients indicated that the number of extracted tooth roots and the total alveolar socket surface area left exposed following multiple tooth extractions in the mandible was strongly and positively related to the number of extracted tooth roots developing MRONJ. Remarkably, it was observed that half of the extracted mandibular tooth roots seem to develop MRONJ in polypharmacy patients undergoing multiple tooth extractions. Although the methodology applied was innovative, it should be noted that Agbaje et al. [22,23] had previously described volumetric CBCT analysis as a clinically valuable tool for assessing delayed or impaired wound healing of extraction sockets in patients who had undergone radiation therapy.

In present study, both upper and lower molars were found to have a larger surface area and at the same time most risk for MRONJ development. The average alveolar socket size of molars was consistent with the findings of Lakhani et al. (2017) [24], who reported an average surface area of 391±435 mm2 and 375±331 mm2 for lower and upper first molar, respectively. Although no significant correlation was found in the upper jaw, a significant positive correlation was observed between the total number of tooth roots extracted in the lower jaw and the extraction sites that developed MRONJ. Indeed, half of the extracted mandibular tooth roots seem to develop MRONJ in polypharmacy patients undergoing multiple tooth extractions. This finding was further supported by a significant positive correlation between the

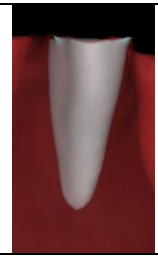
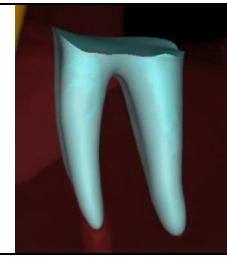
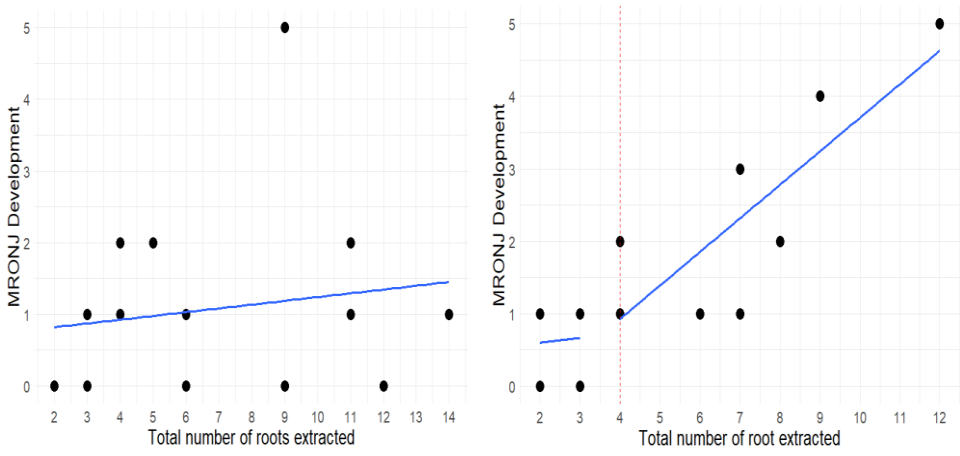
	Incisor	Canine	Premolar	Molar
Upper jaw (n=10)				
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
Surface area (mm^2)	183 ± 8	229 ± 41	213 ± 30	350 ± 62
Lower jaw (n=10)				
	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
Surface area (mm^2)	123 ± 17	177 ± 35	202 ± 33	359 ± 84

Table 5.3. 3D simulation of tooth-specific alveolar socket and related average alveolar socket surface area

X= mean value

SD= standard deviation

alveolar socket surface area with MRONJ and the total surface area exposed after multiple mandibular tooth extractions in patients on multiple medications. As the number of extracted tooth roots increased, so did the exposed surface area of the alveolar socket, demanding greater healing capacity from the body. This increased demand for healing must be considered in the context of decreased vascularization and salivary flow, particularly in patients on multiple medications with chronic dental infections necessitating extraction [12,16,17,25].



(a) (b)

Figure 5.2. The scatter plots depicting the distribution of extraction site with MRONJ development and the total number of tooth roots extracted, in upper jaw (a) and lower jaw (b) with the cutoff value for increased risk of MRONJ development

Interestingly, the analysis also identified a cutoff value of 4 tooth roots extracted, indicating that extracting 4 or more tooth roots will increase the risk of MRONJ development in the lower jaw. This suggests that a larger extraction wound or alveolar socket increases the risk of developing MRONJ. This finding aligns with observations of Buchbender et al. [26]. who reported that the risk profile of MRONJ was highest for osteotomy interventions (14%), followed by multiple extraction (11%) and single extraction (5%). However, it is important to note that the authors did not exclusively focus on patients on multiple medications.

Numerous studies have identified the mandible as being more prone to the development of MORNJ [27–34]. Notably, the mandible, especially in the posterior region, possesses unique characteristics compared to long bones, thereby creating

a distinct environment. In contrast to long bones, which are primarily formed by endochondral ossification, the development of the mandible bone is largely attributed to intramembrane ossification. Additionally, the mandibular bone contains a higher proportion of collagen. These specific anatomical characteristics make mandibular jawbone more susceptible to osteonecrosis [35]. Indeed, the cortication of the mandible may be more susceptible to the effects of multiple medication drugs, impacting the osteoclastic activity. This susceptibility, in an environment with altered salivary flow mechanisms and a decreased immune response, heightens the likelihood of developing MRONJ [25,35]. Moreover, the patterns of vascularization, which significantly vary between the maxilla and mandible, play a crucial role in the healing of alveolar sockets and the development of MRONJ. The maxilla exhibits a more extensive vascularization, with blood vessels dispersing throughout the bone. This extensive vascularization in the maxilla expedites recovery, making it more rapid and optimal [36]. On the other hand, the mandible has a less extensive vascularization, with blood vessels primarily directed through canals. As a result, extractions in the mandible are typically more challenging, leading to a slower healing response [37]. Vascularization is vital as it supplies bone cells with essential elements such as oxygen, nutrients, hormones, and growth factors, all of which are critical for bone regeneration and remodelling. It also plays a role in the transportation of medications, including antibiotics. Impaired vascularization can result in abnormal healing, which may ultimately lead to osteonecrosis [38].

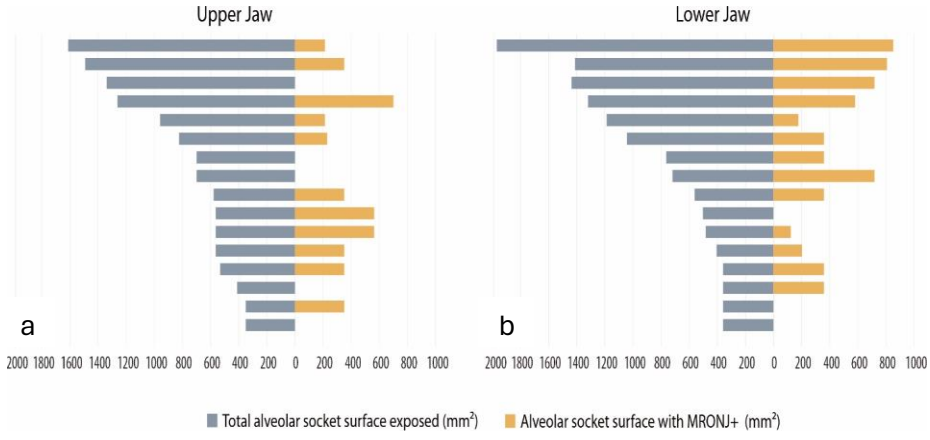


Figure 5.3. The horizontal bar chart shows the surface area of teeth with MRONJ development versus the total alveolar socket surface area exposed after multiple tooth extractions in either upper (a) or lower jaw (b).

The occurrence of MRONJ in polypharmacy patients is complex and influenced by several interconnected factors. One such factor is the disruption of local immune responses. Numerous studies have underscored the importance of the mucosal immune system in protecting against microbial threats and maintaining balance, especially after dental injuries or in the presence of chronic periodontitis [39,40]. The process of bone invasion during multiple tooth extractions compromises the integrity of the mucosal epithelial barrier, thereby enabling increased bacterial invasion and colonisation. This heightened bacterial activity could potentially lead to jaw bone infection, particularly in instances of mucosal ulceration and periodontal disease, which are acknowledged as the initial pathological events of MRONJ [41].

Moreover, in patients with administered zoledronate, local immune response within the oral cavity may be disrupted by inhibiting dendritic cell differentiation and function. This disruption renders the oral microenvironment more favorable for bacterial colonization, thereby increasing the risk of subsequent MRONJ development [42]. In this context of the osteoimmune response, bone modifying agents influence the interaction between the immune system and bone, thus leading to an imbalance of bone homeostasis and low bone turnover. Low bone turnover facilitates the accumulation of microdamage in the jaw and the opportunity of bacterial colonization. This mechanism is being proposed as a contributing factor to the development of MRONJ [43]. Another crucial factor to consider is genetic predisposition. It has been suggested that genetic variations among individuals may either amplify or mitigate the risk of MRONJ [44]. Specifically, Matrix Metalloproteinase-2 (MMP-2), a protein predominantly found in human tissue, has been implicated as a potential gene increasing susceptibility to MRONJ induced by bisphosphonates (BPs) [45].

While the current data provide valuable insights into the heightened risks for MRONJ development following multiple tooth extractions in patients on multiple medications, further studies are needed to corroborate these findings. The retrospective nature of the study, coupled with the limited sample size and single-centre data, may have introduced some sampling bias. Future research should focus on large prospective trials examining tooth-specific healing patterns in patients on multiple medications. It may be beneficial to incorporate salivary and genetic testing, as well as close monitoring of both mucosal wound healing and underlying bone remodelling in both healthy and polypharmacy patients.

In conclusion, the current study on multiple tooth extractions in polypharmacy patients is groundbreaking in its findings. It is the first to establish that both mandibular alveolar socket surface area and number of extracted tooth roots

showed a positive relationship with MRONJ development in polypharmacy patients undergoing multiple tooth extractions. Notably, in patients on polypharmacy who underwent multiple mandibular tooth extractions, up to half of the extracted roots developed MRONJ.

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GENERAL DISCUSSION, CONCLUSION AND FUTURE PERSPECTIVES

General discussion

The incidence rate of polypharmacy among oncology patients is steadily increasing. Anticancer agents, including antiresorptive (AR) and non-AR medications, are commonly prescribed to these patients in order to manage the primary disease, prevent adverse events related to the skeleton, and provide supportive care. Denosumab and bisphosphonate are established AR. Non-AR medications include tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) inhibitors, non-AR angiogenesis inhibitors, chemotherapy, and corticosteroids. Patients taking AR or non-AR medications frequently experience delayed wound healing, an adverse drug reaction that can potentially lead to medication-related osteonecrosis of the jaw (MRONJ). The potential for a substance to impair wound healing may differ based on factors such as its dosage, route of administration, and mechanism of action. A multitude of growth factors and cytokines participate in the healing process, and specific medications have the potential to disrupt each phase of this process [1].

MRONJ is a severe condition characterized by bone exposure and necrosis in the jaw, primarily associated with the use of antiresorptive and, increasingly recognized, non-antiresorptive medications [2–4]. Additionally, MRONJ is detectable via radiographic imaging. Certain changes in the bone's appearance in the affected regions are radiographic predictors of MRONJ, including heterogeneous and sclerotic bone patterns, widened periodontal ligament space and/or periapical lesions, and the absence or incomplete presence of endodontic fillings with cavities [5].

Current evidence indicates that MRONJ is a multifactorial consequence arising from the direct periodontal tissue infection [6–8], distinctive oral microflora or biofilm [9], invasive oral surgical procedures [10,11], systemic risk comorbidities [12], and alteration of the local immune system [13]. Despite the availability of robust data related to the risk factors for developing MRONJ, the pathogenesis of the disease in relation to changes in salivary mediators, polypharmacy used, and the dimension of the socket are still not well-understood.

This doctoral thesis aims to evaluate the impact of polypharmacy and to predict some risk factors on wound healing impairment following tooth extraction and thus prevent or anticipate problematic tooth extractions.

The association between MRONJ and antiresorptive denosumab and bisphosphonates has been well documented. However, with the introduction of a

growing range of non-antiresorptive drugs, it is of vital importance to assess the influence of these drugs on MRONJ development. While the risk of MRONJ development varies depending on the drug administration guidelines and dosage, duration of treatment, and the presence of concurrent systemic pathologies. The evidence remains unclear about the association with MRONJ and non-antiresorptive drugs. Therefore, in **article 1**, we conducted a systematic review and meta-analysis with the aim to provide evidence related to the association between non-antiresorptive medications and MRONJ.

The results of the quantitative synthesis indicated that MRONJ exhibited a stronger correlation with chemotherapeutic agents and corticosteroids. The results of our study were in line with the conclusions drawn by Feng et al. and van den Wyngaert et al. [11,14]. Chemotherapeutic agents inhibit the formation of osteoclasts and suppress the immune system. In addition, the vascularization and metabolism of bones are adversely affected by the cytotoxic effects of these medications, which increases the risk of developing MRONJ. Patients with multiple myeloma had a higher incidence of chemotherapy-related osteonecrosis, according to Zhou et al. [15]. This could be attributed to the combination of chemotherapeutic and antiangiogenic compounds included in the treatment regimens.

Patients undergoing chemotherapy with gemcitabine had an increased incidence of MRONJ, according to DeSesa et al. [16] this may have been due to the anti-angiogenic effect of the drug, which prevents the formation of vascular endothelial growth factor (VEGF). In addition to chemotherapeutic agents, corticosteroids were associated with an increased incidence of MRONJ; nevertheless, the pathway mediated by these medications is complex, suggesting that the underlying mechanism is multifactorial. Prolonged corticosteroid therapy was associated with an increased risk of developing osteonecrosis or avascular necrosis, according to our findings. One potential factor contributing to impaired wound healing is the suppression of VEGF production or a reduction in the recruitment and volume of osteoclastic and osteoblastic precursors. This latter phenomenon not only accelerates apoptosis but also affects the turnover of newly formed cells [17].

To determine the systemic factors related to wound healing impairment, we conducted a retrospective study. In **article 2**, we searched from digital medical records of patients who underwent tooth extraction during a period of six years (September 2015-April 2021) at the Department of Oral and Maxillofacial Surgery, UZ Leuven, Belgium. The inclusion criteria consisted of patients aged ≥40 years with a radiological follow-up. Patients with a history of craniofacial radiotherapy and malignant and metastatic diseases of the jaw were excluded. This study aimed to

investigate the impact of antiresorptive (AR) and non-antiresorptive (non-AR) drugs, alongside other risk factors, on wound healing post-tooth extraction.

The retrospective study comprised 353 patients, aged 40-90 years, with various polypharmacy regimens. Patients receiving both non-AR and AR+ non-AR polypharmacy exhibited significantly impaired wound healing following tooth extraction. Additionally, advanced age and high polypharmacy scores correlated significantly with delayed healing and MRONJ occurrence. Notably, smoking and extraction sites did not significantly impact wound healing. These findings underscore the complex interplay between medication regimen, age, and wound healing outcomes.

The effect of a medication on wound healing process may vary depending on its mechanism of action, dosage, and route of administration. Research has demonstrated that antiresorptive drugs prevent the proliferation, migration, and differentiation of vascular endothelial cells, thereby impeding the process of soft tissue repair and vessel remodelling in the buccal mucosa [18]. Furthermore, non-antiresorptive medications have been proposed as possible contributors to the occurrence of delayed healing. Certain studies observed histologic and volumetric irregularities at the site of tooth extraction subsequent to vascular endothelial growth factor suppression therapy utilizing bevacizumab, a non-AR agent. These findings suggest that the administration of a non-AR drug prolonged the healing process [19,20]. On one hand, this study found that individuals who were prescribed corticosteroids had the highest risk of developing MRONJ. By inducing a heightened rate of apoptosis in osteoblasts and osteocytes, these medications impede the process of bone and soft tissue regeneration [21,22].

Subsequently, we tried to develop specific predictor of wound healing prior to tooth extraction in polypharmacy patients, as we accomplished in **article 3**. In this study, we aimed to develop a prognostic tool, the Adapted-University of Connecticut Osteonecrosis Numerical Scale (A-UCONNS), for predicting wound healing outcomes post-tooth extraction in medically compromised patients. Through meticulous review of digital medical records, the study recruited 353 male patients, with a mean age of 67.4 years. The A-UCONNS parameters, including initial pathology, comorbidities, and administered AR medications, were used to categorize patients into minimal, moderate, and significant risk groups. Higher A-UCONNS scores correlated with an increased likelihood of MRONJ occurrence, emphasizing the tool's potential in predicting healing outcomes and guiding tailored treatment strategies.

Various factors may inhibit the process of wound healing. These elements can be categorized as either local or systemic. The characteristics of a wound are

influenced by local circumstances, which directly affect it. On the other hand, systemic factors are related to the individual's overall health or disease status, and might effect their healing ability [23]. Systemic variables impact the process of wound healing by exerting local effects, and there is a complex interrelationship among many of these elements. Local factors such as oxygenation, infection, the presence of foreign bodies, and venous sufficiency play a role in determining the time it takes for healing to occur [24]. Immunocompromised diseases and immunosuppressive medicines, such as chemotherapy and steroids, are known to be systemic risk factors that can lead to healing failure [11,25]. The present study showed that medically compromised patients with delayed healing or MRONJ commonly received treatment with both corticosteroids and chemotherapy.

The clinical assessment of the A-UCONSS, using the administration of AR medications as a basis, revealed a significant association between the use of AR medications and the occurrence of delayed healing or MRONJ after tooth extraction. Nevertheless, a study discovered that the utilization of alendronate and zoledronic acid did not exhibit a significant correlation with compromised bone and mucosal wound healing subsequent to dental extraction in women with osteoporosis who adhered to a suitable surgical strategy and maintained bisphosphonate therapy [26]. Therefore, it is crucial to recognize and categorize the elements that increase the risk and create personalized protocols for patients to enhance the results of surgical procedures.

Furthermore, to find the local factors related the wound healing impairment following tooth extraction, we conducted analysis in **article 4** and **article 5**. In **article 4** we performed a systematic review to determine whether medication-induced salivary alterations are the cause of osteonecrosis of the jaw. This systematic review delves into the potential impact of medication-induced salivary changes on MRONJ development.

Despite an initial pool of 765 studies, only 10 were deemed eligible, highlighting the scarcity of literature on this subject. These studies encompassed 272 MRONJ cases, with patients administered bisphosphonates, steroids, chemotherapy, thalidomide, interferon, and hormone therapy.

Based on this study, saliva has emerged as a promising diagnostic medium due to advancements in salivaomics, offering non-invasive means to assess biomarkers for various diseases, including medication-related osteonecrosis of the jaw (MRONJ). Studies have identified changes in salivary properties and constituents in response to medications and diseases, suggesting a potential link between decreased saliva production and MRONJ development. Factors such as

chemotherapy [15], polypharmacy [27], and conditions like Sjögren's syndrome and diabetes contribute to xerostomia, increasing the susceptibility to MRONJ [28,29].

The coexistence of acid reflux and inadequate salivary flow may contribute to a low oral pH, which stimulates the proliferation of acidophilic bacteria. Consequently, this can result in the deterioration of mucosa and tooth structure [29]. A significant incidence of xerostomia and MRONJ was identified among patients who were prescribed five or more medications (71%), with xerostomia being identified as a side effect in approximately 80%-100% of these patients. In case-control studies, the incidence of xerostomia and MRONJ was approximately three times greater in patients who received medication as opposed to those who did not [27].

Additionally, the findings of the review also demonstrated that changes in salivary proteins acted as a risk factor for the development of MRONJ. Salivary biomarkers such as IL-6, MMPs, and hypotaurine show promise in identifying MRONJ risk and monitoring disease progression. Bone-modifying medications, with bisphosphonates becoming especially significant for this, increased osteoprotegerin and interleukins-6 (IL-6) production while decreasing receptor activator of nuclear factor kappa-B ligand (RANKL) production. The elevated ratio of RANKL to osteoprotegerin indicates that the stimulation of osteoclast activity is ascribed to IL-6. Furthermore, after drug administration, the enzyme hydroxymethylglutaryl coenzyme A (HMG-CoA) decreases, which further contributes to the elevation of IL-6 release. Due to these alterations in salivary proteins, the incidence of MRONJ is increased [30]. Patients with elevated salivary IL-6 levels after bisphosphonate therapy had an odds ratio 1.01 of developing MRONJ. This odds ratio increased as the disease progressed [31, 32].

In **article 5**, we aimed to assess if alveolar socket surface area may increase the risk for MRONJ development upon multiple tooth extractions in polypharmacy patients. A primary sub-objective was to evaluate tooth-specific alveolar socket surface area. Secondly, it was aimed to examine the relationship between the alveolar socket surface exposed to the oral cavity following extraction of multiple teeth and the alveolar sockets eventually developing MRONJ within polypharmacy patients. The present study on multiple tooth extractions in polypharmacy patients, is the first to relate the number of extracted tooth roots and the total alveolar socket surface area left exposed following multiple extractions in the mandible is positive related to the number of extracted tooth roots developing MRONJ.

A total of 40 patients undergoing multiple extractions were included in this retrospective follow-up study. The sample consisted of 20 polypharmacy patients (with a total of 109 tooth extractions) matched for age and multiple extractions with a control group (with 100 tooth extractions). Assessment of tooth-specific alveolar

socket dimensions was performed. Apart from descriptive analysis, the number of roots and the total alveolar socket surface of the extracted teeth in each patient was related to number of extraction sites, tooth roots and total alveolar socket surface developing MRONJ in polypharmacy patients.

While no significant correlation was found in the upper jaw, in the lower jaw a significant positive correlation was observed between the total number of tooth roots extracted and the extraction sites that developed MRONJ. Indeed, half of the extracted mandibular tooth roots seem to develop MRONJ in polypharmacy patients undergoing multiple tooth extractions. As the number of tooth roots extracted increased, the alveolar socket surface area exposed to the oral cavity also increased. Such increase surely demanded more healing capacity of the body, meanwhile dealing with decreased vascularization and salivary flow considering the polypharmacy status and the chronic dental infections of the teeth with extraction need [4, 33–35].

These findings are in line with the presently observed increase in susceptibility for MRONJ development at multiple mandibular sites following multiple tooth extractions, may be attributed to the different composition of maxilla and mandible, with maxilla primarily composed of trabecular bone and mandible consisting predominantly of cortical bone [36]. Additionally, vascularization patterns differ significantly between the maxilla and mandible, further influencing alveolar socket healing and MRONJ development. While the maxilla is more extensively vascularized with blood vessels tending to spread throughout the bone, in the mandible, blood vessels are more guided through canals. The higher vascularization in the maxilla facilitates a more rapid and optimal recovery [37]. The process of bone invasion during multiple tooth extractions compromises the integrity of the mucosal epithelial barrier, facilitating more bacterial invasion and colonization, meanwhile putting the already impaired immune response of the polypharmacy patient under pressure.

Essentially, future research should aim to conduct longitudinal studies with extended follow-up periods to offer valuable insights into the long-term effects of polypharmacy and other risk factors on wound healing. Increasing the sample size and ensuring a more diverse population could enhance the generalizability of the findings. Moreover, refining the Adapted-University of Connecticut Osteonecrosis Numerical Scale (A-UCONNS) through further validation studies can improve its predictive capability before clinical implementation. It is also essential to explore the impact of specific drug interactions within polypharmacy on wound healing through well-controlled studies that adjust for potential confounding factors. By addressing these issues, future studies may help to provide more robust evidence to aid identifying patients at risk for MRONJ when dealing with polypharmacy patients.

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Conclusions

In conclusion, this PhD projects shed light on various aspects of medication-related osteonecrosis of the jaw (MRONJ), contributing to our understanding of its systemic and local factors. Through systematic reviews and meta-analyses, this study has identified associations between non-antiresorptive medications and the development of MRONJ. However, the limited evidence available underscores the need for further research to confirm these associations and elucidate underlying mechanisms.

Furthermore, the second project was conducted to assess the impact of the role of polypharmacy on wound healing post-dental procedures. This study highlighted the age and specific medication combinations could impair wound healing and increase the risk of MRONJ. These findings underscore the importance of personalized treatment approaches and close monitoring of medically compromised patients undergoing dental interventions.

The development of predictive tools such as the Adapted-University of Connecticut Osteonecrosis Numerical Scale (A-UCONNS) represents a promising step towards prognostic and risk assessment in MRONJ treatment. Further ongoing validation and refinement of these tools are necessary to optimize the utility in clinical practice.

In relation to local factors on the development of MRONJ, the reduction in salivary flow and changes in the concentration of salivary proteins were associated with the development of MRONJ. However, due to the availability of limited evidence, the findings of the review should be interpreted with caution. It is recommended to assess salivary specimen in patients before and after the development of MRONJ, to provide a better understanding of the disease and validate biomarkers for early detection of the disease.

As the first study demonstrating the relation of the number of extracted tooth roots and the total alveolar socket surface area left exposed following multiple extractions, the last project conclude that the mandible is positively correlated to the number of extracted tooth roots developing MRONJ. Indeed, in polypharmacy patients undergoing multiple tooth extractions, up to half of the extracted mandibular tooth roots seem to develop MRONJ.

Future perspective

- Exploring Novel Risk Factors: While current research has identified several risk factors associated with MRONJ, including medication use and salivary changes, future studies could delve into novel risk factors that may contribute to MRONJ development. This may involve investigating genetic predispositions, immunological factors, or environmental influences that could modulate susceptibility to MRONJ.
- Longitudinal Studies: Longitudinal studies tracking patients over extended periods could provide valuable insights into the natural history of MRONJ and its progression over time. By examining factors such as medication adherence, changes in salivary parameters, and the occurrence of adverse events, these studies could enhance our understanding of MRONJ pathogenesis and inform early intervention strategies.
- Mechanistic Studies: Further mechanistic studies are warranted to elucidate the underlying pathways involved in MRONJ development. This may involve in vitro and in vivo experiments to investigate the effects of medications on bone metabolism, oral microbiome composition, and immune response within the jawbone microenvironment.
- Interventional Trials: Clinical trials evaluating the efficacy of preventive interventions for MRONJ are needed to establish evidence-based management strategies. This may include randomized controlled trials assessing the effectiveness of drug holidays, adjunctive therapies, or surgical techniques in reducing MRONJ risk among high-risk patient populations.
- Exploration of Biomarkers: Identifying biomarkers associated with MRONJ susceptibility and progression could aid in early diagnosis and monitoring of the condition. Future research could explore the utility of salivary biomarkers, serum markers of bone turnover, and genetic markers in predicting MRONJ risk and guiding clinical management.
- Development of Predictive Models: Building upon existing predictive tools with artificial intelligence, future research could focus on refining and validating predictive models for MRONJ risk assessment. Incorporating advanced imaging modalities, biomarker profiling, and machine learning algorithms may enhance the accuracy of these models and facilitate personalized risk stratification

Summary

The primary objective of this Ph.D. project was thoroughly assessing the impact of polypharmacy and identify associated risk factors contributing to impaired wound healing following tooth extraction, thereby preventing or anticipating potential issues. It was hypothesized that polypharmacy might negatively correlate with wound healing post-dental extraction, as individuals prescribed multiple medications might encounter delayed or compromised healing due to potential drug interactions, side effects, or compromised physiological processes induced by multidrug administration.

The study was divided into three chapters that investigated risk factors associated with the occurrence of Medication-Related Osteonecrosis of the Jaw (MRONJ). The introduction derived from article 1, while chapter 1 consisted of two studies (Articles 2 and 3) that investigated systemic factors. Chapter 2 included two research (Articles 4 and 5) that examined local risk factors affecting wound healing after tooth extraction.

Article 1 aims to assess the influence of non-antiresorptive drugs on MRONJ development, as the risk of MRONJ development varies depending on drug administration guidelines, dosage, duration of treatment, and concurrent systemic pathologies. This study discusses various studies on medication-related osteonecrosis of the jaw in cancer patients. Factors influencing the severity of this condition include initial experience with conservative treatment, administration of monoclonal antibody, prostate cancer status, and systemic comorbidities. The study also explores the impact of bone antiresorptive drugs, and corticosteroids on the incidence of this condition. The study also explores the reasons behind the development of this condition in some extraction sites and others.

This systematic review identified a substantial correlation between MRONJ (medication-related osteonecrosis of the jaw) and non-antiresorptive medications. The majority of non-antiresorptive medications discussed in the review have a shorter duration of action, which could potentially enable the dentist to implement the concept of a "drug holiday" after obtaining approval from the clinician who prescribed the medication.

Moreover**, Article 2** investigated the effect of both anti-resorptive (AR) and non-AR polypharmacy on healing time after tooth extraction and sought to discover patient-related risk variables impacting healing results. The findings revealed that elderly

patients aged 80 years and above, coupled with major polypharmacy scores, were more predisposed to experience delayed healing, especially when subjected to a combination of AR and non-AR medications. Moreover, patients receiving non-AR drugs and exhibiting hyper polypharmacy demonstrated a heightened likelihood of developing MRONJ. Noteworthy was the association of monoclonal antibodies, hormone therapy, and bisphosphonate intake with delayed healing, whereas a plethora of medications, including methotrexate, immunosuppressants, chemotherapy, corticosteroids, hormone therapy, bisphosphonates, and denosumab, was significantly associated with the development of MRONJ.

The study also identified a significant association between delayed healing, age, smoking status, site of extraction, and type of medication on MRONJ. Factors such as monoclonal antibodies, hormone therapy, and bisphosphonates were linked with delayed healing, highlighting the influence of medication types on healing outcomes. Further research was warranted based on these results.

Furthermore, **article 3** introduced an Adapted-UCONNS (A-UCONNS) tool to predict wound healing outcomes post-tooth extraction in medically compromised patients. The A-UCONNS scores for MRONJ were higher based on initial pathology, comorbidity, and AR drugs. A unit increase in A-UCONNS correlated with a 1.347-fold escalation in the odds of experiencing MRONJ compared to normal healing. Furthermore, a survival analysis revealed a correlation between A-UCONNS risk assessment and healing time, with patients categorized as minimal risk demonstrating superior survival outcomes vis-à-vis those classified under moderate risk.

The A-UCONNS tool could enhance care for medically compromised patients by identifying high-risk individuals prone to developing MRONJ. This facilitated tailored treatment planning and post-operative therapy to enhance healing outcomes post-tooth extraction.

To investigate local risk factors in the development of wound healing impairment, the study was divided into two articles. **Article 4** conducted a systematic review of potential influences of medication-induced salivary changes on MRONJ development. The search encompassed studies evaluating possible associations between salivary changes due to medications and MRONJ occurrence. The most common salivary change observed was xerostomia due to Sjogren's syndrome, with bisphosphonates, chemotherapy, and corticosteroids being the primary pharmacological contributors to MRONJ occurrence. Patients with a history of bisphosphonates, steroids, chemotherapy, thalidomide, interferon, and hormone therapy showed a significantly higher association between salivary flow and MRONJ development. Additionally, bisphosphonates, denosumab, and other bone

modifying agents were associated with a significantly higher risk of developing MRONJ due to changes in saliva microstructure. Overexpression of matrix metalloproteinases (MMPs) and hypotaurine were observed in MRONJ patients.

The study explored the role of interleukin-6 concentration changes in plasma and saliva in bisphosphonate-related osteonecrosis of the jaws. Saliva emerged as a potential early detection marker for medication-related osteonecrosis of the jaw. The combined administration of bisphosphonates, chemotherapy agents, and targeted drugs increased the risk for stage 3 osteonecrosis of the jaw. The immune response played a role in the development of medication-related osteonecrosis of the jaw. The study also highlighted the importance of salivary hypotaurine as a potential early detection marker for medication-related osteonecrosis.

Article 5 aims to assess if alveolar socket surface area may increase the risk for MRONJ development upon multiple tooth extractions in polypharmacy patients. A primary sub-objective was to evaluate tooth-specific alveolar socket surface area. Secondly, it was aimed to examine the relationship between the alveolar socket surface exposed to the oral cavity following extraction of multiple teeth and the alveolar sockets eventually developing MRONJ within polypharmacy patients.

This study found a significant positive correlation was observed between the total number of tooth roots extracted in the lower jaw and the extraction sites that developed MRONJ. Indeed, half of the extracted mandibular tooth roots seem to develop MRONJ in polypharmacy patients undergoing multiple tooth extractions. Susceptibility for MRONJ development following multiple tooth extractions in the mandible only, may be attributed to the different composition and vascularisation of maxilla and mandible

Samenvatting

Het primaire doel van dit promotieproject was het grondig beoordelen van de impact van polyfarmacie en het identificeren van bijbehorende risicofactoren die bijdragen aan een verminderde wondgenezing na tandextractie, om zo potentiële problemen te voorkomen of te anticiperen. Er werd gehypothiseerd dat polyfarmacie mogelijk negatief gecorreleerd zou zijn met wondgenezing na tandextractie, aangezien personen die meerdere medicijnen voorgeschreven krijgen, vertraagde of gecompromitteerde genezing zouden kunnen ervaren als gevolg van mogelijke geneesmiddelinteracties, bijwerkingen, of aangetaste fysiologische processen door multidrug toediening.

Het onderzoek was verdeeld in drie hoofdstukken die risicofactoren onderzochten die verband houden met het optreden van Medicatiegerelateerde Osteonecrose van de Kaak (MRONJ). De inleiding was afgeleid van artikel 1, terwijl hoofdstuk 1 bestond uit twee studies (**Artikelen 2 en 3**) die systemische factoren onderzochten. Hoofdstuk 2 omvatte twee onderzoeken (**Artikelen 4 en 5**) die lokale risicofactoren onderzochten die van invloed zijn op wondgenezing na tandextractie.

Artikel 1 heeft tot doel de invloed van niet-antiresorptieve geneesmiddelen op de ontwikkeling van MRONJ te beoordelen, aangezien het risico op het ontwikkelen van MRONJ varieert afhankelijk van de richtlijnen voor medicijngebruik, dosering, behandelingsduur, en gelijktijdige systemische pathologieën. Deze studie bespreekt verschillende studies over medicatiegerelateerde osteonecrose van de kaak bij kankerpatiënten. Factoren die de ernst van deze aandoening beïnvloeden zijn onder andere de initiële ervaring met conservatieve behandeling, toediening van monoklonale antilichamen, prostaatkankerstatus, en systemische comorbiditeiten. De studie onderzoekt ook de impact van botantiresorptieve medicijnen en corticosteroïden op de incidentie van deze aandoening. De studie onderzoekt ook de redenen achter de ontwikkeling van deze aandoening op sommige extractieplaatsen en andere niet.

Deze systematische review identificeerde een substantiële correlatie tussen MRONJ (medicatiegerelateerde osteonecrose van de kaak) en niet-antiresorptieve medicijnen. De meeste niet-antiresorptieve medicijnen die in de review werden besproken hebben een kortere werkingsduur, wat de tandarts mogelijk in staat zou stellen het concept van een "medicijnvakantie" toe te passen na goedkeuring van de clinici die het medicijn hebben voorgeschreven.

Bovendien onderzocht **Artikel 2** het effect van zowel anti-resorptieve (AR) als niet-AR polyfarmacie op genezingstijd na tandextractie en probeerde het patiëntgerelateerde risicovariabelen te ontdekken die van invloed zijn op genezingsresultaten. De bevindingen toonden aan dat oudere patiënten van 80 jaar en ouder, in combinatie met hoge scores op polyfarmacie, meer vatbaar waren voor vertraagde genezing, vooral wanneer zij werden blootgesteld aan een combinatie van AR en niet-AR medicijnen. Bovendien vertoonden patiënten die niet-AR medicijnen kregen en hyperpolyfarmacie vertoonden een verhoogde kans op het ontwikkelen van MRONJ. Opmerkelijk was de associatie van monoklonale antilichamen, hormoontherapie, en bisfosfonaten met vertraagde genezing, terwijl een overvloed aan medicijnen, waaronder methotrexaat, immunosuppressiva, chemotherapie, corticosteroïden, hormoontherapie, bisfosfonaten, en denosumab, significant geassocieerd werden met de ontwikkeling van MRONJ.

De studie identificeerde ook een significante associatie tussen vertraagde genezing, leeftijd, rookstatus, extractieplaats, en medicatietype bij MRONJ. Factoren zoals monoklonale antilichamen, hormoontherapie, en bisfosfonaten werden in verband gebracht met vertraagde genezing, wat de invloed van medicatietypen op genezingsresultaten benadrukt. Verdere onderzoek was gerechtvaardigd op basis van deze resultaten.

Bovendien introduceerde **Artikel 3** een Adapted-UCONNS (A-UCONNS) tool om wondgenezing na tandextractie bij medisch gecompromitteerde patiënten te voorspellen. De A-UCONNS scores voor MRONJ waren hoger op basis van initiële pathologie, comorbiditeit, en AR-medicijnen. Een eenheidstoename in A-UCONNS correleerde met een 1.347-voudige toename in de kans om MRONJ te ervaren in vergelijking met normale genezing. Bovendien toonde een overlevingsanalyse een correlatie tussen risicobeoordeling met A-UCONNS en genezingstijd, waarbij patiënten gecategoriseerd als minimaal risico superieure overlevingsresultaten vertoonden ten opzichte van degenen die werden ingedeeld als matig risico.

De A-UCONNS-tool kan de zorg voor medisch gecompromitteerde patiënten verbeteren door hoogrisicopersonen te identificeren die vatbaar zijn voor het ontwikkelen van MRONJ. Dit vergemakkelijkte op maat gemaakte behandelplanning en postoperatieve therapie om genezingsresultaten na tandextractie te verbeteren.

Om lokale risicofactoren bij de ontwikkeling van een verstoorde wondgenezing te onderzoeken, werd de studie verdeeld in twee artikelen. **Artikel 4** voerde een systematische review uit van potentiële invloeden van medicatie-geïnduceerde veranderingen in speeksel op de ontwikkeling van MRONJ. De zoektocht omvatte

studies die mogelijke verbanden tussen speekselveranderingen door medicijnen en het optreden van MRONJ evalueerden. De meest voorkomende speekselverandering die werd waargenomen was xerostomie door het syndroom van Sjögren, waarbij bisfosfonaten, chemotherapie, en corticosteroïden de belangrijkste farmacologische bijdragers waren aan het optreden van MRONJ. Patiënten met een voorgeschiedenis van bisfosfonaten, steroïden, chemotherapie, thalidomide, interferon, en hormoontherapie vertoonden een significant hogere associatie tussen speekselstroom en het optreden van MRONJ. Bovendien werden bisfosfonaten, denosumab, en andere bot-modificerende middelen in verband gebracht met een significant hoger risico op het ontwikkelen van MRONJ door veranderingen in de speekselmicrostructuur. Overexpressie van matrixmetalloproteïnasen (MMP's) en hypotaurine werden waargenomen bij MRONJ-patiënten.

De studie onderzocht de rol van veranderingen in de concentratie van interleukine-6 in plasma en speeksel bij bisfosfonaatgerelateerde osteonecrose van de kaken. Speeksel kwam naar voren als een potentieel vroeg detectiemerk voor medicatiegerelateerde osteonecrose van de kaak. De gecombineerde toediening van bisfosfonaten, chemotherapie-agents, en doelgerichte medicijnen verhoogde het risico op stadium 3 osteonecrose van de kaak. De immuunrespons speelde een rol bij de ontwikkeling van medicatiegerelateerde osteonecrose van de kaak. De studie benadrukte ook het belang van salivary hypotaurine als een potentieel vroeg detectiemerk voor medicatiegerelateerde osteonecrose van de kaak.

Artikel 5 heeft als doel om te beoordelen of alveolaire socket oppervlakte het risico op de ontwikkeling van MRONJ kan verhogen bij meervoudige tandextracties bij polyfarmaciepatiënten. Een primaire subdoelstelling was het evalueren van de tandspecifieke alveolaire komoppervlakte. Ten tweede was het de bedoeling om de relatie te onderzoeken tussen het alveolaire komvlak dat aan de mondholte wordt blootgesteld na extractie van meerdere tanden en de alveolaire komvlakken die uiteindelijk MRONJ ontwikkelen bij polyfarmaciepatiënten.

In dit onderzoek werd een significante positieve correlatie waargenomen tussen het totale aantal geëxtraheerde tandwortels in de onderkaak en de extractieplaatsen die MRONJ ontwikkelden. Inderdaad leek de helft van de geëxtraheerde mandibulaire tandwortels MRONJ te ontwikkelen bij polyfarmaciepatiënten die meerdere tandextracties ondergingen. De gevoeligheid voor de ontwikkeling van MRONJ op meerdere extractieplaatsen na meervoudige tandextracties in alleen de onderkaak, kan worden toegeschreven aan de verschillende samenstelling en vascularisatie van de bovenkaak en onderkaak.

Scientific acknowledgement

The Ministry of Education and Culture of Republic Indonesia ´s scholarship (BPPLN) supported the author of this thesis. This work would not successfully reach its completion without the commitment from other contributors, whom I would like to extend my gratitude.

Article 1: Isti Rahayu Suryani: study design, manuscript preparation, data analysis, and interpretation. Iraj Ahmadzai: data collection and data interpretation. Sohaib Shujaat: study supervision, manuscript review and critical revision. Hongyang Ma: statistical analysis. Reinhilde Jacobs: conceived ideas, study supervision, critical revision.

Article 2: Isti Rahayu Suryani: study design, manuscript preparation, data analysis, and interpretation. Una Ivković: data collection. Wim Coucke: statistical analysis. Sohaib Shujaat: study supervision, manuscript review and critical revision. Ruxandra Coropciuc: critical revision. Reinhilde Jacobs: study supervision, critical revision.

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I would like to thank Prof. dr. Carine Wouters and Prof. dr. Simon (Mariano N) Pedano de Piero for acted as internal examining committee during the PhD program for the insightful comments to improve the quality of the doctoral projects and thesis. Lastly, I would like to sincerely acknowledge my promotor Prof. dr. Reinhilde Jacobs

and Prof. dr. Sohaib Shujaat for their scientific support and closely follow-up on the progress of thesis and papers and for all the supports throughout the duration of the PhD.

Personal contribution

Isti Rahayu Suryani is the first author of all published thesis chapters and corresponding articles. For the final chapter, she is the second author. Isti Rahayu Suryani conceptualized the projects, gathered, organized, analysed all clinical and radiographic data in collaboration with other researchers at OMFS-Impath research group. Furthermore, her supervisors Prof. dr. Reinhilde Jacobs and Prof. dr. Sohaib Shujaat, as well as all her co-authors, provided significant support as mentioned under scientific acknowledgments.

Conflict of interest

The authors declare have no potential conflicts of interest concerning the publications of this work.

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Curriculum Vitae

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Contribution to (inter)national conferences

10/07/2021	The Indonesian Dental Association (PDGI) conference Lecture and hands-on: CBCT; what, how, where, when?
20/10/2021	Three Countries Webinar (Thailand, Indonesia, Vietnam) Lecture: Integrating CBCT into your dental practices: visualize your treatment from endo to maxillofacial surgery.
05-08/07/2023	International Association of DentoMaxilloFacial Radiology (IADMFR): World Tour Congress Pitch presentation: Risk of healing impairment following tooth extraction in patients administered with antiresorptive and non-antiresorptive polypharmacy

Polypharmacy and Medication-Related Osteonecrosis of the Jaw (MRONJ): Identifying Patients at Risk

The Author

Isti Rahayu Suryani obtained her Doctor of Dental Medicine (2006) from Faculty of Dentistry, UGM-Indonesia, Master of Biomedical Engineering (2012) from Graduate School of UGM-Indonesia and Specialist in Oral Radiology (2017) from Padjajaran University-Indonesia. From December 2019 till June 2024, she was a PhD candidate in OMFS-IMPATH research group with Professor Reinhilde Jacobs as her promotor. Her research focus on risk factors of Medication-related osteonecrosis of the jaw (MRONJ) in correlation to patients with polypharmacy. Currently, she is a lecturer in the Departement of Dentomaxillofacial Radiology, Faculty of Dentistry, UGM-Indonesia and also as Radiology Specialist at UGM Dental Hospital-Indonesia.

The Thesis

This PhD projects shed light on various aspects of medication-related osteonecrosis of the jaw (MRONJ), contributing to our understanding of its systemic and local factors.

1. Systemic factors:
This study highlighted advanced age and high polypharmacy scores correlated significantly with delayed healing and MRONJ occurrence. These findings underscore the importance of personalized treatment approaches and close monitoring of medically compromised patients undergoing dental interventions. Additionally, higher A-UCONNS scores correlated with an increased likelihood of MRONJ occurrence, emphasizing the tool's potential in predicting healing outcomes and guiding tailored treatment strategies.

2. Local factors:
Changes in salivary properties and constituents in response to medications and diseases, suggesting a potential link between decreased saliva production and MRONJ development. Factors such as polypharmacy, conditions like Sjögren's syndrome and diabetes contribute to xerostomia, increasing the susceptibility to MRONJ. In relation to site extraction, the last study showed a significant positive correlation was observed between the total number of tooth roots extracted in the lower jaw and the extraction sites that developed MRONJ. Indeed, half of the extracted mandibular tooth roots seem to develop MRONJ in polypharmacy patients undergoing multiple tooth extractions. As the number of tooth roots extracted increased, the alveolar socket surface area exposed to the oral cavity also increased.

KU LEUVEN

OMFS IMPATH

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