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HYPERGLYCAEMIA AS A SIGNIFICANT RISK FACTOR IN MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)

PhD thesis

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List of Abbreviations

AI – Artificial Intelligence

AAOMS – American Association of Oral and Maxillofacial Surgeons

AGEs – Advanced Glycation End Products

AIDS – Acquired Immune Deficiency Syndrome

ARONJ – Antiresorptive Agent-Related Osteonecrosis of the Jaw

BPs – Bisphosphonates

BRONJ – Bisphosphonate-Related Osteonecrosis of the Jaw

CBCT – Cone Beam Computed Tomography

COVID-19 – Coronavirus Disease 2019

CRP – C-reactive Protein

CT – Computed Tomography

DM – Diabetes Mellitus

FPG – Fasting Plasma Glucose

FPPS – Farnesyl Pyrophosphate Synthase

GDM – Gestational Diabetes Mellitus

GTP – Guanosine Triphosphate

HbA1c – Hemoglobin A1c (Glycated Hemoglobin)

HBO – Hyperbaric Oxygen

IFG – Impaired Fasting Glucose

IGT – Impaired Glucose Tolerance

IL-1 β – Interleukin-1 Beta

IL-6 – Interleukin-6

LPS – Lipopolysaccharide

MRI – Magnetic Resonance Imaging

MRONJ – Medication-Related Osteonecrosis of the Jaw

NBF – Nano-Bio Fusion

OGTT – Oral Glucose Tolerance Test

ONJ – Osteonecrosis of the Jaw

OPG – Osteoprotegerin

PET/CT – Positron Emission Tomography/Computed Tomography

PKC – Protein Kinase C

PRF – Platelet-Rich Fibrin

RANK – Receptor Activator of Nuclear Factor κ B

RANKL – Receptor Activator of Nuclear Factor κ B Ligand

SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2

SICMF – Italian Society of Maxillofacial Surgery

SIPMO – Italian Society of Oral Pathology and Medicine

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

TGF- β – Transforming Growth Factor Beta

TNF- α – Tumor Necrosis Factor Alpha

VEGF – Vascular Endothelial Growth Factor

WHO – World Health Organization

1. Introduction

1.1. Main Objective of the Dissertation

This dissertation investigates the impact of hyperglycaemia, a common metabolic disorder characterised by elevated blood glucose levels, on the development of medication-related osteonecrosis of the jaw (MRONJ). The increasing use of antiresorptive and antiangiogenic therapies, together with the rising prevalence of diabetes mellitus (DM) and prediabetes worldwide, has resulted in a growing number of patients affected by both conditions. A better understanding of the relationship between hyperglycaemia and MRONJ is therefore important for risk assessment, prevention and clinical management.

1.2. Overview of MRONJ

1.2.1. Definition and Key Characteristics of MRONJ

MRONJ is a chronic inflammatory condition that develops in patients with previous or ongoing exposure to antiresorptive agents, such as bisphosphonates (BPs) or subcutaneous denosumab injection. Its pathogenesis is multifactorial and involves suppression of bone remodelling, local infection and repeated microtrauma in the maxillofacial region. Clinically, MRONJ typically presents as a non-healing lesion with exposed necrotic bone and may be associated with pain, swelling or fistula formation. The condition may occur during treatment or even months to years after discontinuation of therapy, reflecting the long-lasting effects of antiresorptive medications on bone metabolism [1].

MRONJ is characterized by one or more areas of exposed necrotic bone in the maxillofacial region (*Figure 1.*) that can be identified during clinical examination or through intraoral or extraoral fistulas probing to bone and persisting for at least 8 weeks despite appropriate management. For diagnosis, patients must have no history of radiation therapy to the jaws and no evidence of metastatic disease involving the jawbones [2, 3].

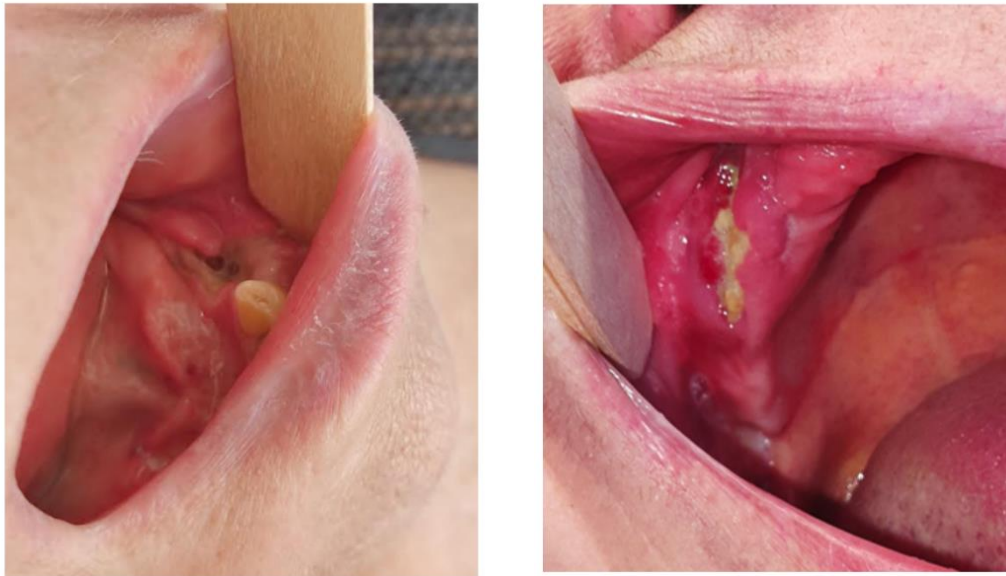


Figure 1. Clinical presentation of MRONJ affecting the left side of the mandible and the right side of the maxilla. Exposed necrotic bone with surrounding mucosal inflammation and erythema is visible. Both patients were referred to our clinic several months after tooth extraction because of persistent non-healing extraction sites. Images from the research group's own clinical documentation.

1.2.2. Pathophysiology and Pharmacological Background of MRONJ

The first formal description of bisphosphonate-related osteonecrosis of the jaw was published by *Marx* in 2003. He reported persistent areas of exposed, non-healing jawbone in patients receiving intravenous bisphosphonate therapy, predominantly pamidronate and zoledronic acid [4]. These observations identified a previously unrecognised adverse effect of antiresorptive treatment and provided the basis for the current concept of MRONJ [4, 5, 6]. The pathogenesis of MRONJ is multifactorial and remains incompletely understood. Current evidence suggests that suppression of bone remodelling, impaired angiogenesis, local inflammation, microbial colonisation and altered immune responses contribute to disease development [7, 8]. BPs are synthetic analogues of inorganic pyrophosphate with a high affinity for hydroxyapatite. After administration, they accumulate in areas of active bone remodelling and become incorporated into the mineralised bone matrix. During osteoclastic bone resorption, BPs are released from the bone surface and internalised by osteoclasts, where they interfere

with intracellular metabolic pathways [13]. Nitrogen-containing BPs, including zoledronic acid, pamidronate, alendronate, ibandronate and risedronate, inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme of the mevalonate pathway. This disrupts the prenylation of small Guanosine Triphosphate (GTP)-binding proteins required for normal osteoclast function, resulting in impaired bone resorption and eventual osteoclast apoptosis [13, 14, 15]. In addition to their effects on osteoclasts, BPs may influence other cell types involved in bone homeostasis. Experimental studies have demonstrated adverse effects on osteoblast differentiation, endothelial cell proliferation, soft-tissue healing and local immune responses. Prolonged suppression of bone turnover may also reduce the ability of bone to repair microdamage and respond to physiological or surgical trauma. Because BPs remain incorporated within the skeleton for extended periods, their biological effects may persist for years after treatment cessation, contributing to the long-term risk of MRONJ [16].

Denosumab is a fully human monoclonal antibody directed against receptor activator of nuclear factor- κ B ligand (RANKL), the principal regulator of osteoclast formation and activity. Under physiological conditions, RANKL binds to its receptor, receptor activator of nuclear factor κ B (RANK) on osteoclast precursors and promotes osteoclast differentiation and activation. Osteoprotegerin (OPG) acts as a natural inhibitor of this process. By binding RANKL with high affinity, denosumab prevents the RANK–RANKL interaction and markedly suppresses osteoclast formation, function and survival, resulting in reduced bone resorption and bone turnover [17, 18]. Although denosumab does not accumulate in bone and has a shorter biological persistence than BPs, its potent antiresorptive effect may similarly impair physiological bone remodelling and contribute to the development of MRONJ. In addition, treatment discontinuation may be associated with rebound osteoclast activation and rapid bone loss [17, 18].

Antiangiogenic therapies represent another group of medications associated with MRONJ. These agents are widely used in oncology because tumour growth and metastatic spread depend on angiogenesis. Vascular endothelial growth factor (VEGF) plays a central role in blood vessel formation and is also involved in bone repair and tissue regeneration [9, 10]. Antiangiogenic agents, such as bevacizumab, inhibit VEGF-mediated signalling and suppress neovascularisation. Reduced vascular supply may

impair oxygen and nutrient delivery to healing tissues, delay bone regeneration and increase susceptibility to secondary infection [9, 10, 11, 12].

Current evidence indicates that MRONJ results from the interaction of several biological mechanisms. Suppression of bone turnover reduces the capacity of bone to repair microdamage, while impaired angiogenesis compromises tissue vascularisation. At the same time, local infection and inflammation further disrupt tissue homeostasis. The jawbones appear particularly susceptible because of their high physiological turnover, continuous exposure to the oral microbiota and frequent dentoalveolar interventions. Together, these factors may create conditions that favour the development and persistence of necrotic bone lesions [19]. *Figure 2.* illustrates the distinct mechanisms of action of BPs and denosumab in the inhibition of osteoclast activity [19].

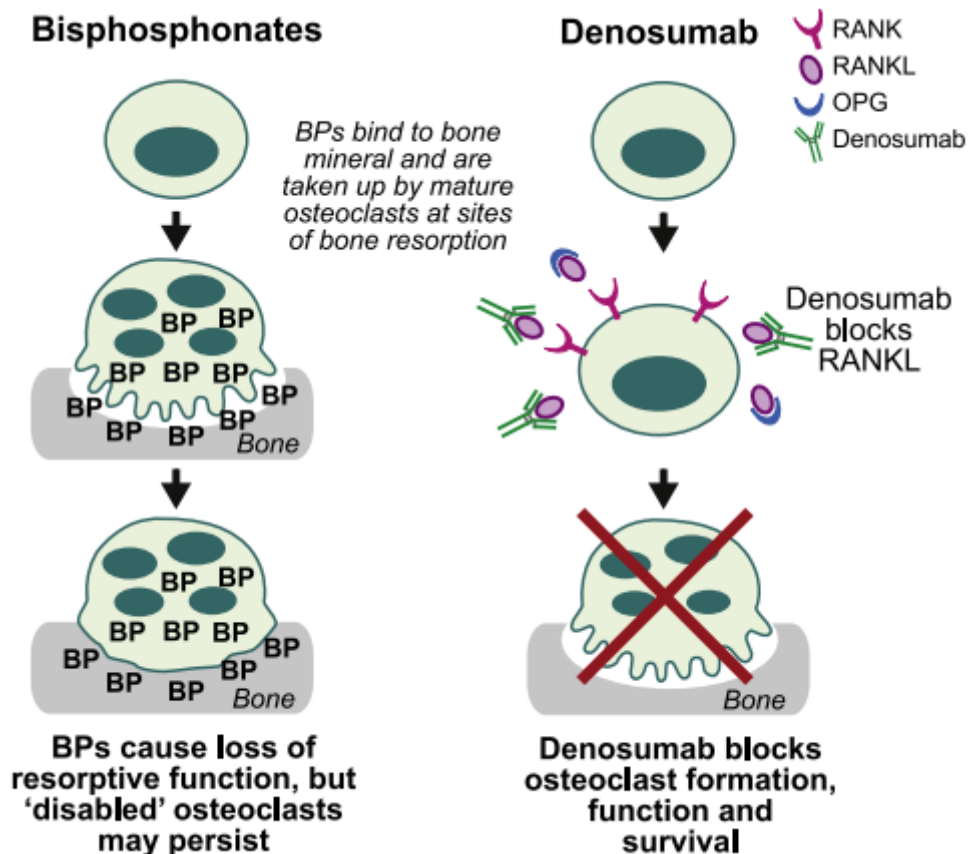


Figure 2. Mechanisms of action of BPs and denosumab in the inhibition of osteoclast activity. BPs act intracellularly after uptake by osteoclasts, whereas denosumab acts extracellularly by blocking the RANK–RANKL pathway [19].

1.2.3. Nomenclature Evolution: ONJ, BRONJ, ARONJ and MRONJ

The terminology used to describe osteonecrosis of the jaw has changed over time as knowledge of the disease has expanded. In 2003, *Marx* reported the first cases of persistent, non-healing jawbone exposure in patients receiving intravenous nitrogen-containing BPs and referred to the condition as osteonecrosis of the jaw (ONJ) [4]. In 2004, *Ruggiero* and colleagues linked the disease to BP therapy and introduced the term bisphosphonate-related osteonecrosis of the jaw (BRONJ), which was widely adopted in the literature [22]. Following reports that subcutaneous denosumab injection could also cause jaw osteonecrosis, the term antiresorptive agent-related osteonecrosis of the jaw (ARONJ) was proposed to include cases associated with both BPs and subcutaneous denosumab injection [23, 24]. As additional evidence emerged showing that antiangiogenic agents may also contribute to disease development, the American Association of Oral and Maxillofacial Surgeons (AAOMS) introduced the term medication-related osteonecrosis of the jaw (MRONJ) in its 2014 position paper. This terminology was retained in the updated AAOMS recommendations published in 2022 and is currently the accepted designation for the condition [2, 25, 26].

1.2.4. Staging and Therapeutic Approaches in MRONJ

1.2.4.1. AAOMS Staging System of MRONJ

The staging of MRONJ in this dissertation was based on the 2022 AAOMS position paper. The classification includes five categories. The ‘at risk’ category comprises patients receiving antiresorptive therapy without clinical evidence of MRONJ. Stage 0 is characterised by the absence of exposed bone but the presence of nonspecific symptoms or clinical and radiographic findings. Stage 1 is defined by exposed necrotic bone or an intraoral fistula probing to bone without signs of infection. Stage 2 includes exposed necrotic bone or fistula accompanied by pain, erythema and evidence of local infection. Stage 3 represents advanced disease and includes stage 2 findings together with complications such as pathologic fracture, extraoral fistula, oroantral or oronasal communication or extensive bone involvement extending beyond the alveolar process (*Table 1.*) [26].

Table 1. Clinical characteristics of MRONJ according to the AAOMS 2022 staging system [26].

Stage	Clinical characteristics (AAOMS 2022)
At risk (No MRONJ)	History of antiresorptive or antiangiogenic therapy but no clinical evidence of necrotic bone.
Stage 0 (Early/Prodromal)	No clinical evidence of necrotic bone, but non-specific clinical findings, symptoms, and radiographic changes may be present.
Stage 1 (Mild)	Exposed necrotic bone or intraoral fistula probing to bone in the absence of infection.
Stage 2 (Moderate)	Exposed necrotic bone or fistula associated with infection and symptomatic disease. • Pain, erythema, swelling, and/or purulent drainage may be present.
Stage 3 (Severe)	All Stage 2 features plus one or more of the following: • Pathologic fracture • Extraoral fistula • Oroantral/oronasal communication • Osteolysis extending beyond the region of alveolar bone (e.g., inferior border of the mandible, maxillary sinus, zygomatic arch).

Because the clinical presentation of MRONJ may resemble other maxillofacial conditions, including alveolar osteitis, chronic osteomyelitis, sinusitis, fibro-osseous lesions and malignant diseases, accurate diagnosis requires careful clinical evaluation supported by appropriate imaging studies [26].

Table 2. Recommended management strategies for MRONJ according to disease stage based on the AAOMS 2022 position paper [26].

Stage	Recommended management (AAOMS 2022)
At risk (No MRONJ)	Preventive dental care, patient education, optimization of oral hygiene, and regular follow-up during antiresorptive or antiangiogenic therapy.
Stage 0 (Early/Prodromal)	Symptomatic treatment, management of local contributing factors, and close clinical and radiographic monitoring.
Stage 1 (Mild)	Antibacterial mouth rinse and regular clinical follow-up. Surgical treatment is generally not indicated.
Stage 2 (Moderate)	Antibacterial mouth rinse, systemic antibiotic therapy, pain control, and limited debridement if required for symptom relief.
Stage 3 (Severe)	Surgical management of necrotic bone combined with antimicrobial therapy, pain control, and multidisciplinary care.

1.2.4.2. Initial Evaluation and Treatment Planning

Figure 4. illustrates the clinical workflow used for the evaluation and management of patients with MRONJ. Assessment begins with a detailed medical history, clinical examination and radiographic evaluation using panoramic imaging and, when necessary, Computed Tomography (CT), Cone Beam Computed Tomography (CBCT), Magnetic Resonance Imaging (MRI) or Positron Emission Tomography/Computed Tomography (PET/CT). Based on these findings, the disease is staged and initial conservative treatment is initiated, including antimicrobial mouth rinses, systemic antibiotics and sequestrectomy when indicated. Follow-up clinical and radiographic assessment allows disease restaging and evaluation of treatment response. If progression is observed or symptoms persist, the patient's suitability for surgical treatment is considered, taking into account systemic health, comorbidities and factors that may affect healing. The final treatment decision is made jointly by the patient and the multidisciplinary care team, with

the choice between continued conservative management and surgical intervention based on individual clinical circumstances [26].

1.2.4.3. Non-Operative Management of MRONJ

The workflow summarises the recommended non-operative management of MRONJ according to disease stage. Conservative treatment in all stages includes local wound care, antimicrobial mouth rinses (chlorhexidine) and removal of loose sequestra when indicated. In Stage 1, management focuses primarily on local measures and regular follow-up. Patients with stable disease continue conservative treatment, whereas progression requires restaging. In Stage 2, local therapy is combined with systemic antibiotics and pain control. Patients showing improvement or stable disease remain on non-operative treatment, while progression necessitates further evaluation. Stage 3 management includes local wound care, antimicrobial rinses, sequestrectomy when appropriate, systemic antibiotic therapy and pain management. Patients with stable disease may continue conservative treatment, whereas those with advanced lesions or unfavourable systemic conditions may be considered for surgical intervention. The overall aim of this stage-based approach is to control infection, relieve symptoms and limit disease progression while avoiding unnecessary surgical procedures [26].

1.2.4.4. Surgical Management of MRONJ

Surgical management of maxillary MRONJ is determined by the extent of necrosis and its relationship to the maxillary sinus. In Stage 1 disease, where necrotic bone remains confined below the sinus floor, treatment usually consists of localised alveolectomy and debridement. Stage 2 lesions extending to the sinus floor generally require systemic antibiotic therapy followed by partial infrastructure maxillectomy to remove necrotic bone and affected sinus tissues. In Stage 3 disease, characterized by extensive bone involvement, oroantral communication or extension towards the zygomatic buttress, systemic antibiotics and partial infrastructure maxillectomy are typically required. Regular postoperative clinical and radiographic follow-up is essential to monitor healing and detect recurrence or disease progression [26]. The surgical management of mandibular MRONJ also depends on disease stage and anatomical extent. Stage 1 lesions are generally treated with localized alveolectomy and debridement. In Stage 2 disease, systemic antibiotic therapy is combined with more extensive debridement or marginal

resection to remove necrotic bone while preserving mandibular continuity. Stage 3 MRONJ, associated with pathologic fracture, extraoral fistula or extensive bone destruction, often requires segmental resection, with or without immediate reconstruction. Postoperative monitoring remains an important component of treatment in all stages [26]. Despite advances in diagnosis and management, MRONJ continues to represent a significant clinical challenge, partly because no universally accepted treatment protocol exists. Current therapeutic approaches primarily aim to control pain, manage secondary infection and promote healing of the affected bone and surrounding soft tissues [26].

Antibiotic therapy – Systemic antibiotics are commonly prescribed to manage secondary bacterial infection associated with MRONJ. Penicillin-based regimens, clindamycin and metronidazole are among the most frequently used agents, with the choice of antibiotic and treatment duration depending on the severity of infection, patient comorbidities and local treatment protocols [26].

Pain control – Pain control is an important component of MRONJ management and is typically achieved with analgesic therapy tailored to symptom severity and individual patient needs [26].

Chlorhexidine rinses – Chlorhexidine mouth rinses are commonly used to reduce the oral bacterial load and support local infection control in patients with MRONJ [26].

Local debridement – Local debridement involves the removal of superficial necrotic bone and loose sequestra to reduce local irritation and facilitate soft-tissue healing [26].

Sequestrectomy – Sequestrectomy involves the removal of necrotic bone fragments and loose sequestra to promote healing and reduce the burden of necrotic tissue. The procedure may be performed under local or general anaesthesia, depending on the extent of the lesion and the patient's clinical condition [26].

Segmental resection – Segmental resection is reserved for advanced cases of MRONJ with extensive bone involvement. The procedure involves removal of the affected mandibular segment and may be followed by immediate or delayed reconstruction, depending on the extent of the defect and the patient's overall condition [26].

Adjunctive hyperbaric oxygen (HBO) therapy – Adjunctive HBO therapy involves the administration of 100% oxygen under increased atmospheric pressure and has been

investigated as a supportive treatment for MRONJ. Although some studies have reported beneficial effects on wound healing, the available evidence remains limited and its routine use is not currently recommended [26].

1.2.4.5. Prevention and Multidisciplinary Care

Comprehensive dental care – Comprehensive dental care, including regular dental examinations and maintenance of good oral hygiene, plays an important role in reducing the risk of MRONJ in patients receiving antiresorptive or antiangiogenic therapy. Regular professional oral hygiene care, including periodontal maintenance and dental scaling provided by a trained dental hygienist or dentist, is strongly recommended. In addition, individualized oral hygiene education, patient instruction, and continuous motivation are essential to promote long-term oral health and to minimize the risk of MRONJ-related complications [26].

Avoidance of dentoalveolar surgery – Prevention of MRONJ includes maintaining oral health and preserving teeth whenever possible, thereby reducing the need for dentoalveolar surgical procedures in patients receiving antiresorptive or antiangiogenic therapy [26].

Drug holidays – Drug holidays have been proposed as a strategy to reduce the risk of MRONJ; however, their effectiveness remains uncertain. Decisions regarding temporary interruption of antiresorptive therapy should be made on an individual basis in consultation with the treating physician and with careful consideration of the underlying disease and associated risks [26].

Particular attention should be paid to oral surgical procedures in patients receiving antiresorptive or antiangiogenic therapy. Whenever possible, a comprehensive dental examination and elimination of potential sources of oral infection should be completed before treatment is initiated. Teeth with a poor prognosis should be extracted before therapy, allowing adequate time for soft-tissue and bone healing. If dentoalveolar surgery is required during treatment, atraumatic surgical techniques, smoothing of sharp bony edges and primary wound closure should be performed whenever feasible. Postoperative management may include chlorhexidine mouth rinses, appropriate antibiotic therapy and regular follow-up examinations to monitor healing and facilitate early detection of

MRONJ. These measures represent an important part of current MRONJ prevention strategies (*Table 2.*) [26].

Management of MRONJ requires close collaboration between oral and maxillofacial surgeons, dentists, oncologists and endocrinologists. Treatment should be tailored to the stage of disease and the individual patient's clinical condition. Conservative management is generally considered the initial approach, whereas surgical treatment is reserved for selected advanced or refractory cases. Prevention remains a key aspect of patient care and should be incorporated into the management of all individuals at risk of developing MRONJ [26]. *Figure 3.* Representative clinical presentation of MRONJ from the institution where the study was conducted. The intraoral photograph shows exposed necrotic bone associated with a persistent non-healing mucosal defect (arrow).



Figure 3. Intraoral photograph showing a non-healing wound with exposed necrotic bone (arrow) on the left side of the maxilla, characteristic of MRONJ. Image from the research group's own clinical documentation.

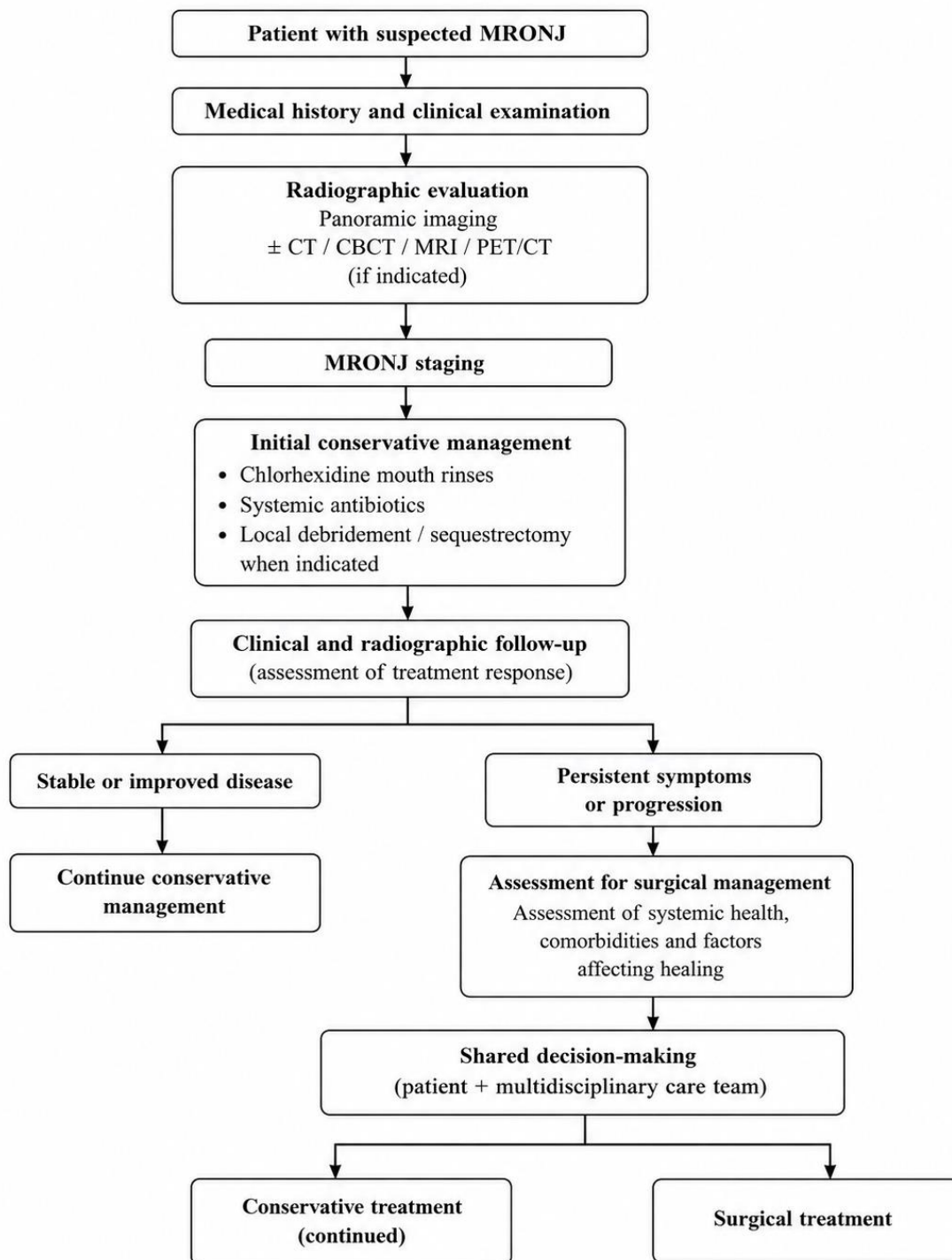


Figure 4. Clinical workflow for the evaluation and management of patients with MRONJ according to the AAOMS 2022 recommendations [26].

1.2.5. Risk Factors for the Development of MRONJ

Knowledge of the risk factors associated with MRONJ is essential for prevention, early diagnosis and appropriate patient management. Identification of high-risk individuals allows preventive measures to be implemented before invasive dental procedures are performed and may reduce the likelihood of disease development. Both systemic and local factors contribute to the pathogenesis of MRONJ. Systemic factors include underlying diseases, concomitant medications and metabolic conditions, whereas local factors are primarily related to oral health status and dentoalveolar interventions. Recognition and management of modifiable risk factors, such as oral infection, poor oral hygiene and uncontrolled systemic disease, may help reduce the risk of MRONJ. Effective prevention requires close collaboration between dental professionals, physicians and patients throughout the course of antiresorptive or antiangiogenic therapy. Patient education and regular dental follow-up also play an important role in maintaining oral health and facilitating early detection of disease [26–29]. One of the most comprehensive recent summaries of MRONJ risk factors was published in the 2023 position paper jointly issued by the Italian Society of Oral Pathology and Medicine (SIPMO) and the Italian Society of Maxillofacial Surgery (SICMF) [30].

1.2.5.1. Drug-related factors

The risk of MRONJ is influenced by the type, potency and duration of antiresorptive or antiangiogenic therapy. Intravenous BPs and subcutaneous denosumab injection are associated with a higher risk than oral antiresorptive agents. The likelihood of MRONJ increases with longer treatment duration and cumulative drug exposure. Nitrogen-containing BPs, particularly zoledronic acid, have been linked to a greater risk of disease development. Concomitant treatment with antiangiogenic agents, such as bevacizumab or sunitinib, may further increase susceptibility. The potential benefit of temporary interruption of antiresorptive therapy remains uncertain and should be considered on an individual basis [30].

1.2.5.2. Systemic (patient-related) factors

Several patient-related factors may influence the risk of MRONJ. Advanced age and female sex have been associated with a higher incidence of the disease, partly

reflecting the population receiving antiresorptive therapy for osteoporosis. Comorbidities such as DM, anaemia, renal impairment, rheumatoid arthritis and immunosuppressive conditions may further increase susceptibility. The risk may also be affected by concomitant medications, including corticosteroids, chemotherapy, hormonal therapies and antiangiogenic agents. In addition, smoking, excessive alcohol consumption, poor nutritional status and vitamin D deficiency have all been identified as potential contributing factors [30].

1.2.5.3. Local (oral and dental) factors

Local oral factors play an important role in the development of MRONJ. Dentoalveolar procedures, particularly tooth extractions, implant placement, apicoectomy and periodontal surgery, are recognised risk factors. Pre-existing oral infections, including periodontitis, periapical pathology and peri-implantitis, may further increase the likelihood of disease development. Chronic mucosal trauma caused by ill-fitting dentures has also been associated with MRONJ. The mandible is affected more frequently than the maxilla, possibly because of differences in vascular supply. In addition, poor oral hygiene may contribute to disease development by promoting local inflammation and bacterial colonisation [30].

1.2.5.4. Other contributing factors

Patients receiving high-dose intravenous antiresorptive therapy for oncologic indications are at the greatest risk of developing MRONJ. Previous radiotherapy of the head and neck region may further compromise bone healing and increase the risk of osteonecrosis. In addition, genetic factors have been proposed to influence individual susceptibility. Polymorphisms affecting receptor activator of RANK, receptor activator of RANKL and OPG signaling pathways have been investigated, although their precise role in MRONJ development remains unclear [30].

Figure 5. Clinical presentation of MRONJ in the anterior mandible. The intraoral photograph shows a persistent non-healing wound, while CBCT images demonstrate sequestrum formation and associated bone destruction.

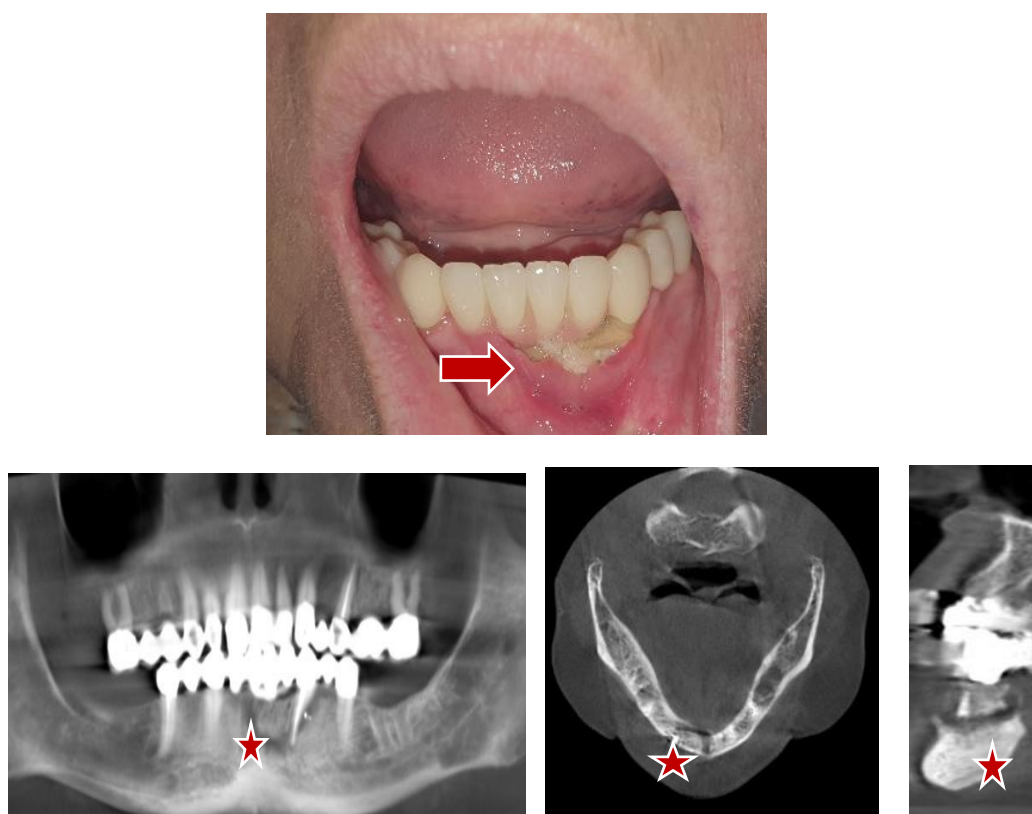


Figure 5. Clinical and radiographic presentation of MRONJ in the anterior mandible. The intraoral photograph demonstrates a non-healing lesion (arrow), while the CBCT images reveal the associated sequestrum (asterisk) and surrounding bone destruction. Images from the research group’s own clinical documentation.

1.2.6. Epidemiology of MRONJ

The incidence of MRONJ varies according to the underlying disease, type of medication, route of administration and duration of treatment. According to the AAOMS 2022 position paper, the risk of MRONJ in patients receiving oral BPs for osteoporosis ranges from 0.02% to 0.05%, whereas the reported risk associated with subcutaneous denosumab injection is 0.04%–0.3%. In contrast, patients receiving high-dose antiresorptive therapy for oncologic indications may have an MRONJ incidence of up to 1%–10% [26]. Similar findings have been reported in population-based studies. A Swedish prospective study found an MRONJ incidence of approximately 0.04% among patients treated with oral BPs for osteoporosis, compared with about 1% in patients

receiving intravenous BPs for cancer-related bone disease [31]. A large Japanese population-based study reported an incidence of 1.47% among cancer patients treated with intravenous antiresorptive agents and 0.09% among patients treated for osteoporosis. Longer treatment duration, intravenous administration and concomitant corticosteroid therapy were identified as important risk factors [32]. Likewise, another Japanese cohort study reported an MRONJ incidence of 0.21% in oral BP users and 1.6% in patients receiving intravenous BPs following tooth extraction, with the highest risk observed in cancer patients undergoing prolonged high-dose treatment [33].

1.3. Overview of Hyperglycaemia

1.3.1. Definition and Pathophysiology of Diabetes Mellitus

DM is a group of metabolic disorders characterized by chronic hyperglycaemia resulting from impaired insulin secretion, impaired insulin action or both. Persistent hyperglycaemia is associated with long-term damage to multiple organ systems, particularly the eyes, kidneys, nerves, heart and blood vessels. The underlying mechanisms include autoimmune destruction of pancreatic β -cells leading to absolute insulin deficiency, as well as peripheral insulin resistance. In most patients, impaired insulin secretion and reduced tissue responsiveness occur simultaneously and contribute to disturbances in carbohydrate, lipid and protein metabolism [34].

Chronic hyperglycaemia promotes the development of microvascular and macrovascular complications through endothelial dysfunction, oxidative stress and persistent low-grade inflammation. Several interconnected biochemical pathways have been implicated, including increased polyol pathway activity, accumulation of advanced glycation end products (AGEs), activation of protein kinase C (PKC) and increased flux through the hexosamine pathway. Excess intracellular glucose enhances oxidative stress, alters cellular signalling and promotes inflammatory and profibrotic responses. Brownlee proposed that these mechanisms are linked by mitochondrial overproduction of reactive oxygen species, which represents a central event in the development of diabetic complications [35].

Sustained hyperglycaemia damages small blood vessels, resulting in diabetic retinopathy, nephropathy and neuropathy. At the same time, large-vessel disease

contributes to atherosclerosis, coronary artery disease, cerebrovascular disease and peripheral arterial disease [36–38].

1.3.2. Epidemiology of Diabetes: Current Status and Future Trends

DM worldwide in 2021, corresponding to a prevalence of 10.5%.nem értelmes mondat This number is projected to rise to 643 million by 2030 and 783 million by 2045, with T2DM accounting for most cases. The largest numbers of affected individuals are found in the Western Pacific, South-East Asia and Europe, while the greatest relative increase is expected in Africa. China, India, Pakistan and the United States accounted for the highest numbers of people living with DM in 2021 [39].

In Hungary, the prevalence of T2DM has increased substantially over recent decades. Analysis of data from the National Health Insurance Fund demonstrated that the number of diagnosed patients nearly doubled between 2001 and 2014, increasing from approximately 400,000 to almost 800,000 individuals. The burden was greatest among older adults, although a rising incidence was also observed in younger age groups. In parallel, healthcare expenditures related to DM increased considerably, reflecting the growing clinical and economic impact of the disease in Hungary [40].

1.3.3. Classification of Diabetes

Disorders of glucose metabolism encompass a spectrum ranging from normal glucose regulation through prediabetes to overt DM. Prediabetes includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), both of which are associated with an increased risk of progression to type 2 diabetes mellitus (T2DM) [41, 42]. DM comprises several distinct clinical entities. Type 1 diabetes mellitus (T1DM) is characterized by autoimmune destruction of pancreatic β -cells, resulting in absolute insulin deficiency and accounting for approximately 5–10% of diabetes cases. In contrast, T2DM, which represents approximately 90–95% of diagnosed cases, is primarily associated with insulin resistance and progressive β -cell dysfunction [43]. Gestational diabetes mellitus (GDM) refers to hyperglycaemia first recognized during pregnancy and is associated with an increased risk of future metabolic disorders, particularly T2DM. Secondary DM may develop as a consequence of several underlying diseases and medical conditions. Pancreatic disorders, including chronic pancreatitis, pancreatic tumors, cystic

fibrosis and hemochromatosis, can impair insulin production and lead to disturbances in glucose metabolism. Endocrine diseases such as Cushing's syndrome, acromegaly, hyperthyroidism and pheochromocytoma may also result in hyperglycaemia. In addition, certain medications, most notably glucocorticoids, may contribute to the development of secondary DM [44]. The classification of diabetes reflects the heterogeneity of disorders leading to chronic hyperglycaemia. Individuals may progress, regress or remain stable over time depending on the underlying pathophysiology and effectiveness of treatment (Table 3.) [41–44].

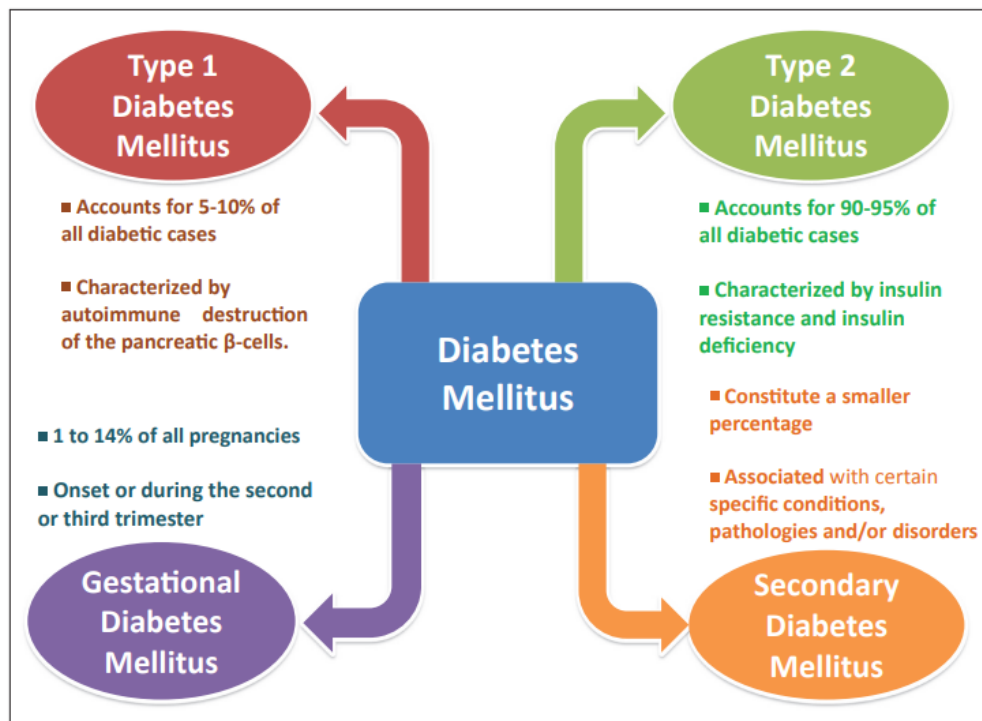


Figure 6. The figure summarizes the major categories of DM and their characteristic features, including T1DM, T2DM, GDM and secondary DM. The diagram illustrates the underlying pathophysiological mechanisms and relative prevalence of each subtype, highlighting the heterogeneity of disorders affecting glucose metabolism [44].

Table 3. Classification of DM and disorders of glucose metabolism, including their principal characteristics and clinical relevance [44].

Category	Main Characteristics	Prevalence / Clinical Relevance
Normal glucose regulation	Normal fasting and postprandial glucose levels	Physiological glucose homeostasis
Prediabetes (IFG and/or IGT)	Impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT); intermediate state between normoglycaemia and diabetes	Increased risk of progression to T2DM
Type 1 diabetes mellitus (T1DM)	Autoimmune destruction of pancreatic β -cells resulting in absolute insulin deficiency	Approximately 5–10% of all diabetes cases
Type 2 diabetes mellitus (T2DM)	Insulin resistance combined with relative insulin deficiency and progressive metabolic dysregulation	Approximately 90–95% of diagnosed diabetes cases
Gestational diabetes mellitus (GDM)	Hyperglycaemia first recognized during pregnancy, usually during the second or third trimester	Approximately 1–14% of pregnancies; increased future risk of T2DM
Secondary diabetes mellitus	Diabetes caused by pancreatic diseases, endocrinopathies, genetic disorders or medications	Etiologically heterogeneous group

T1DM is an autoimmune disease characterized by destruction of pancreatic β -cells and accounts for approximately 5–10% of all DM cases. T2DM, which represents 90–95% of diagnosed cases, is characterized by insulin resistance combined with relative insulin deficiency. GDM develops during pregnancy, most commonly in the second or

third trimester and is associated with an increased risk of developing T2DM later in life. Secondary DM includes forms of diabetes resulting from underlying diseases, pathological conditions or medications that impair insulin secretion or insulin action (*Figure 6.*). Although the underlying mechanisms differ, all forms of DM ultimately lead to chronic hyperglycaemia and disturbances in glucose metabolism [44].

1.3.4. Diagnostic Criteria for Diabetes and Hyperglycaemia

The diagnosis of hyperglycaemia is based on standardized measurements of blood glucose and hemoglobin A1c (HbA1c), which provide complementary information on short- and long-term glucose regulation. Fasting plasma glucose (FPG), measured after at least eight hours of fasting, is considered impaired at levels of 100–125 mg/dL (5.6–6.9 mmol/L), whereas values ≥ 126 mg/dL (≥ 7.0 mmol/L) are diagnostic of DM. The oral glucose tolerance test (OGTT), performed using a 75 g glucose load, is considered normal when the 2-hour plasma glucose value is < 140 mg/dL (< 7.8 mmol/L), indicates IGT at 140–199 mg/dL (7.8–11.0 mmol/L) and confirms DM at ≥ 200 mg/dL (≥ 11.1 mmol/L). Random plasma glucose levels ≥ 200 mg/dL (≥ 11.1 mmol/L) may also establish the diagnosis in the presence of classic symptoms of hyperglycaemia [45,46]. HbA1c reflects average glycaemic exposure over the preceding two to three months and is widely used for both diagnosis and monitoring. Values below 5.7% are considered normal, levels between 5.7% and 6.4% indicate prediabetes and values $\geq 6.5\%$ are diagnostic of DM. In asymptomatic individuals, repeat testing is generally recommended to confirm the diagnosis [47–49]. FPG and HbA1c represent two of the most important laboratory parameters used to assess glucose metabolism. FPG reflects short-term glucose homeostasis, whereas HbA1c provides information on long-term glycaemic control. Compared with FPG, HbA1c is less influenced by recent food intake, acute illness or short-term metabolic fluctuations, resulting in greater analytical stability and lower intra-individual variability. However, its accuracy may be affected by conditions that alter red blood cell turnover, such as anaemia or haemoglobinopathies. Although FPG is simple, inexpensive and widely available, it reflects glucose metabolism at a single time point and may fail to detect intermittent or postprandial hyperglycaemia. Consequently, the

combined use of FPG and HbA1c provides a more comprehensive assessment of glucose regulation than either parameter alone [50].

1.3.5. Oral Complications of Diabetes Mellitus

DM is associated with a range of oral manifestations, among which its relationship with periodontitis is particularly important. Chronic hyperglycaemia promotes the production of inflammatory mediators, impairs immune function and enhances the accumulation of AGEs, all of which contribute to periodontal tissue destruction. As a result, individuals with DM are more likely to develop periodontitis and often experience more severe disease progression. Conversely, periodontal inflammation may adversely affect glycaemic control by increasing systemic inflammatory burden and reducing insulin sensitivity. Several studies have shown that periodontal therapy can result in modest but clinically relevant improvements in HbA1c levels, highlighting the bidirectional relationship between these conditions [51]. DM also influences the local inflammatory response within periodontal tissues. Elevated concentrations of tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and bacterial lipopolysaccharide (LPS) have been detected in the gingival crevicular fluid of patients with DM and periodontitis. This enhanced inflammatory environment is associated with greater alveolar bone loss and accelerated periodontal destruction, providing a biological explanation for the increased severity of periodontal disease observed in patients with hyperglycaemia [52]. Epidemiological studies further support DM as an independent risk factor for periodontitis, demonstrating higher disease incidence and more rapid progression in individuals with poor glycaemic control. Increasing HbA1c levels have consistently been associated with greater periodontal susceptibility [53]. Beyond periodontal disease, DM is linked to a variety of other oral manifestations. Altered immune function, microvascular changes and salivary gland dysfunction contribute to an increased risk of oral infections, particularly candidiasis, as well as xerostomia, dental caries and gingivitis. Neuropathic symptoms such as burning mouth syndrome, glossodynia and other sensory disturbances may occur as manifestations of diabetic neuropathy. Oral mucosal disorders, including lichen planus, have also been reported more frequently in individuals with DM. Reduced salivary flow and taste disturbances may further impair oral function and quality of life.

In some cases, these oral findings may represent the first clinical signs of previously undiagnosed DM, emphasizing the importance of dental professionals in the early recognition of the disease [54]. Children with T1DM may exhibit oral health differences that are closely related to the quality of glycaemic control. Poor metabolic control has been associated with increased caries experience, reduced salivary flow and less favourable salivary characteristics. Although periodontal parameters do not differ substantially between diabetic and non-diabetic children, higher plaque accumulation has been observed in patients with inadequate glycaemic control. These findings highlight the importance of metabolic control in maintaining oral health and support the potential role of chairside HbA1c screening in dental practice [55]. Recent Hungarian studies have also examined the relationship between hyperglycaemia and oral cancer. Retrospective data demonstrated a higher prevalence of DM and IFG among patients with oral cancer compared with the general population. In addition, a prospective study using point-of-care HbA1c measurements found that oral cancer patients frequently presented with elevated long-term glycaemic levels. These findings suggest a possible association between disturbed glucose metabolism and oral malignancies and emphasize the importance of metabolic screening in this patient population [56,57]. Metformin has also attracted interest in periodontal therapy. A systematic review and meta-analysis reported that locally administered 1% metformin gel improved clinical attachment levels and reduced probing pocket depth when used as an adjunct to conventional non-surgical periodontal treatment. Additional benefits included reduced gingival inflammation and favourable effects on periodontal regeneration. The available studies reported a favourable safety profile, supporting the potential role of local metformin therapy as an adjunctive treatment in periodontitis [58]. Assessment of HbA1c and blood glucose levels before oral surgical procedures may help identify patients at increased risk of complications. Poor glycaemic control has been associated with delayed wound healing, higher rates of postoperative infection and less predictable treatment outcomes. Chairside HbA1c testing provides a practical method for evaluating metabolic status before oral surgery and implant treatment [59]. DM may increase susceptibility to MRONJ through several pathophysiological mechanisms, including impaired bone remodelling, reduced angiogenesis and microvascular dysfunction (*Figure 7.*). Chronic hyperglycaemia promotes the accumulation of AGEs, which impair osteoblast function and disrupt normal

bone turnover. In addition, altered immune responses and neutrophil dysfunction may increase the risk of infection and delay wound healing. DM may also enhance the skeletal effects of antiresorptive medications, further contributing to the development of MRONJ. Clinical studies have suggested that MRONJ occurs more frequently and may present with greater severity in patients with DM [60].

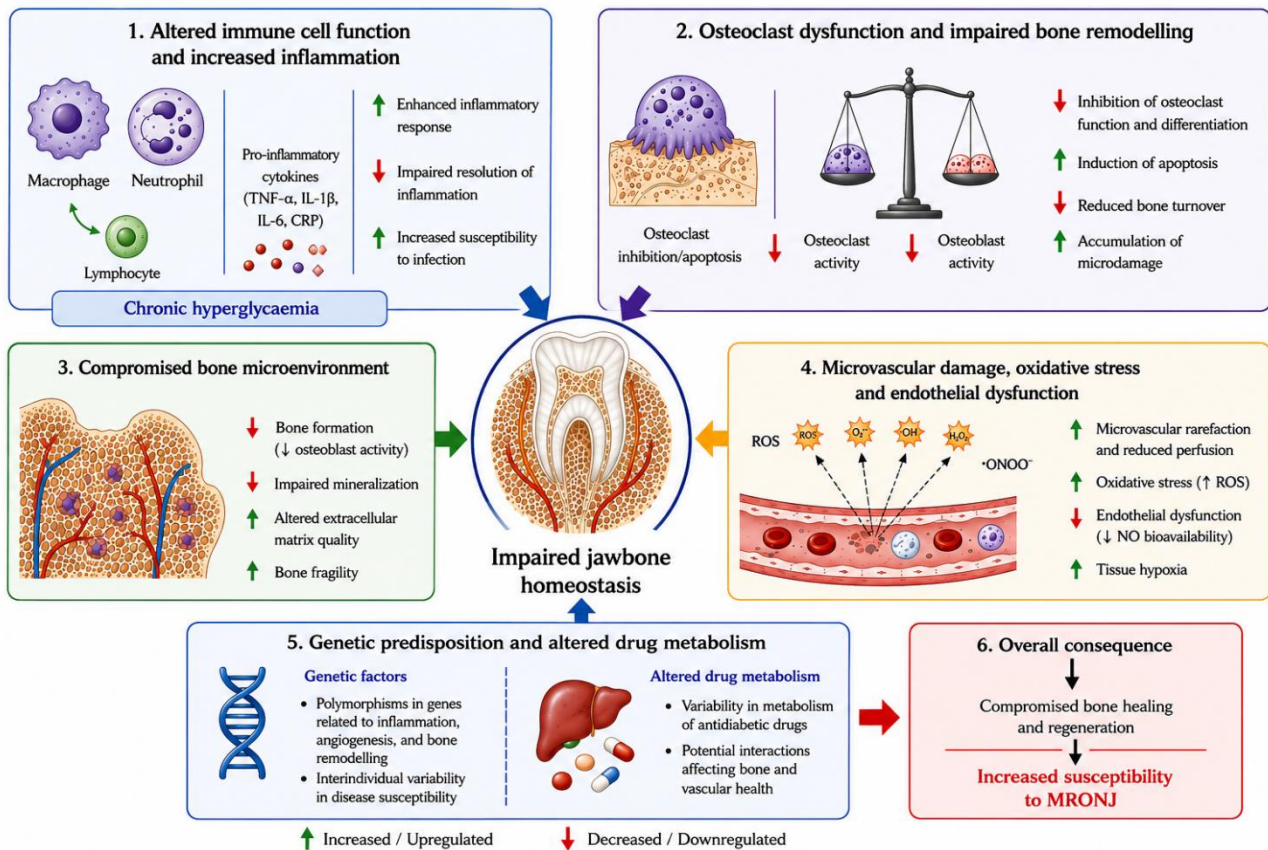


Figure 7. Proposed mechanisms linking hyperglycaemia to impaired jawbone homeostasis and increased susceptibility to MRONJ. Chronic hyperglycaemia contributes to immune dysregulation, persistent inflammation, impaired bone remodelling, microvascular damage, oxidative stress and endothelial dysfunction, collectively compromising bone healing and tissue repair [60].

In summary, DM has a substantial impact on oral health and is associated with an increased risk of inflammatory, infectious and wound-healing complications. Chronic hyperglycaemia promotes inflammation, impairs immune function and increases susceptibility to oral infections. Periodontitis is more common and often more severe in

individuals with DM, while periodontal inflammation may further compromise glycaemic control, reinforcing the bidirectional relationship between these conditions. Impaired wound healing, reduced salivary flow and an increased prevalence of oral infections contribute to poorer oral health outcomes. Hyperglycaemia-related changes in bone metabolism, microvascular function and tissue repair may also increase the risk of peri-implant disease and MRONJ. Collectively, these findings highlight the close relationship between metabolic control and oral health and emphasize the importance of interdisciplinary collaboration in the management of patients with DM.

2. Objectives

The primary objective of this research was to investigate the role of hyperglycaemia in the development of MRONJ. Particular attention was given to determining whether elevated blood glucose levels and impaired glycaemic control are associated with an increased risk of disease onset and recurrence. Given the rising prevalence of hyperglycaemia and the widespread use of antiresorptive therapies, identification of metabolic risk factors may contribute to improved prevention, risk assessment and clinical management of patients at risk of MRONJ. Furthermore, the findings of this dissertation may support the future implementation of blood glucose screening as part of the routine evaluation of patients receiving antiresorptive treatment.

The specific aims of the study were:

- To determine the prevalence of hyperglycaemia among patients with MRONJ.
- To evaluate whether hyperglycaemia and DM are associated with an increased risk of MRONJ development and recurrence.
- To analyse the distribution of MRONJ lesions according to glycaemic status, with particular emphasis on mandibular and maxillary involvement.
- To assess the underlying diseases for which antiresorptive or antiangiogenic therapy was prescribed.
- To investigate the influence of drug type (BPs, subcutaneous denosumab injection and antiangiogenic agents), route of administration and treatment duration on the development of MRONJ.
- To investigate the association between MRONJ and lifestyle-related risk factors, particularly smoking and alcohol consumption.
- To compare the clinical characteristics of patients with MRONJ treated before and after the Coronavirus Disease 2019 (COVID-19) pandemic, including blood glucose levels, length of hospital stay, lesion localization and underlying diseases.
- To identify potential strategies for the prevention and management of MRONJ in patients with impaired glucose metabolism.

Null hypothesis (H_0): Hyperglycaemia does not influence the risk of MRONJ development or recurrence and no association can be demonstrated between the occurrence of MRONJ and the investigated clinical factors.

Alternative hypothesis (H_1): Hyperglycaemia contributes to an increased risk of MRONJ development and recurrence and the occurrence of MRONJ is associated with selected clinical and treatment-related factors.

3. Methods

3.1. Study design and setting

This dissertation is based on four retrospective case–control studies conducted at the Department of Oro-Maxillofacial Surgery and Stomatology, Semmelweis University, Budapest, Hungary. The department serves as a major national referral centre for the management of maxillofacial trauma, tumours, MRONJ and orthognathic conditions. Patients included in the analyses were admitted either for the diagnosis and treatment of MRONJ or for other oral and maxillofacial conditions, including facial trauma, impacted third molar surgery and benign tumour or cyst removal. Depending on the clinical presentation, patients with MRONJ received conservative treatment, surgical treatment or a combination of both. The diagnosis of MRONJ was established according to the criteria defined by the AAOMS [26].

Diagnosis of MRONJ required fulfillment of all of the following criteria:

- Presence of exposed necrotic bone or an intraoral or extraoral fistula probing to bone, persisting for more than 8 weeks
- Current or previous treatment with antiresorptive or antiangiogenic agents
- No history of radiotherapy involving the jaws or craniofacial region

The following exclusion criteria were applied:

- Age younger than 18 years
- Pregnancy
- Inability to comply with clinical examinations or treatment procedures
- Chronic immunodeficiency disorders (e.g., Acquired Immune Deficiency Syndrome [AIDS], systemic lupus erythematosus, rheumatoid arthritis or myasthenia gravis)
- Ongoing systemic corticosteroid therapy
- Previous radiotherapy of the head and neck region
- Active substance abuse

3.2. Data collection

The following demographic, clinical and treatment-related variables were collected for all patients included in the study:

Demographic data: Age and sex were recorded from the patients' medical records. Sex was documented as male or female according to the information available in the clinical documentation.

Lifestyle habits: Information on smoking status and alcohol consumption was obtained from the medical records and patient interviews.

Glycaemic status: FPG values were collected retrospectively from the patients' medical records. Measurements were performed before hospital admission as part of routine preoperative or outpatient assessment according to standard clinical practice. Blood samples were obtained after an overnight fast and fasting status was confirmed verbally by healthcare personnel at the time of sampling. The laboratory results were subsequently recorded in the electronic medical record system and reviewed by the treating clinicians.

Classification of glucose status followed World Health Organization (WHO) 2006 criteria:

- Normoglycaemia: <6.1 mmol/L
- IFG: 6.1–6.9 mmol/L
- DM: ≥ 7.0 mmol/L

Underlying systemic disease: The primary medical condition for which antiresorptive or antiangiogenic therapy had been prescribed was recorded from the medical documentation. These conditions, including osteoporosis, breast cancer, prostate cancer, renal carcinoma and multiple myeloma, represented the original indication for treatment before the development of MRONJ.

Medication-related variables: The type of antiresorptive or antiangiogenic agent, route of administration (oral, intravenous or subcutaneous) and total duration of treatment were recorded. Among patients receiving subcutaneous denosumab injection, both osteoporosis-related treatment (Prolia®) and oncological treatment (Xgeva®) were documented and analysed separately. For medications administered at six-month intervals, such as subcutaneous denosumab injection (Prolia®), each administration was

considered equivalent to six months of treatment exposure, as treatment duration was expressed in months throughout the analysis.

MRONJ localisation: The anatomical location of MRONJ was recorded as mandibular, maxillary or involving both jaws.

COVID-19-related parameters: In the study evaluating the impact of the COVID-19 pandemic on MRONJ management, additional variables were collected to compare patients treated before and after the pandemic. These included FPG levels, lesion localisation, underlying diseases, length of hospital stay (days) and the use of platelet-rich fibrin (PRF) during surgical treatment.

3.3. Overview of the Four Previous Studies Conducted in Our Research

Study I.:

Between 1 June 2018 and 31 December 2020, the medical records of 349 hospitalized patients were retrospectively reviewed. Patients were divided into two groups: an MRONJ group and a control group consisting of patients admitted for other oral and maxillofacial conditions, including benign tumours, cysts and maxillofacial trauma. The MRONJ group comprised 77 patients, whereas 272 patients were included in the control group. The primary aim of the study was to investigate the association between hyperglycaemia and MRONJ. In addition, the localisation of MRONJ lesions, the underlying diseases requiring antiresorptive therapy and the antiresorptive medications associated with disease development were analysed [61].

Study II.:

Between 1 January 2019 and 31 December 2020, a total of 260 patients were retrospectively evaluated. The study population consisted of 60 patients diagnosed with MRONJ and 200 control patients admitted for other oral and maxillofacial conditions, including facial trauma, impacted third molar surgery and benign tumour or cyst removal. All eligible patients treated during the study period were included consecutively. The primary objective was to investigate the association between hyperglycaemia and the development of MRONJ. In addition, oral risk behaviours, including smoking and alcohol

consumption, were assessed. Demographic and clinical variables recorded included age, sex, glycaemic status, underlying disease, type and route of administration of antiresorptive therapy and lesion localisation [62].

Study III.:

This retrospective study was conducted to evaluate the impact of the COVID-19 pandemic on the management of patients with MRONJ. Patients treated at the Department of Oro-Maxillofacial Surgery and Stomatology, Semmelweis University, were divided into two groups according to the time of admission: a pre-COVID-19 group (16 March 2018–16 March 2020) and a post-COVID-19 group (1 June 2022–1 June 2024). The period between 16 March 2020 and 1 June 2022 corresponded to the COVID-19 pandemic and the associated restrictions in Hungary and was therefore excluded from the comparative analysis. A total of 217 patients with MRONJ were included, comprising 75 patients in the pre-COVID-19 group and 142 patients in the post-COVID-19 group. Clinical and demographic data were collected retrospectively from the medical records, including age, sex, length of hospital stay, FPG levels, lesion localisation, underlying diseases requiring antiresorptive therapy and the use of PRF during surgical treatment. The study aimed to compare patient characteristics and treatment-related parameters between the pre- and post-pandemic periods [63].

Study IV.:

This retrospective study included 60 patients with MRONJ who underwent surgical treatment between 1 January 2020 and 31 July 2023. The primary objective was to investigate the association between glycaemic status and MRONJ recurrence. Only patients treated surgically for MRONJ were eligible for inclusion. MRONJ recurrence was defined as the reappearance of necrotic bone lesions at the previously treated site following at least 6 months of clinically confirmed symptom-free healing. Clinical and demographic data, including age, sex, medical history and laboratory findings, were collected from the medical records. Information regarding the type, route of administration and duration of antiresorptive or antiangiogenic therapy was also recorded. For medications administered at intervals of 15–30 days, treatment duration was rounded to one month. For agents administered every six months, such as subcutaneous denosumab injection (Prolia®), six months were added for each completed dosing

interval when calculating cumulative drug exposure. Additional variables included lesion localisation, glycaemic status, MRONJ recurrence and the duration of antiresorptive therapy. Patients receiving subcutaneous denosumab injection were further classified according to treatment with Prolia® or Xgeva®, allowing separate evaluation of osteoporosis-related and oncological denosumab therapy. At the time of completion of this dissertation, the results of this study had not yet been published and the manuscript was under peer review.

3.4. Ethical considerations

The research was conducted in accordance with the principles of the Declaration of Helsinki (1964) and its subsequent amendments and was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE-RKEB 204/2018). Owing to the retrospective nature of the studies, the requirement for individual informed consent was waived. All data were anonymised prior to analysis and were stored securely with access restricted to members of the research team.

3.5. Statistical analysis

Data were analysed using GraphPad Prism version 8.4.2 (GraphPad Software, San Diego, CA, USA) and Microsoft Excel 2018. Descriptive statistics were used to summarise the data and included means, standard deviations, frequencies and percentages. Comparisons between groups were performed using appropriate parametric or non-parametric statistical tests, depending on the type and distribution of the variables. Associations between categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test, as appropriate. Statistical significance was defined as a two-sided p -value <0.05 .

4. Results

4.1. Results of Study I

In the MRONJ (case) group, 77 patients were included, consisting of 46 females (60.0%) and 31 males (40.0%), with a mean age of 68 years (range: 34–81). Among these, 20.8% (n=16) were diagnosed with IFG, while 22.1% (n=17) had DM. The control group comprised 272 patients, including 92 females (33.8%) and 180 males (66.2%), with a mean age of 50 years (range: 18–90). Within this group, 11.4% (n=31) presented with IFG and 9.1% (n=25) were diagnosed with DM. Overall, 42.8% of patients in the MRONJ group had an abnormal glucose metabolism, compared with only 20.5% in the control group. Statistical analysis revealed a significant association between hyperglycaemia and MRONJ: both the prevalence of DM ($p=0.00000026$) and the occurrence of IFG ($p=0.00645$) were significantly higher in the MRONJ group (*Figure 8.*) [61].

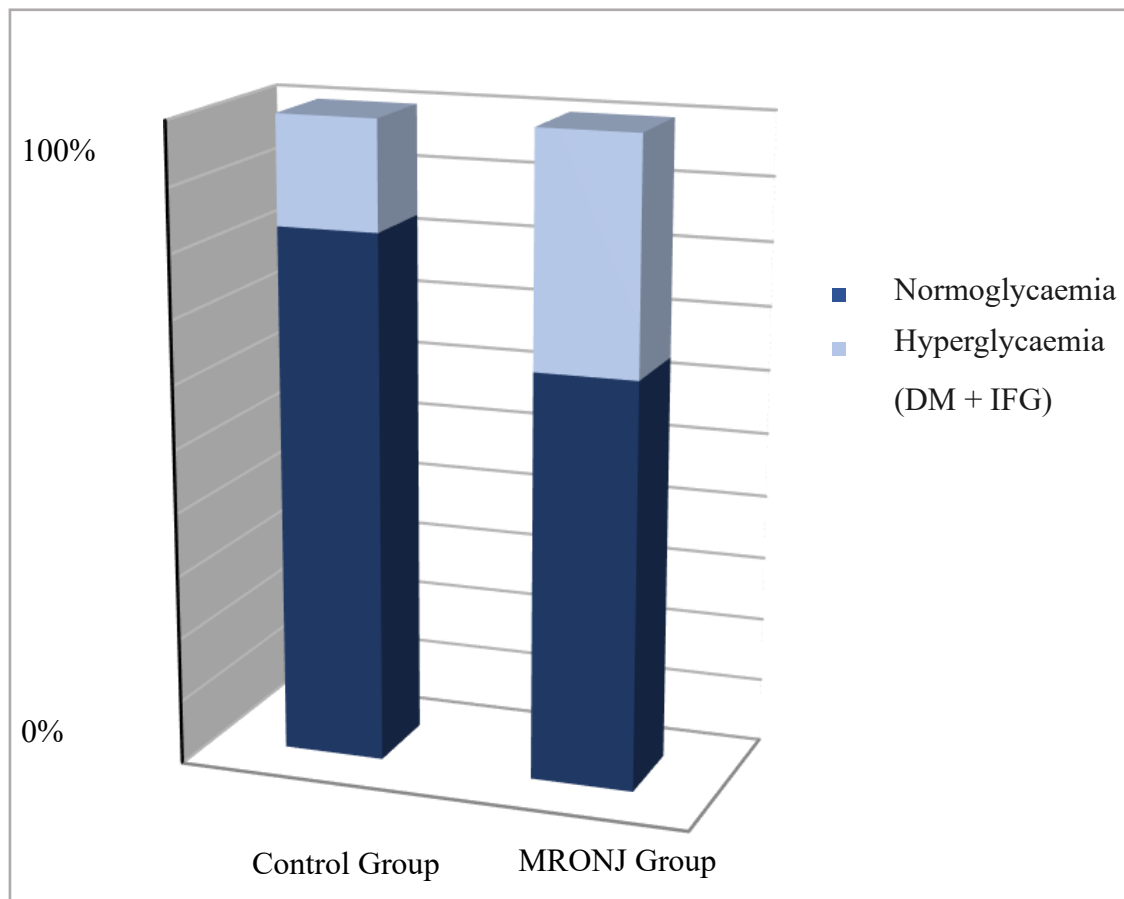


Figure 8. Distribution of normoglycaemia and dysglycaemia (DM + IFG) in the control and MRONJ groups. Dysglycaemia was more frequent among patients with MRONJ. DM

and IFG showed a significant association with MRONJ (DM: $p=0.00000026$; IFG: $p=0.00645$) (Frequency [%]) [61].

In the MRONJ group, irrespective of glycaemic status, more than two-thirds of the cases (71.4%, $n=55$) involved the mandible. In 22.1% of cases ($n=17$), necrosis was limited to the maxilla, while 6.5% ($n=5$) presented with MRONJ affecting both jaws. The relationship between abnormal glucose metabolism and the localisation of lesions was also analysed, with particular attention to the distribution of mandibular and maxillary involvement (*Figure 9.*) [61].

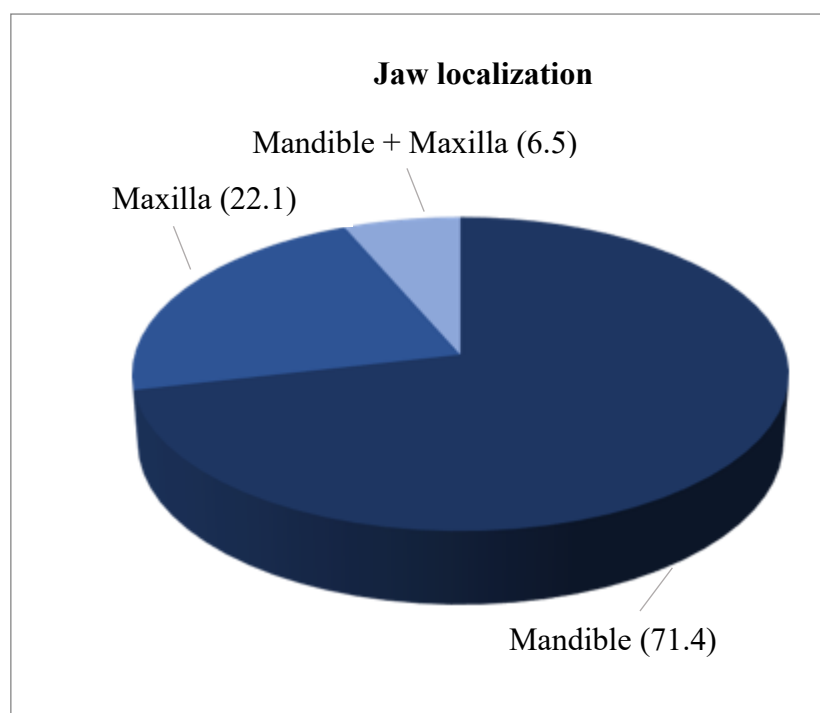


Figure 9. Jaw localisation of MRONJ (Frequency [%]) [61].

Analysis of MRONJ localization revealed that the mandible was the most frequently affected anatomical site regardless of glycaemic status. Among all MRONJ patients, mandibular involvement accounted for 16.9% of DM, 15.6% of IFG and 39.0% of normoglycaemic cases, representing a total of 71.5% of the study population. Maxillary involvement was less common, occurring in 3.9% of DM patients, 3.9% of IFG patients and 14.3% of normoglycaemic patients. Simultaneous involvement of both jaws was the least frequent presentation, observed in 1.3%, 1.3% and 3.9% of patients, respectively. Overall, mandibular localisation predominated in all glycaemic groups,

whereas maxillary and combined mandibular–maxillary involvement were considerably less frequent (*Figure 10.*) [61].

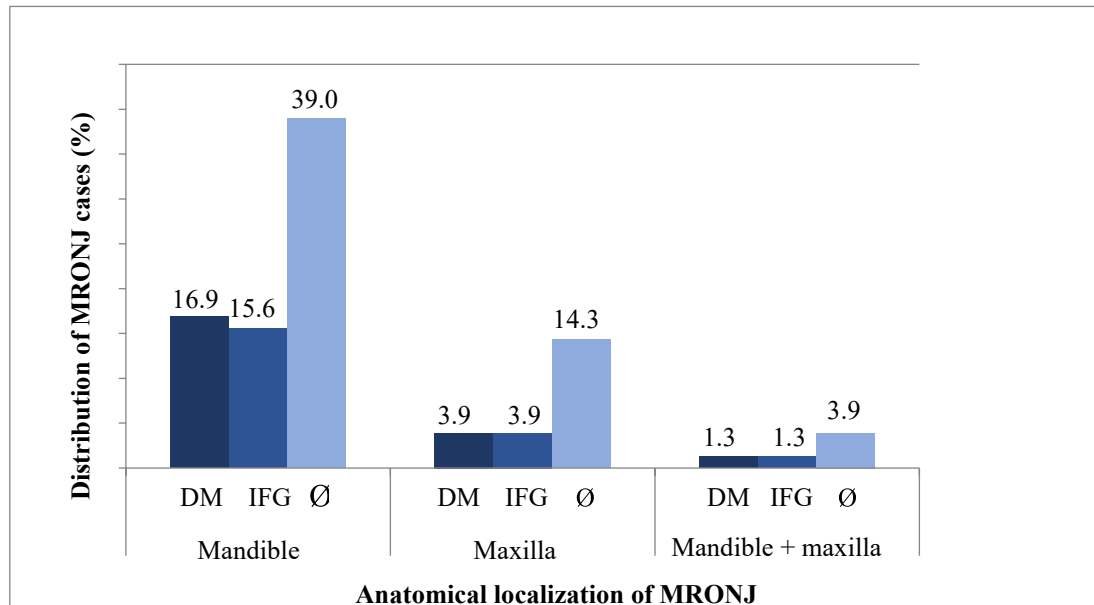


Figure 10. Distribution of MRONJ localisation according to glycaemic status. Percentages represent the proportion of all MRONJ patients included in the study. The mandible was the most frequently affected anatomical site across all glycaemic groups [61].

We also examined the underlying conditions for which patients in the MRONJ group received antiresorptive pharmacotherapy. Among the cases analysed, 36.4% (n=28) were treated for breast cancer, 26.0% (n=20) for prostate cancer, 11.7% (n=9) for osteoporosis, 9.1% (n=7) for multiple myeloma, 9.1% (n=7) for other malignancies (including non-Hodgkin’s lymphoma, urinary bladder cancer and colorectal cancer) and 7.8% (n=6) for lung cancer (*Figure 11.*) [61].

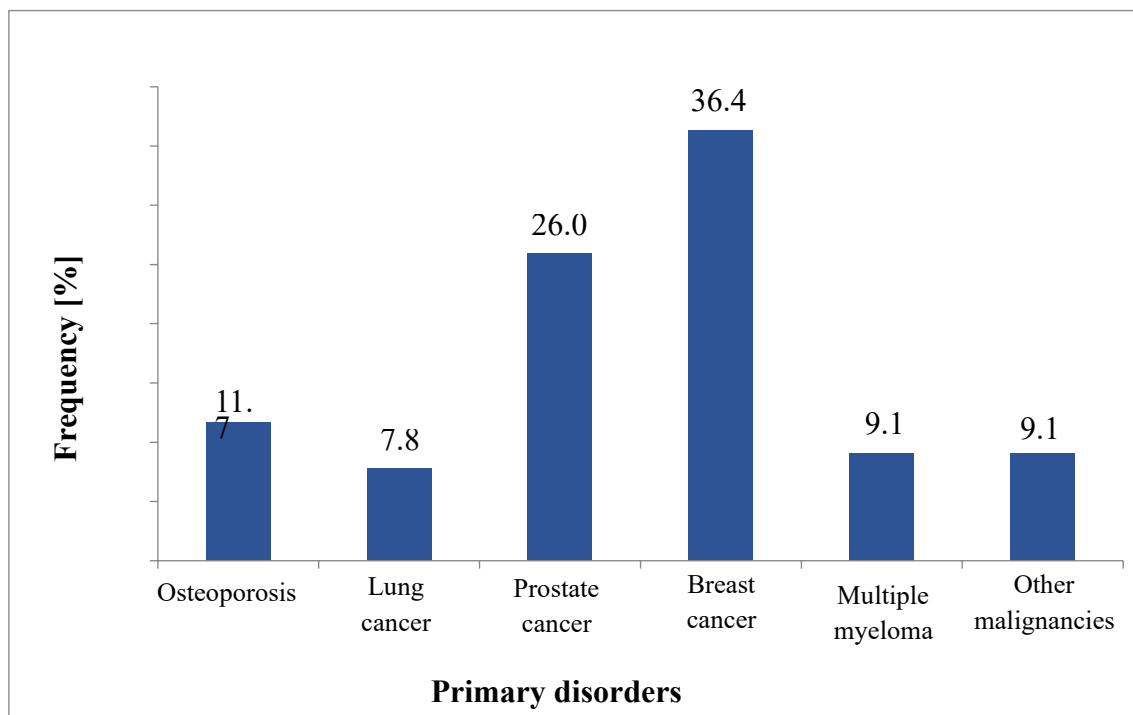


Figure 11. Percentage distribution of the most common primary diseases requiring antiresorptive therapy (Frequency [%]) [61].

In the MRONJ group, we also analysed the distribution of underlying primary diseases according to glycaemic status. Breast cancer was the most frequent indication for antiresorptive therapy, accounting for 19.5% (n=15) of all cases, followed by prostate cancer with 13.0% (n=10) and osteoporosis with 9.1% (n=7). Multiple myeloma and lung cancer were each observed in 6.5% (n=5) of patients, while other malignancies (such as non-Hodgkin's lymphoma, bladder or colorectal cancer) represented 5.2% (n=4) of cases (Figure 12.) [61].

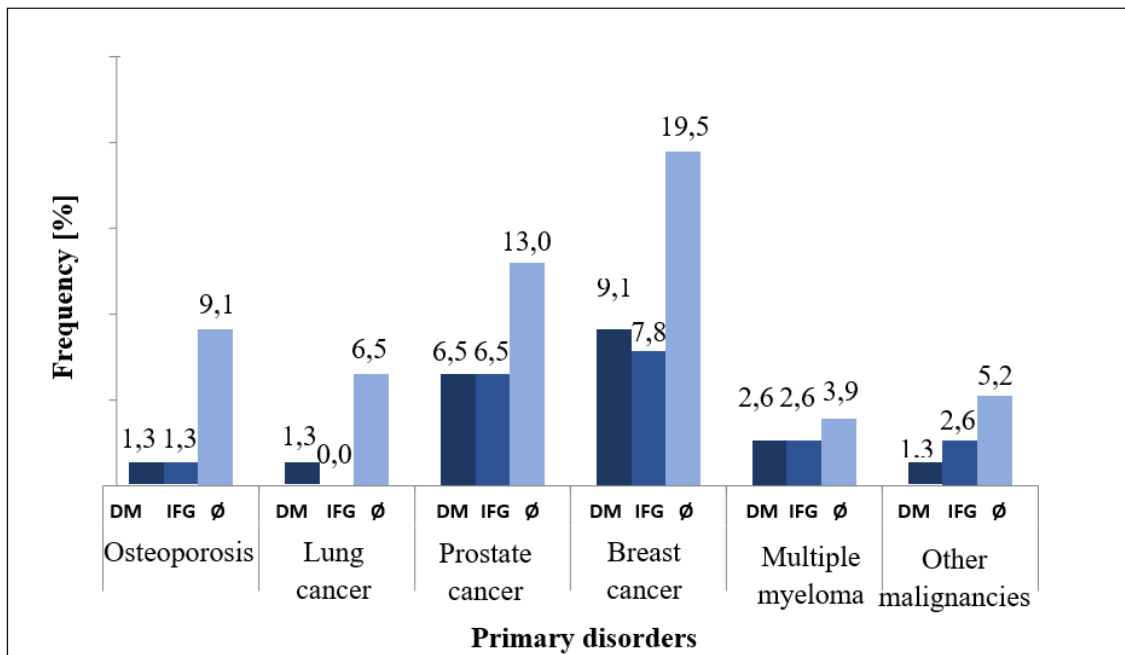


Figure 12. Occurrence of MRONJ with abnormal vs. normal glucose metabolism, considering the patient's primary disease (Ø = no underlying disease), (Frequency [%]) [61].

When stratified by glucose metabolism, breast cancer was associated with DM in 9.1%, IFG in 7.8% and normoglycaemia in 19.5% of patients. Prostate cancer was equally distributed across the groups, with 6.5% of patients presenting with DM, IFG or normal glucose values. Osteoporosis occurred in 1.3% of patients with DM, 1.3% with IFG and 9.1% with normoglycaemia. Multiple myeloma was present in 2.6% of DM, 2.6% of IFG and 3.9% of normoglycaemic cases. Lung cancer accounted for 1.3% of DM and 6.5% of IFG cases, but was not observed among normoglycaemic patients. Other malignancies were observed in 1.3% of DM, 2.6% of IFG and 5.2% of normoglycaemic cases. These findings indicate that while breast and prostate cancer were the leading primary diseases among MRONJ patients, abnormalities in glucose metabolism were also frequently represented across the different diagnostic groups (*Figure 12.*) [61].

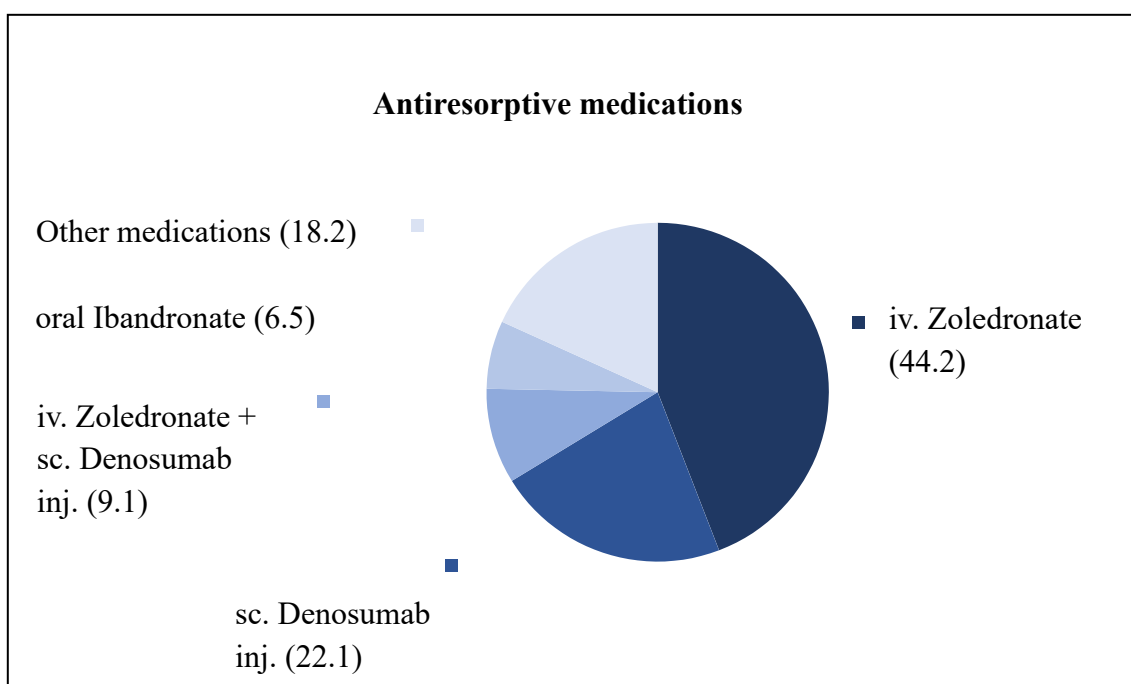


Figure 13. Percentage distribution of the most common pharmacotherapeutic agents associated with the development of MRONJ (Frequency [%]) [61].

Results indicate that MRONJ most frequently developed in patients treated with parenteral zoledronic acid. A total of 44.2% of the study population (n=34) had received this treatment. Subcutaneous denosumab inj. were administered in 22.1% of cases (n=17). A combination of intravenous zoledronic acid and subcutaneous denosumab injection was reported in 9.1% of patients (n=7). A total of 6.5% of the patients received oral ibandronate treatment (n=5). In addition to these agents, 18.2% of cases (n=14) received other antiresorptive therapies, including oral BPs (such as risedronate, alendronate, clodronate), either alone or in combination with subcutaneous denosumab injection and/or intravenous zoledronic acid (*Figure 13.*) [61].

4.2. Results of Study II

The MRONJ (case) group consisted of 60 patients, of whom 39 were women (65%) and 21 were men (35%). The mean age was 65 years. Hyperglycaemia was observed in approximately 40% of these patients. In comparison, the control group included 200 patients, comprising 72 women (36%) and 128 men (64%), with a mean age of 50 years. In this group, hyperglycaemia was present in 21% of patients. Statistical

analysis revealed a significant association between hyperglycaemia and MRONJ ($p = 0.003$, $p < 0.05$). The MRONJ group showed a substantially higher proportion of hyperglycaemic patients compared with the control group. *Table 4.* summarises blood glucose levels and sex distribution of the participants [62].

Table 4. Prevalence of hyperglycaemia and normoglycemia both in the case and in the control groups [62].

Sex	Glycaemic status	Case Group		Control Group	
		Patients	Frequency (%)	Patients	Frequency (%)
Male	Hyp	10	16.7	27	13.5
Male	Norm	11	18.3	101	50.5
Female	Hyp	14	23.3	15	7.5
Female	Norm	25	41.7	57	28.5
		$\Sigma 60$	$\Sigma 100.0$	$\Sigma 200$	$\Sigma 100.0$

Independent of glycaemic status, 75% of patients in the MRONJ group (n=45) presented with necrosis of the mandible. In contrast, maxillary involvement alone was observed in 18.4% (n=11), while both jaws were affected in 6.6% of patients (n=4). Statistical analysis revealed no significant association between the localisation of necrosis and blood glucose levels ($p=0.825$, $p>0.05$). Overall, MRONJ was more frequently localised to the mandible, as illustrated in *Table 5.* [62].

Table 5. The location of MRONJ and the glucose levels were expressed as percentages in the MRONJ group [62].

Location	Glycaemic status	Patients	Frequency (%)
Maxilla	Hyp	4	6.7
Maxilla	Norm	7	11.7
Mandible	Hyp	18	30.0
Mandible	Norm	27	45.0
Mandible + Maxilla	Hyp	2	3.3
Mandible + Maxilla	Norm	2	3.3
		Σ 60	Σ 100.0

Approximately 38.3% (n=23) of the examined patients received antiresorptive therapy due to breast carcinoma, while 23.3% (n=14) were treated for prostate carcinoma. Osteoporosis accounted for 15% (n=9) of cases, multiple myeloma for 10% (n=6), lung carcinoma for 8.3% (n=5) and other malignant conditions, including non-Hodgkin's lymphoma, urothelial carcinoma and colorectal carcinoma, for 5% (n=3). The highest proportion of BP therapy was administered to patients with breast and prostate carcinoma. With respect to medication type, 39.9% (n=24) of the patients were treated with parenteral BPs and subcutaneous denosumab injection. Subcutaneous denosumab injection alone was administered in 21.7% (n=13) of cases, while 11.8% (n=7) received a combination of intravenous zoledronate and subcutaneous denosumab injection. Oral ibandronate therapy was given in 8.3% (n=5) and a further 8.3% (n=5) received combined treatment with intravenous zoledronate, subcutaneous denosumab injection and oral ibandronate. Additionally, 5% (n=3) of patients were treated with a combination of intravenous zoledronate, subcutaneous denosumab injection and oral clodronate; 3.3% (n=2) received oral alendronate; and 1.7% (n=1) oral risedronate. When examining the relationship between primary disease, glucose balance and MRONJ location, it was observed that all patients with multiple myeloma and lung carcinoma were treated with intravenous zoledronate, while patients with osteoporosis were predominantly managed with oral therapy. Overall, parenteral administration represented the most common treatment modality (*Table 6.*) [62].

Table 6. Different parameters; primary disease and its associated medications, glucose balance and location of MRONJ [62].

Primary disorder	Antiresorptive medication	Hyp	Norm	Mand	Max	Both Jaws	Patients
Lung cancer	iv. zoledronate	1	4	3	2	0	5
Prostate cancer	iv. zoledronate + sc. denosumab inj.	3	1	3	1	0	4
Prostate cancer	iv. zoledronate	1	2	2	1	0	3
Prostate cancer	sc. denosumab inj.	3	4	4	1	2	7
Osteoporosis	iv. zoledronate + sc. denosumab inj. + oral clodronate	0	1	1	0	0	1
Osteoporosis	iv. zoledronate + sc. denosumab inj. + oral clodronate	0	1	0	1	0	1
Osteoporosis	iv. zoledronate + sc. denosumab inj.	0	1	0	1	0	1
Osteoporosis	oral risedronate	0	2	2	0	0	2
Osteoporosis	oral ibandronate	0	2	1	1	0	2
Osteoporosis	sc. denosumab inj.	1	1	2	0	0	2
Multiple myeloma	oral alendronate	3	3	4	1	1	6
Breast cancer	iv. zoledronate	1	4	4	1	0	5
Breast cancer	iv. zoledronate + sc. denosumab	0	2	2	0	0	2

	inj. + oral ibandronate						
Breast cancer	iv. zoledronate + sc. denosumab inj. + oral clodronate	1	0	1	0	0	1
Breast cancer	iv. zoledronate	3	5	7	1	0	8
Breast cancer	oral ibandronate	2	1	2	0	1	3
Breast cancer	sc. denosumab inj.	3	1	4	0	0	4
Other malignancies	iv. zoledronate + sc. denosumab inj.	1	0	1	0	0	1
Other malignancies	iv. zoledronate	1	1	2	0	0	2
		Σ24	Σ36	Σ45	Σ11	Σ4	Σ60

Analysis of oral habits and glucose status in the MRONJ group revealed that hyperglycaemia was among the most relevant risk factors. A total of 26.7% (n=16) of patients with MRONJ presented with hyperglycaemia, while 43.3% (n=26) showed normoglycemia. Additional lifestyle-related factors included smoking in 8.3% (n=5) and alcohol consumption in 6.7% (n=4) of patients. Combined risk factors were also present: 5% (n=3) of patients reported both smoking and alcohol consumption, whereas 1.7% (n=1) presented with all three-hyperglycaemia, smoking and alcohol consumption. Hyperglycaemia was the most frequently observed risk factor, either alone or in combination with smoking and alcohol consumption (*Table 7.*) [62].

Table 7. Bad oral habits and glucose status of the MRONJ group [62].

Alcohol	Smoking	Glycaemic status	Patients	Frequency (%)
No	No	Norm	26	43.3
No	No	Hyp	16	26.7
No	Yes	Norm	5	8.3
No	Yes	Hyp	4	6.7
Yes	No	Norm	2	3.3
Yes	No	Hyp	3	5.0
Yes	Yes	Norm	3	5.0
Yes	Yes	Hyp	1	1.7
			Σ 60	Σ 100.0

4.3. Results of Study III

Of the 217 patients evaluated in this study, 75 were assigned to the pre-COVID-19 group and 142 to the post-COVID-19 group. In the pre-COVID-19 group, 61.3% (n=46) were female and 38.7% (n=29) were male, while in the post-COVID-19 group, 64.0% (n=91) were female and 36.0% (n=51) were male. The mean age in the pre-COVID-19 group was 74.5 years (74.3 for females and 74.7 for males), compared with 69.6 years in the post-COVID-19 group (68.9 for females and 70.7 for males) (*Table 8.*) [63].

Table 8. Total number of patients in the two groups and gender distribution [63].

Pre-COVID-19 Group	Male	Female	Total (Σ)
Number	29	46	75
Ratio	2/5	3/5	1
Frequency (%)	38.7	61.3	100.0
Post-COVID-19 Group	Male	Female	Total (Σ)
Number	51	91	142
Ratio	1/3	2/3	1
Frequency (%)	36.0	64.0	100.0

The average duration of hospitalization was 4 days in the pre-COVID-19 group and 5 days in the post-COVID-19 group. In the pre-COVID-19 group, no differences were observed in relation to lesion location, with an average of 4 days of hospital stay across mandibular and maxillary cases. In contrast, in the post-COVID-19 group, patients who underwent mandibular surgery had an average stay of 5 days, while those with maxillary surgery remained hospitalized for an average of 6 days. When stratified by primary disease, patients with multiple myeloma, non-Hodgkin lymphoma, breast cancer or prostate cancer had an average hospital stay of 4 days pre-COVID-19 and 5 days post-COVID-19. For those with osteoporosis or lung cancer, the average duration increased from 4 days before the pandemic to 6 days afterward. Renal tumor cases were only observed in the post-COVID-19 group, with an average hospital stay of 3 days [63].

Regarding the use of PRF following sequestrectomy, hospitalization in the pre-COVID-19 group consistently lasted 4 days, irrespective of whether PRF was applied. In the post-COVID-19 group, the average stay extended to 5 days, also independent of PRF usage [63]. The average duration of hospital stay was longer in the post-COVID-19 group than in the pre-COVID-19 group [63]. According to WHO diagnostic criteria, normoglycemia was defined as a FPG level below 6.1 mmol/L, IFG as levels between 6.1 and 6.9 mmol/L and DM as levels equal to or above 7.0 mmol/L. In our study, the average FPG level was 5.5 mmol/L in the pre-COVID-19 group and 5.9 mmol/L in the post-COVID-19 group. When stratified by jawbone location, the mean FPG level in the pre-COVID-19 group was 5.7 mmol/L in patients with mandibular MRONJ and 5.3 mmol/L in those with maxillary MRONJ. In the post-COVID-19 group, these values increased to 6.1 mmol/L in the mandible and 5.7 mmol/L in the maxilla (*Table 9.*). Mean FPG levels were higher in the post-COVID-19 group than in the pre-COVID-19 group across both jaw locations (*Table 9.*) [63].

Table 9. Average FPG level by jawbone location [63].

Location	Pre-COVID-19 Group	Post-COVID-19 Group
Mandible	5.7 mmol/L	6.1 mmol/L
Maxilla	5.3 mmol/L	5.7 mmol/L

The total number of MRONJ lesions was 80 in the pre-COVID-19 group and 166 in the post-COVID-19 group, as several patients developed necrosis in both jaws. In the pre-COVID-19 group, 76.2% (n=61) of MRONJ cases were located in the mandible, whereas 23.8% (n=19) occurred in the maxilla. In contrast, in the post-COVID-19 group, 63.2% (n=105) of cases were localised to the mandible and 36.8% (n=61) to the maxilla (*Figure 14.*). The proportion of maxillary lesions increased from 23.8% in the pre-COVID-19 group to 36.8% in the post-COVID-19 group (*Figure 14.*) [63].

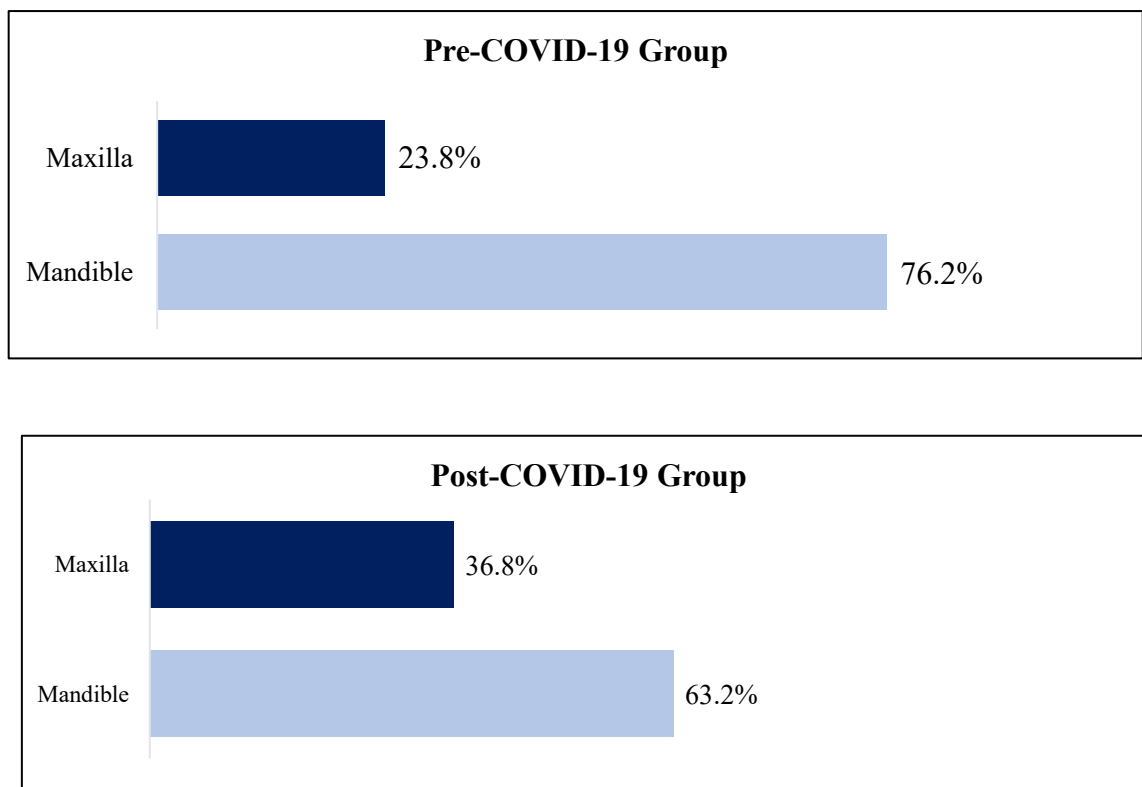


Figure 14. Distribution of MRONJ localization (mandible vs. maxilla) in pre- and post-COVID-19 groups [63].

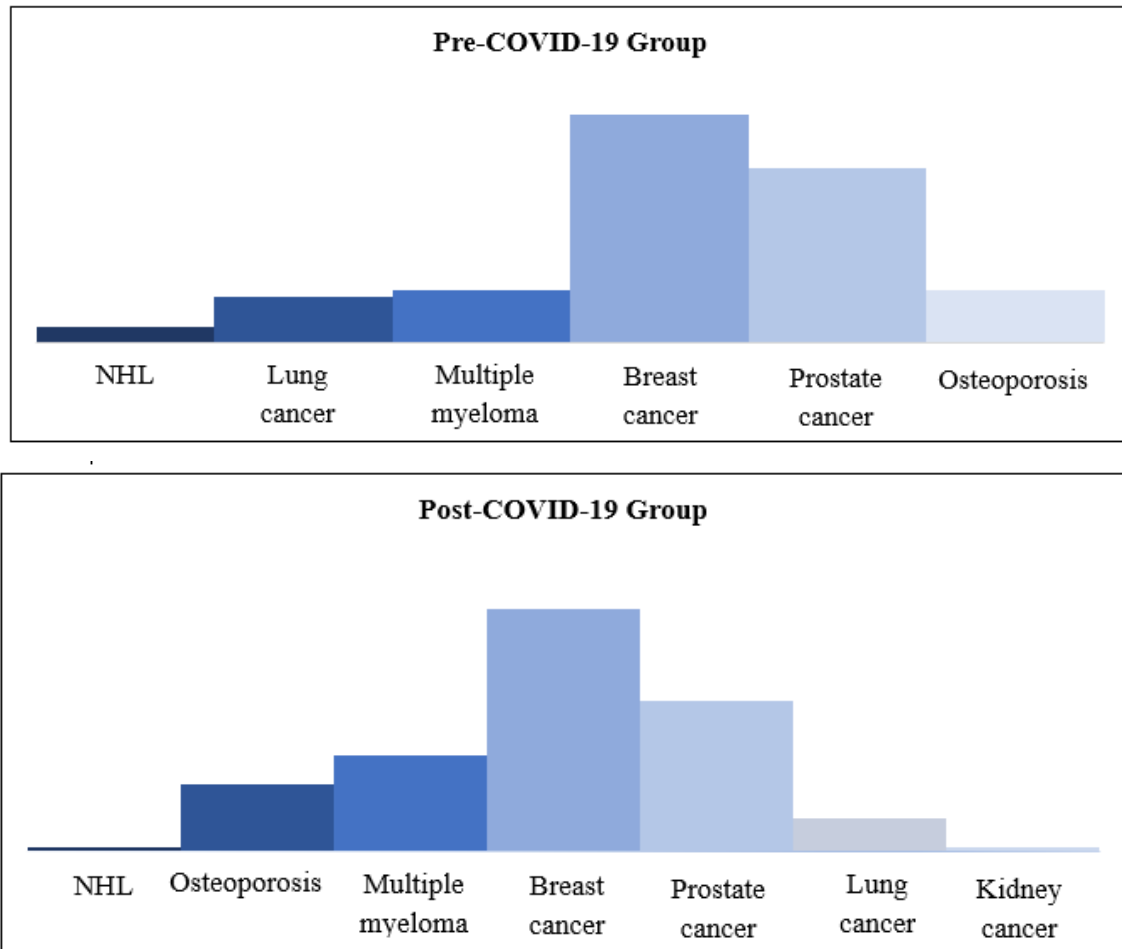


Figure 15. Primary diseases in pre- and post-COVID-19 groups [63].

In the pre-COVID-19 group, the most frequent underlying condition was breast cancer, 40.0%, (n=30), followed by prostate cancer, 30.7%, (n=23), multiple myeloma 9.3%, (n=7), osteoporosis 9.3%, (n=7), lung cancer 8.0%, (n=6) and non-Hodgkin lymphoma 2.7%, (n=2). In the post-COVID-19 group, breast cancer remained the most prevalent underlying condition 40.7%, (n=57), followed by prostate cancer 25.2%, (n=36), multiple myeloma 16.2%, (n=23), osteoporosis 11.2%, (n=16), lung cancer 5.5%, (n=8), non-Hodgkin lymphoma 0.6%, (n=1) and kidney cancer 0.6%, (n=1) (*Figure 15*). These findings indicate that breast and prostate cancers were consistently the leading underlying conditions in both groups, while multiple myeloma showed a marked increase in prevalence in the post-COVID-19 group [63].

As this study was designed as a descriptive retrospective comparison of MRONJ patients treated before and after the COVID-19 pandemic, no formal statistical testing was performed. The primary objective was to identify trends and differences in patient numbers, hospitalization time, fasting glucose levels, lesion localization and underlying diseases between the two periods. Therefore, the findings are presented using descriptive statistics, including means, percentages and frequency distributions.

4.4. Results of Study IV

A total of 60 patients with MRONJ were included in the study, 40 women (66.7%) and 20 men (33.3%); mean age, 61 years. All patients underwent surgical treatment for MRONJ. Surgical procedures included sequestrectomy and segmental resection, depending on the clinical presentation and extent of the disease. In the dysglycaemic group, MRONJ recurred in 12 of 30 patients (40.0%), while 18 of 30 (60.0%) remained recurrence-free. In the normoglycaemic group, recurrence was observed in 5 of 30 patients (16.7%), with 25 of 30 (83.3%) showing no recurrence. A significant association was identified between hyperglycaemia and MRONJ recurrence (*Figure 16., Table 10.*)

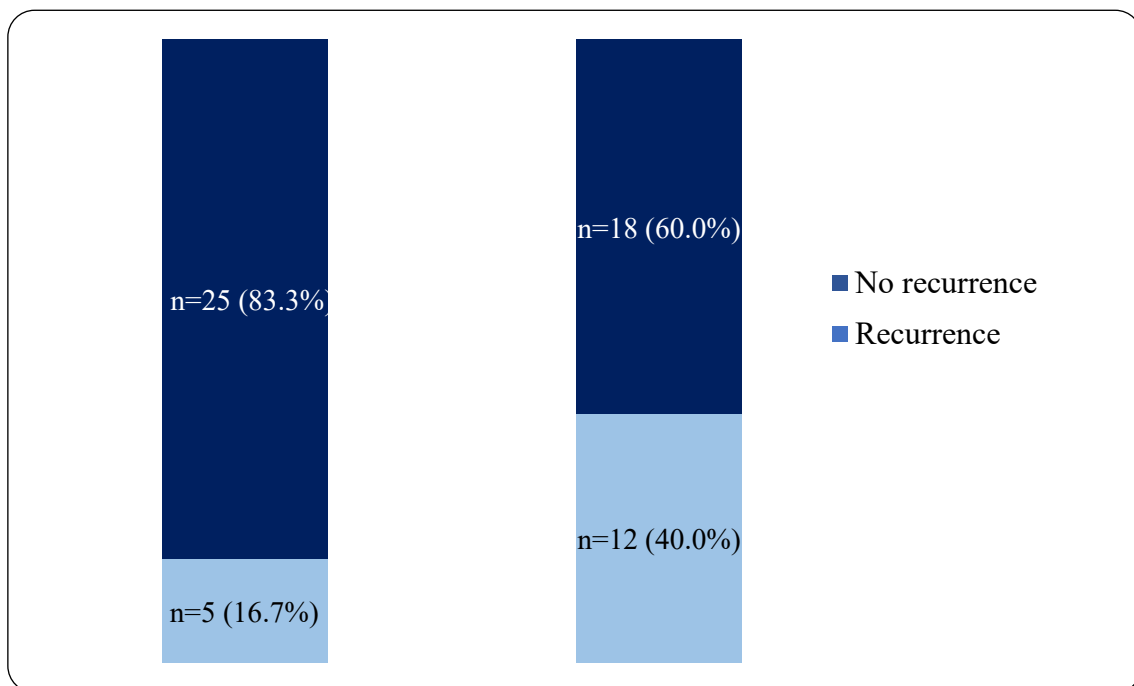


Figure 16. Relationship between the glycaemic status and MRONJ recurrence (1st column: normoglycaemic patients, 2nd column: hyperglycaemic patients), (n= number of patients).

Table 10. MRONJ recurrence according to the glycaemic status (n=number of patients).

Necrosis recurrence	Normoglycaemia (n=30)	Hyperglycaemia (n=30)
MRONJ recurrence	5 (16.7%)	12 (40.0%)
No MRONJ recurrence	25 (83.3%)	18 (60.0%)

The distribution of antiresorptive medications and their association with MRONJ recurrence is summarized in *Table 10*. Zoledronate was the most frequently administered drug, prescribed in 25 of 60 patients, 41.7%, (n=25). Among these, 7 patients 28.0%, (n=7) experienced recurrence, while 18 72.0%, (n=18) did not subcutaneous denosumab injection (Xgeva®) was the second most common agent, used in 11 patients 18.3%, (n=11), with 2 recurrences 18.2%, (n=2) and 9 non-recurrences 81.8%, (n=9). Combination therapy with zoledronate and subcutaneous denosumab injection was reported in 5 patients (8.3%, (n=5), where recurrence occurred in 2 cases 40.0%, (n=2). The triple therapy of zoledronate, subcutaneous denosumab injection (Xgeva®) and ibandronate was used in 2 patients 3.3%, (n=2), resulting in one recurrence 50.0%, (n=1). Other agents were less frequently represented. Ibandronate monotherapy was used in 4 patients 6.7%, (n=4), with 1 recurrence 25.0%, (n=1). Alendronate was given to 1 patient 1.7%, (n=1) and risedronate also to 1 patient 1.7%, (n=1); recurrence occurred in the alendronate-treated patient (n=1). Rare drug combinations included zoledronate plus bevacizumab 1.7%, (n=1) and clodronate plus subcutaneous denosumab injection (Xgeva®) 1.7%, (n=1), both without recurrence (n=0). Overall, recurrence was most frequently associated with zoledronate monotherapy (41.2% of all recurrence cases, n=7), while subcutaneous denosumab injection and combined therapies also showed recurrence, though at lower absolute frequencies. Oral BPs and rare combinations were rarely implicated. These findings indicate that the type of antiresorptive regimen, particularly intravenous zoledronate, may substantially influence recurrence patterns in MRONJ.

As shown in *Table 11.*, among patients receiving subcutaneous denosumab injection therapy, Xgeva® was associated with a markedly higher frequency of MRONJ compared with Prolia®.

Table 11. Association of antiresorptive medications with MRONJ recurrence (n=number of patients).

Antiresorptive medication	MRONJ recurrence (n=17)	No MRONJ recurrence (n=43)	Total Σ (n=60)
iv. zoledronate	7	18	25
oral alendronate	1	0	1
oral risedronate	0	1	1
sc. denosumab inj.	1	1	2
oral ibandronate	1	3	4
oral ibandronate, iv. zoledronate	0	1	1
oral clodronate, iv. zoledronate	1	0	1
iv. zoledronate, sc. denosumab inj.	1	0	1
iv. zoledronate, sc. bevacizumab inj.	0	1	1
sc. denosumab inj.(Prolia®), oral ibandronate	0	1	1
sc. denosumab inj. (Xgeva®)	2	9	11
sc. denosumab inj. (Xgeva®), oral ibandronate	0	2	2
sc. denosumab inj. (Xgeva®), iv. Zoledronate	0	1	1
oral clodronate, sc. denosumab inj. (Xgeva®)	0	1	1
iv. zoledronate, sc. denosumab inj. (Xgeva®)	2	3	5
iv. zoledronate, sc. denosumab inj. (Xgeva®), oral ibandronate	1	1	2

The average duration of antiresorptive or antiangiogenic therapy prior to the diagnosis of MRONJ varied considerably across different agents and combinations.

Figure 17. summarises the average duration of therapy, in months, for each antiresorptive medication regimen, whether administered as monotherapy or in combination. It is evident that in cases involving combination therapy, patients most frequently received an additional antiresorptive or antiangiogenic agent alongside subcutaneous denosumab injection or intravenous zoledronate.

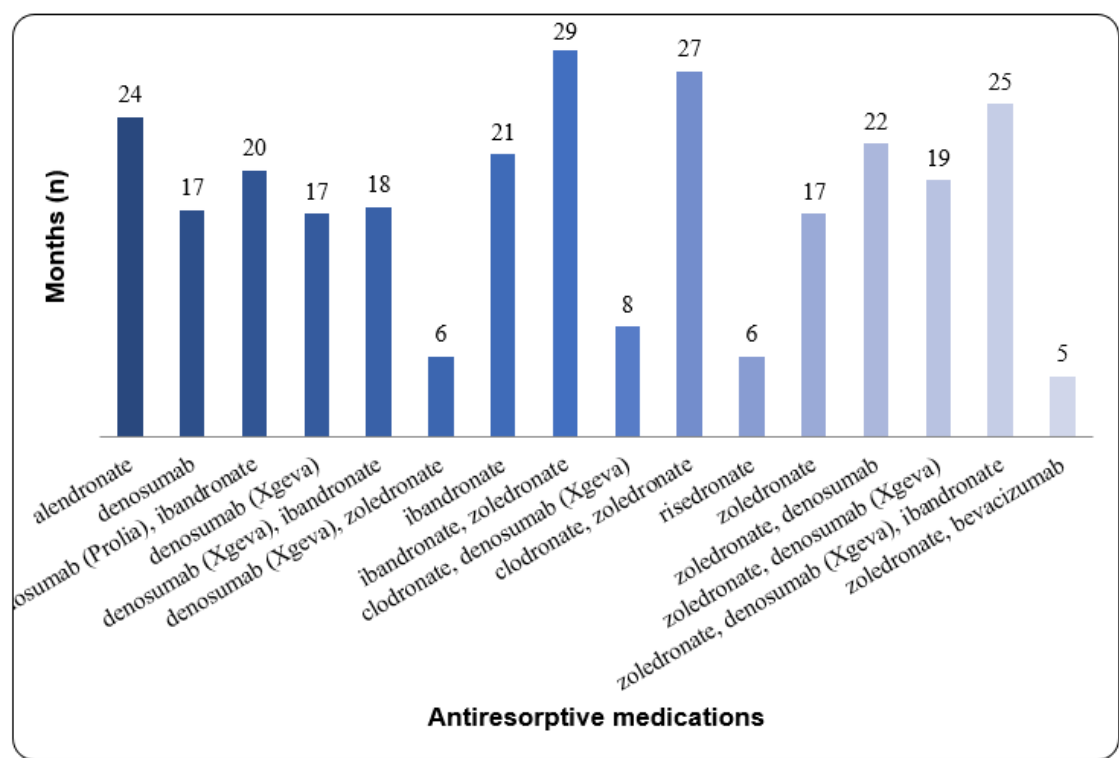


Figure 17. Average duration of administration of various antiresorptive and antiangiogenic medications (n=number of months).

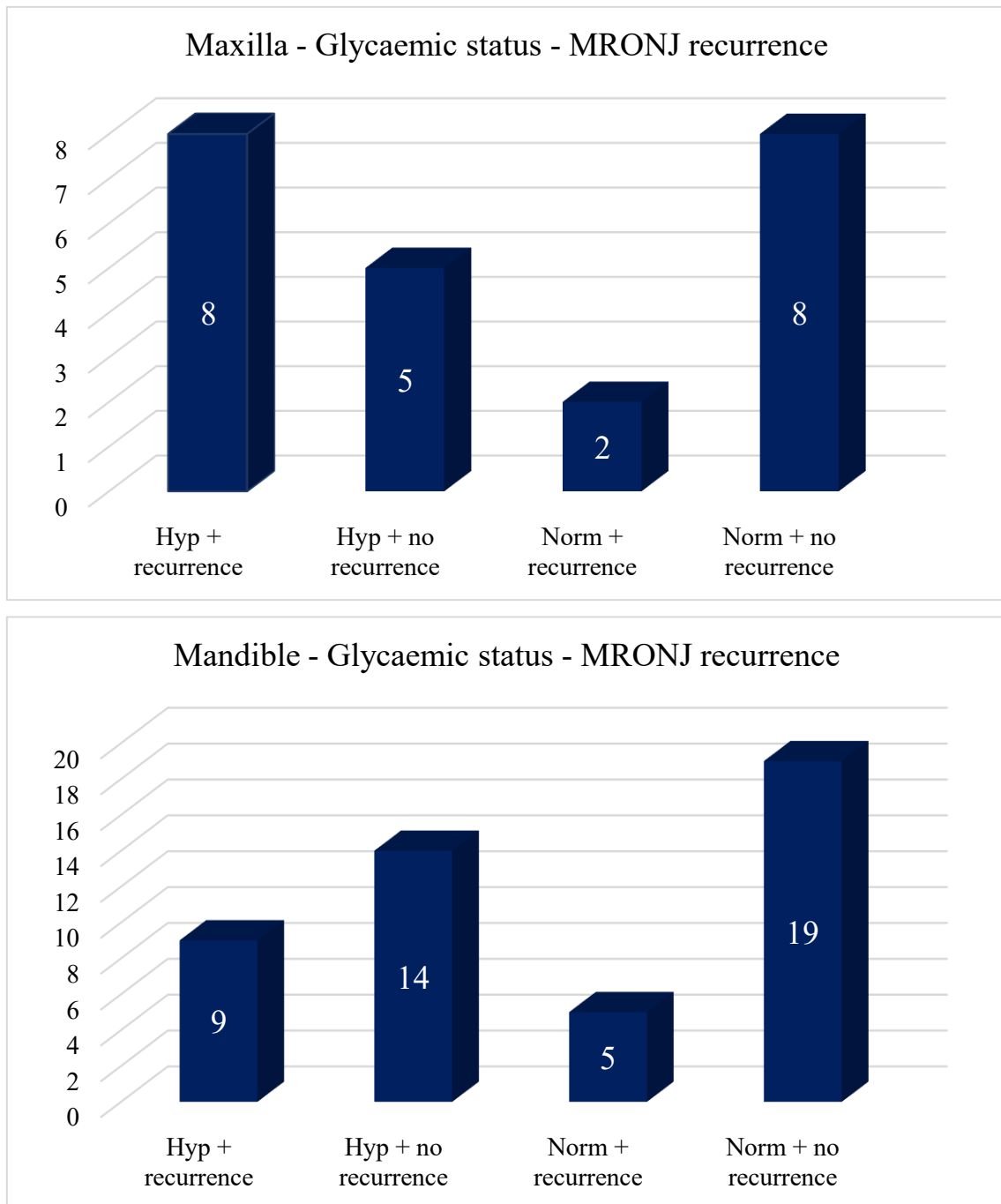


Figure 18. Distribution of MRONJ lesions according to jaw location, glycaemic status and recurrence (n = number of lesions).

The distribution across subgroups was as follows:

- Mandible + hyperglycaemia + MRONJ recurrence: n=9 (12.9%)
- Mandible + hyperglycaemia + no MRONJ recurrence: n=14 (20.0%)
- Mandible + normoglycaemia + MRONJ recurrence: n=5 (7.1%)
- Mandible + normoglycaemia + no MRONJ recurrence: n=19 (27.1%)
- Maxilla + hyperglycaemia + MRONJ recurrence: n=8 (11.4%)
- Maxilla + hyperglycaemia + no MRONJ recurrence: n=5 (7.1%)
- Maxilla + normoglycaemia + MRONJ recurrence: n=2 (3.0%)
- Maxilla + normoglycaemia + no MRONJ recurrence: n=8 (11.4%)

Analysis of lesion localisation in relation to glycaemic status and recurrence revealed notable distribution patterns. In the mandible, hyperglycaemic patients demonstrated the highest proportion of recurrence (12.9%, n=9), followed by normoglycaemic patients (7.1%, n=5). Among cases without recurrence, 27.1% (n=19) of lesions occurred in normoglycaemic individuals and 20.0% (n=14) in those with hyperglycaemia. Maxillary lesions followed a similar pattern, with recurrence observed more frequently in hyperglycaemic patients (11.4%, n=8) compared with normoglycaemic individuals (3.0%, n=2). Non-recurrent maxillary lesions were documented in 11.4% (n=8) of normoglycaemic and 7.1% (n=5) of hyperglycaemic patients. Overall, mandibular involvement predominated and recurrence occurred more frequently among hyperglycaemic patients across both jaw regions, suggesting a potential association between impaired glucose regulation and unfavourable MRONJ outcomes (*Figure 18*).

The average duration of antiresorptive drug administration was also assessed according to glycaemic status and the presence or absence of MRONJ recurrence. In normoglycaemic patients with recurrence (Group 1), the mean treatment duration was 26 months, whereas in hyperglycaemic patients with recurrence (Group 2) it was 28 months. Among normoglycaemic patients without recurrence (Group 3), the mean duration was 14 months and in hyperglycaemic patients without recurrence (Group 4) it was 15 months. These findings demonstrate that patients with recurrence (Groups 1 and 2) had

substantially longer exposure to antiresorptive medication compared with those without recurrence (Groups 3 and 4). This suggests that prolonged therapy - especially in combination with hyperglycaemia - may contribute to an increased risk of MRONJ recurrence (*Figure 19*). The subgroup-specific mean treatment durations were as follows:

- Group 1: Normoglycaemia + MRONJ recurrence: n=26 months
- Group 2: Hyperglycaemia + MRONJ recurrence: n=28 months
- Group 3: Normoglycaemia + no MRONJ recurrence: n=14 months
- Group 4: Hyperglycaemia + no MRONJ recurrence: n=15 months

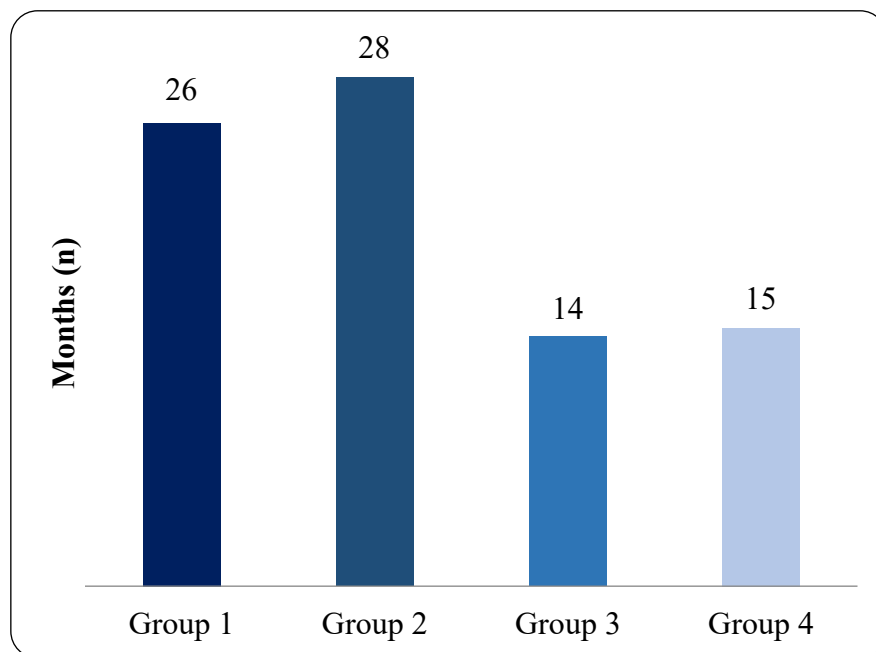


Figure 19. Average duration of antiresorptive drug use according to glycaemic status and MRONJ recurrence (n=number of months).

5. Discussion

5.1. Overview of Main Findings

This doctoral research investigated the role of hyperglycaemia in the development and recurrence of MRONJ, providing further insight into the complex interactions among metabolic disturbances, antiresorptive therapy and oral surgical outcomes. MRONJ is a severe complication with a multifactorial pathogenesis that remains incompletely understood. Growing evidence indicates that DM represents an important systemic risk factor, although the biological mechanisms linking impaired glucose metabolism to MRONJ have not yet been fully elucidated. In the present studies, patients with dysglycaemia exhibited a significantly higher prevalence of MRONJ than normoglycaemic individuals, particularly following invasive dentoalveolar procedures. Elevated FPG levels were associated with both the occurrence of MRONJ and an increased risk of recurrence. Mandibular involvement predominated in all patient groups. Hyperglycaemia was associated with a higher frequency of MRONJ across all anatomical locations. Intravenous zoledronate and subcutaneous denosumab injection were the antiresorptive agents most frequently associated with MRONJ. Among patients receiving subcutaneous denosumab injection, MRONJ was observed more frequently in those treated with Xgeva® than in those receiving Prolia®, although this finding may partly reflect differences in treatment indication and dosing regimens. Lifestyle-related factors, particularly smoking and alcohol consumption, were also frequently present among affected patients and may have contributed to impaired healing and disease progression. The post-COVID-19 period was characterised by a higher number of MRONJ cases, increased mean FPG levels and a relative increase in maxillary involvement. These findings may reflect the indirect consequences of the pandemic, including reduced access to dental care, delays in treatment and interruptions in routine follow-up. During this period, aerosol-generating dental procedures were often restricted, resulting in a greater reliance on tooth extraction as a treatment option and consequently increasing the frequency of dentoalveolar trauma. In addition, many patients attended routine dental examinations and specialist consultations less frequently, potentially allowing oral disease to progress before treatment was initiated. Treatment duration and cumulative antiresorptive exposure were also associated with disease severity and recurrence. Longer

treatment periods, particularly when combined with dysglycaemia, were observed more frequently among patients with recurrent MRONJ. Hyperglycaemia showed a significant association with MRONJ recurrence, with relapse occurring more than twice as frequently among dysglycaemic patients as among normoglycaemic individuals. Surgical factors, including the extent of dentoalveolar trauma and adherence to perioperative management protocols, may further influence the relationship between metabolic status and MRONJ risk. Taken together, the findings of this dissertation support the role of hyperglycaemia as an important contributing factor in both the development and recurrence of MRONJ. The results further emphasise that metabolic disturbances, antiresorptive therapy, systemic comorbidities and lifestyle-related factors interact in a cumulative manner, influencing both disease onset and clinical outcome.

5.2. Comparison with Previous Studies

Several studies have investigated the relationship between DM and MRONJ, although the available evidence remains partly inconsistent. In a large retrospective study of patients receiving zoledronic acid or subcutaneous denosumab injection for advanced malignancies, *Kajizono et al.* identified DM as a significant predictor of MRONJ. Multivariate logistic regression analysis demonstrated a more than sixfold increase in risk among diabetic patients ($p=0.016$). Regular dental maintenance during antiresorptive therapy significantly reduced disease occurrence, highlighting the importance of preventive oral care in high-risk populations [65]. Similarly, the Austrian position paper by *Svejda et al.* listed DM among the comorbidities potentially associated with an increased risk of MRONJ. Other contributing factors included invasive dental procedures, chemotherapy, periodontal disease, local infection, glucocorticoid therapy, smoking, anemia, dialysis and advanced age [66]. In contrast, *Belch et al.* reported that although DM and anemia were among the most common comorbidities in patients with MRONJ, no statistically significant association could be demonstrated, which was attributed to the limited sample size of the study population. The authors nevertheless confirmed the importance of established risk factors such as intravenous antiresorptive therapy, previous dentoalveolar surgery, female sex and older age [67]. More recently, *Rahimi-Nedjat et al.* reported a significant association between DM and MRONJ, supporting the hypothesis that diabetes may contribute to disease development [68]. Our findings partially support

this concept but also suggest a more nuanced interpretation. While DM itself was not consistently associated with MRONJ across all analyses, disturbances of glucose metabolism, particularly hyperglycaemia and IFG, showed a clear relationship with both MRONJ occurrence and recurrence. These observations indicate that metabolic control may be more relevant than the mere presence of a diabetes diagnosis. This interpretation is biologically plausible, as chronic hyperglycaemia adversely affects bone metabolism, angiogenesis, immune function and wound healing. Patients with poorly controlled or previously undiagnosed DM may therefore be at increased risk of impaired tissue repair following dentoalveolar interventions. The present findings support the growing body of evidence suggesting that hyperglycaemia represents a clinically relevant risk factor in MRONJ and emphasise the importance of routine glucose screening, perioperative metabolic assessment and close collaboration between oral and maxillofacial surgeons, dentists and diabetologists in the management of patients receiving antiresorptive therapy [68]. Park and Lee combined clinical and histological evidence to investigate the relationship between T2DM and MRONJ in postmenopausal women receiving BP therapy. Although no major quantitative or morphological differences in osteoclasts were observed between diabetic and non-diabetic patients, osteoclast differentiation and activity were reduced in the diabetic group. Increased cortical bone thickness and proportion further suggested alterations in bone remodelling. These findings indicate that T2DM may not directly initiate MRONJ but may impair bone quality and healing capacity, thereby contributing to disease persistence and delayed recovery [69]. *Khamaisi et al.* reported a substantially higher prevalence of DM and IFG among patients with BP-related osteonecrosis compared with both the general population and oncological patients receiving BP therapy without osteonecrosis. The authors concluded that impaired glucose metabolism may represent an important risk factor for osteonecrosis development and emphasized the need for closer clinical monitoring of diabetic patients undergoing antiresorptive treatment [70]. Similar observations were reported by *Molcho et al.*, who demonstrated that more than two-thirds of patients with BRONJ had either DM or IFG. Furthermore, DM and dysglycaemia increased the risk of BRONJ nearly threefold, while diabetic microvascular complications, particularly nephropathy, were significantly more common among affected individuals. These findings support the hypothesis that both impaired glucose metabolism and diabetes-related vascular dysfunction contribute to

osteonecrosis pathogenesis [71]. Not all studies, however, have confirmed a direct causal relationship. Recent Mendelian randomization analyses based on large-scale GWAS datasets did not demonstrate a causal association between genetically predicted DM and osteonecrosis at skeletal sites such as the femoral head. These findings suggest that the associations observed in observational studies may be influenced by additional metabolic, environmental or treatment-related factors. Nevertheless, the unique biological environment of the jaws, including dentoalveolar trauma, oral infection and exposure to antiresorptive medications, may limit the direct applicability of these findings to MRONJ [72–76]. The COVID-19 pandemic introduced additional challenges in the management of patients at risk of MRONJ. *Dar-Odeh et al.* suggested that COVID-19 may contribute to MRONJ both directly, through thrombotic and inflammatory mechanisms and indirectly through disruptions in healthcare delivery. Delays in dental treatment, restricted access to routine care and postponement of elective procedures may all have contributed to disease progression and delayed diagnosis [77]. Similar concerns were raised by *Morales et al.*, who demonstrated that lockdown-related interruptions in dental care adversely affected patients with type 2 diabetes and severe periodontitis, potentially compromising both metabolic control and oral health outcomes [78]. *Vardas et al.* further reported that COVID-19-related osteomyelitis occurred predominantly in patients with DM and corticosteroid exposure and most frequently affected the maxilla, emphasizing the combined effects of immune dysregulation and impaired healthcare access during the pandemic [79]. Persistent hyperglycaemia following Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection may represent another contributing factor. *Salve et al.* demonstrated that more than one-fifth of patients exhibited persistent hyperglycaemia for at least two months after recovery, including individuals without a previous diagnosis of DM. These findings suggest that post-COVID metabolic disturbances may contribute to impaired wound healing and increased susceptibility to oral complications [80]. In addition, isolated case reports have described the development of MRONJ following COVID-19 treatment with immunomodulatory agents such as tocilizumab, although further evidence is required to establish a causal relationship [81].

Taken together, the findings of this doctoral research support the growing body of evidence indicating that hyperglycaemia is an important contributing factor in both the development and recurrence of MRONJ. Patients with dysglycaemia showed a

significantly higher prevalence of MRONJ and a markedly increased rate of recurrence compared with normoglycaemic individuals. The results further suggest that impaired metabolic control may interact with antiresorptive therapy, local risk factors and systemic comorbidities to influence disease onset and clinical outcome. From a clinical perspective, these findings support routine assessment of glycaemic status, including FPG and, where available, HbA1c measurements, in patients receiving antiresorptive or antiangiogenic therapy. Close collaboration between oral and maxillofacial surgeons, dentists and diabetologists may contribute to improved risk stratification, optimized perioperative management and better long-term outcomes. Future prospective multicentre studies are warranted to confirm these observations, further elucidate the underlying biological mechanisms and establish evidence-based risk assessment models for patients at increased risk of MRONJ.

5.3. Limitations

This research has several limitations. First, all studies were retrospective in design; therefore, causal relationships between hyperglycaemia and MRONJ cannot be established with certainty. Second, glycaemic status was assessed primarily using plasma FPG values obtained from available medical records. Although routinely used in clinical practice, FPG reflects glucose metabolism at a single time point and does not provide information on long-term glycaemic control. Furthermore, periodontal status and several potentially relevant lifestyle and socioeconomic factors were not systematically recorded. Finally, as the studies were conducted at a single tertiary referral centre, the generalisability of the findings may be limited.

5.4. Future Perspectives

As part of the translational aspect of this doctoral research, the key findings and scientific results of our research group were summarized and translated into evidence-based professional recommendations aimed at strengthening the integration of oral health into systemic disease management. These recommendations were submitted for consideration during the development of the Hungarian National Diabetes Strategy and

emphasize the importance of oral health screening, dental prevention and early detection of metabolic disturbances in patients with DM. According to official governmental feedback, these proposals are planned to be incorporated into the forthcoming National Diabetes Strategy, highlighting the potential clinical and public health relevance of the present research. Future research will focus on prospective clinical studies investigating the relationship between hyperglycaemia and MRONJ. Particular attention will be given to the role of long-term glycaemic control assessed by HbA1c, as well as to the histological and immunohistochemical characteristics of MRONJ lesions in patients with impaired glucose metabolism. Further studies are also planned to evaluate the effects of metformin on bone regeneration and wound healing, given its potential osteogenic and anti-inflammatory properties. Another area of interest is the development of novel supportive therapies aimed at improving oral wound healing. Recent studies have suggested that Nano-Bio Fusion (NBF) gel may have beneficial effects on tissue regeneration and local inflammation control. Given the central role of impaired healing in both DM and MRONJ, further research is warranted to evaluate the potential application of NBF gel as an adjunctive therapeutic option in these conditions [82, 83].

As the prevalence of DM continues to increase worldwide and the use of antiresorptive and antiangiogenic therapies is becoming increasingly common, improved risk assessment, prevention and interdisciplinary patient management will remain important priorities. Continued clinical and translational research may contribute to the development of more effective preventive strategies and individualized treatment approaches for patients at risk of MRONJ.

6. Conclusions

The cumulative findings of this doctoral research provide evidence that hyperglycaemia and impaired glucose metabolism are important factors in both the development and recurrence of MRONJ. Dysglycaemia appears to contribute to impaired wound healing, vascular dysfunction and altered bone metabolism, all of which are considered central mechanisms in the pathogenesis of MRONJ. Across the studies included in this dissertation, patients with abnormal glucose metabolism consistently demonstrated a higher prevalence of MRONJ and a higher risk of recurrence than normoglycaemic individuals, particularly following invasive dentoalveolar procedures. An important observation of the present research is that disturbances of glucose metabolism were more closely associated with MRONJ than the diagnosis of DM alone. This finding suggests that metabolic control may be of greater clinical relevance than the mere presence of diabetes and highlights the importance of identifying previously unrecognized hyperglycaemia in patients receiving antiresorptive or antiangiogenic therapy. From a clinical perspective, these findings emphasise the importance of comprehensive patient assessment. In addition to detailed dental and medical history taking, evaluation of glycaemic status and systemic comorbidities should form an integral part of preoperative risk assessment. Preventive dental care before the initiation of antiresorptive treatment, careful surgical planning, optimisation of metabolic status and close postoperative follow-up remain essential components of MRONJ prevention and management. Lifestyle-related factors, including smoking and alcohol consumption, may further contribute to impaired healing and increase the overall risk profile of susceptible patients. Age, sex, the type and route of antiresorptive therapy, treatment duration and the underlying systemic disease were also associated with variations in MRONJ occurrence and recurrence, further supporting the multifactorial nature of the disease. The analysis of patients treated before and after the COVID-19 pandemic revealed a marked increase in MRONJ cases during the post-pandemic period, accompanied by higher FPG levels and changes in lesion distribution. These observations highlight the potential impact of disruptions in healthcare delivery and delayed access to dental care on patients at risk of MRONJ. Overall, the findings of this dissertation indicate that hyperglycaemia should be regarded as a clinically relevant risk factor in patients receiving antiresorptive or antiangiogenic therapy. The results further underline the importance of interdisciplinary

collaboration among dentists, oral and maxillofacial surgeons, diabetologists, endocrinologists, oncologists and primary care physicians in the prevention and management of MRONJ. Patients with impaired glucose regulation represent a particularly vulnerable subgroup and may benefit from closer monitoring and individualized treatment strategies. Beyond its scientific contribution, this research also had translational relevance. The main findings and professional recommendations derived from this work contributed to proposals submitted for consideration during the development of the Hungarian National Diabetes Strategy, supporting the integration of oral health into national diabetes prevention and management programs. Taken together, this work demonstrates that incorporating metabolic assessment into routine dental and maxillofacial care may contribute to improved risk assessment, earlier identification of vulnerable patients and ultimately better clinical outcomes for individuals at risk of MRONJ.

7. Summary

This doctoral research investigated the relationship between hyperglycaemia and MRONJ and provides evidence that impaired glucose metabolism represents an important contributing factor in both the development and recurrence of the disease. The findings indicate that disturbances in glucose homeostasis may adversely affect jawbone healing and remodelling, thereby increasing susceptibility to MRONJ and unfavourable clinical outcomes. In particular, dysglycaemic patients demonstrated a higher prevalence of MRONJ and a greater likelihood of recurrence following surgical treatment. The results highlight the importance of incorporating metabolic assessment into routine dental and oral surgical care, especially in patients receiving antiresorptive or antiangiogenic therapy. Comprehensive patient evaluation should include not only dental and medical history but also assessment of glycaemic status and other relevant systemic risk factors. Early identification of hyperglycaemia may facilitate more accurate risk stratification and support the implementation of preventive measures before invasive dentoalveolar procedures. The studies included in this dissertation further demonstrate that preventive dental care, careful treatment planning and structured postoperative follow-up remain essential components of MRONJ prevention and management. Patients with DM, IFG or other disturbances of glucose metabolism represent a particularly vulnerable subgroup that may benefit from closer monitoring and individualized treatment approaches. As the prevalence of DM and hyperglycaemia continues to increase worldwide and the use of antiresorptive and antiangiogenic therapies expands with advances in modern oncology and osteoporosis management, the clinical burden of MRONJ is expected to grow. These developments underscore the importance of improving professional awareness and strengthening interdisciplinary collaboration among dentists, oral and maxillofacial surgeons, diabetologists, endocrinologists, oncologists and primary care physicians. Such cooperation will be essential for optimizing prevention, facilitating early diagnosis and improving outcomes in patients at increased risk of MRONJ.

8. References

1. AlRowis R, Aldawood A, AlOtaibi M, Alnasser E, AlSaif I, Aljaber A, Natto Z. Medication-related osteonecrosis of the jaw (MRONJ): a review of pathophysiology, risk factors, preventive measures and treatment strategies. *Saudi Dent J*. 2022 Mar;34(3):202–10.
2. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O’Ryan F; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg*. 2014 Oct;72(10):1938–56.
3. Limones A, Sáez-Alcaide LM, Díaz-Parreño SA, Helm A, Bornstein MM, Molinero-Mourelle P. Medication-related osteonecrosis of the jaws in cancer patients treated with denosumab vs zoledronic acid: a systematic review and meta-analysis. *Med Oral Patol Oral Cir Bucal*. 2020 May 1;25(3):e326–e336.
4. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg*. 2003 Sep;61(9):1115–7.
5. Khan AA, Rios LP, Sándor GK, Khan N, Peters E, Rahman MO, Clokie CM, Dore E, Dubois S. Bisphosphonate-associated osteonecrosis of the jaw in Ontario: a survey of oral and maxillofacial surgeons. *J Rheumatol*. 2011 Jul;38(7):1396–402.
6. Hellstein JW, Adler RA, Edwards B, Jacobsen PL, Kalmar JR, Koka S, Migliorati CA, Ristic H; American Dental Association Council on Scientific Affairs Expert Panel on Antiresorptive Agents. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: executive summary of recommendations from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc*. 2011 Nov;142(11):1243–51.
7. Cerrato A, Zanette G, Boccuto M, Angelini A, Valente M, Bacci C. Actinomyces and MRONJ: a retrospective study and a literature review. *J Stomatol Oral Maxillofac Surg*. 2021 Nov;122(5):499–504.

- 8.** Jiang A, Zhang Z, Qiu X, Guo Q. Medication-related osteonecrosis of the jaw (MRONJ): a review of pathogenesis hypothesis and therapy strategies. *Arch Toxicol*. 2024 Mar;98(3):689–708.
- 9.** Sacco R, Woolley J, Patel G, Calasans-Maia MD, Yates J. Systematic review of medication-related osteonecrosis of the jaw (MRONJ) in patients undergoing only antiangiogenic drug therapy: surgery or conservative therapy? *Br J Oral Maxillofac Surg*. 2022 Feb;60(2):e216–e230.
- 10.** Chang J, Hakam AE, McCauley LK. Current understanding of the pathophysiology of osteonecrosis of the jaw. *Curr Osteoporos Rep*. 2018 Oct;16(5):584–95.
- 11.** Ofek P, Tiram G, Satchi-Fainaro R. Angiogenesis regulation by nanocarriers bearing RNA interference. *Adv Drug Deliv Rev*. 2017 Sep 15;119:3–19.
- 12.** Mijiritsky E, Assaf HD, Kolerman R, Mangani L, Ivanova V, Zlatev S. Autologous platelet concentrates (APCs) for hard tissue regeneration in oral implantology, sinus floor elevation, peri-implantitis, socket preservation and medication-related osteonecrosis of the jaw (MRONJ): a literature review. *Biology (Basel)*. 2022 Aug 23;11(9):1254.
- 13.** Anastasilakis AD, Pepe J, Napoli N, Palermo A, Magopoulos C, Khan AA, Zillikens MC, Body JJ. Osteonecrosis of the jaw and antiresorptive agents in benign and malignant diseases: a critical review organized by the ECTS. *J Clin Endocrinol Metab*. 2022 Apr 19;107(5):1441–60.
- 14.** Nicolatou-Galitis O, Schiødt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, Niepel D, Van den Wyngaert T. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019 Feb;127(2):117–35.
- 15.** Khan AA, Morrison A, Hanley DA, et al.; International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res*. 2015 Jan;30(1):3–23.

- 16.** Mbese Z, Aderibigbe BA. Bisphosphonate-based conjugates and derivatives as potential therapeutic agents in osteoporosis, bone cancer and metastatic bone cancer. *Int J Mol Sci.* 2021 Jun 26;22(13):6869.
- 17.** Jain S. Prevention and management of denosumab discontinuation rebound fractures. *Endocrinol Metab Clin North Am.* 2024 Dec;53(4):559–83.
- 18.** Srivastava A, Nogueras Gonzalez GM, Geng Y, et al. Prevalence of medication-related osteonecrosis of the jaw in patients treated with sequential antiresorptive drugs: systematic review and meta-analysis. *Support Care Cancer.* 2021 May;29(5):2305–17.
- 19.** Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: different mechanisms of action and effects. *Bone.* 2011 Apr 1;48(4):677–92.
- 20.** Matuoka JY, Kahn JG, Secoli SR. Denosumab versus bisphosphonates for the treatment of bone metastases from solid tumors: a systematic review. *Eur J Health Econ.* 2019 Jun;20(4):487–99.
- 21.** Guarneri V, Miles D, Robert N, Diéras V, Glaspy J, Smith I, Thomssen C, Biganzoli L, Taran T, Conte P. Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. *Breast Cancer Res Treat.* 2010 Jul;122(1):181–8.
- 22.** Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg.* 2004 May;62(5):527–34.
- 23.** Khosla S, Burr D, Cauley J, et al.; American Society for Bone and Mineral Research. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force. *J Bone Miner Res.* 2007 Oct;22(10):1479–91.

- 24.** Khan AA, Morrison A, Kendler DL, Rizzoli R, Hanley DA, Felsenberg D, McCauley LK, O’Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Dabagh RA, Davison KS, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J; International Task Force on Osteonecrosis of the Jaw. Case-based review of osteonecrosis of the jaw (ONJ) and application of the international recommendations for management from the International Task Force on ONJ. *J Clin Densitom.* 2017 Jan–Mar;20(1):8–24.
- 25.** Ruggiero SL, Dodson TB, Assael LA, et al.; AAOMS Task Force. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaw—2009 update. *Aust Endod J.* 2009 Dec;35(3):119–30.
- 26.** Ruggiero SL, Dodson TB, Aghaloo T, Carlson ER, Ward BB, Kademani D. American Association of Oral and Maxillofacial Surgeons’ position paper on medication-related osteonecrosis of the jaws—2022 update. *J Oral Maxillofac Surg.* 2022 May;80(5):920–43.
- 27.** Kujanpää M, Vuollo V, Tiisanoja A, Laitala ML, Sándor GK, Karki S. Incidence of medication-related osteonecrosis of the jaw and associated antiresorptive drugs in adult Finnish population. *Sci Rep.* 2025 May 19;15(1):17377.
- 28.** McGowan K, McGowan T, Ivanovski S. Risk factors for medication-related osteonecrosis of the jaws: a systematic review. *Oral Dis.* 2018 May;24(4):527–36.
- 29.** Radi S, Jans DS, Moreno-Rabié C, Beuselinck B, Cleynen I, Jacobs R. Understanding the genetic basis of medication-related osteonecrosis of the jaw: a systematic review. *Bone.* 2025 Dec;201:117623.
- 30.** Bedogni A, Mauceri R, Fusco V, Bertoldo F, Bettini G, Di Fede O, Lo Casto A, Marchetti C, Panzarella V, Saia G, Vescovi P, Campisi G. Italian position paper (SIPMO-

SICMF) on medication-related osteonecrosis of the jaw (MRONJ). *Oral Dis.* 2024 Sep;30(6):3679–3709.

31. Hallmer F, Andersson G, Götrick B, Warfvinge G, Anderud J, Bjørnland T. Prevalence, initiating factor and treatment outcome of medication-related osteonecrosis of the jaw: a 4-year prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2018 Dec;126(6):477–85.

32. Ishimaru M, Ono S, Morita K, Matsui H, Hagiwara Y, Yasunaga H. Prevalence, incidence rate and risk factors of medication-related osteonecrosis of the jaw in patients with osteoporosis and cancer: a nationwide population-based study in Japan. *J Oral Maxillofac Surg.* 2022 Apr;80(4):714–27.

33. Yamazaki T, Yamori M, Ishizaki T, Asai K, Goto K, Takahashi K, Nakayama T, Bessho K. Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study. *Int J Oral Maxillofac Surg.* 2012 Nov;41(11):1397–403.

34. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2011 Jan;34(Suppl 1):S62–9.

35. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001 Dec 13;414(6865):813–20.

36. Rümenapf G, Morbach S, Rother U, Uhl C, Görtz H, Böckler D, Behrendt CA, Hochlenert D, Engels G, Sigl M; Kommission PAVK und Diabetisches Fußsyndrom der DGG e. V. Diabetisches Fußsyndrom – Teil 1: Definition, Pathophysiologie, Diagnostik und Klassifikation. *Chirurg.* 2021 Jan;92(1):81–94.

37. Lu M, Kuroki M, Amano S, Tolentino M, Keough K, Kim I, Bucala R, Adamis AP. Advanced glycation end products increase retinal vascular endothelial growth factor expression. *J Clin Invest.* 1998 Mar 15;101(6):1219–24.

- 38.** American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024 Jan 1;47(Suppl 1):S20–42.
- 39.** Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022 Jan;183:109119.
- 40.** Kempler P, Putz Z, Kiss Z, Ábrahám G, Hidvégi T, Jermendy G. Trends in the incidence and prevalence of type 2 diabetes mellitus in Hungary between 2001 and 2014: results from the National Health Insurance Fund database. *Diabetologia Hung*. 2017;25(2):109–17.
- 41.** Rooney MR, Fang M, Ogurtsova K, Ozkan B, Echouffo-Tcheugui JB, Boyko EJ, Magliano DJ, Selvin E. Global prevalence of prediabetes. *Diabetes Care*. 2023 Jul 1;46(7):1388–94.
- 42.** Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, Pavkov ME, Ramachandaran A, Wild SH, James S, Herman WH, Zhang P, Bommer C, Kuo S, Boyko EJ, Magliano DJ. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract*. 2022 Jan;183:109119.
- 43.** Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. *Cochrane Database Syst Rev*. 2018 Oct 29;10(10):CD012661.
- 44.** Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: an overview. *Avicenna J Med*. 2020 Oct 13;10(4):174–88.

45. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care*. 2009 Jul;32(7):1327–34.
46. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes Care*. 2022 Jan 1;45(Suppl 1):S17–38.
47. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2010 Jan;33(Suppl 1):S62–9.
48. Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K, Tsuji H, Kodama S, Hsieh SD, Mori Y, Shimano H, Yamada N, Kosaka K, Sone H. HbA1c 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *Lancet*. 2011 Jul 9;378(9786):147–55.
49. Luo H, Wu B, Kamer AR, Adhikari S, Sloan F, Plassman BL, Tan C, Qi X, Schwartz MD. Oral health, diabetes and inflammation: effects of oral hygiene behaviour. *Int Dent J*. 2022 Aug;72(4):484–90.
50. Ho-Pham LT, Nguyen UDT, Tran TX, Nguyen TV. Discordance in the diagnosis of diabetes: comparison between HbA1c and fasting plasma glucose. *PLoS One*. 2017 Aug 17;12(8):e0182192.
51. Preshaw PM, Alba AL, Herrera D, et al. Periodontitis and diabetes: a two-way relationship. *Diabetologia*. 2012 Jan;55(1):21–31.
52. Jiang ZL, Cui YQ, Gao R, et al. Study of TNF- α , IL-1 β and LPS levels in the gingival crevicular fluid of a rat model of diabetes mellitus and periodontitis. *Dis Markers*. 2013;34(5):295–304.

- 53.** Nascimento GG, Leite FRM, Vestergaard P, Scheutz F, López R. Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies. *Acta Diabetol.* 2018 Jul;55(7):653–67.
- 54.** Ship JA. Diabetes and oral health: an overview. *J Am Dent Assoc.* 2003 Oct;134(Spec No):4S–10S.
- 55.** Triebel Z, Bencze B, Bányai D, et al. Poor glycemic control impairs oral health in children with type 1 diabetes mellitus: a systematic review and meta-analysis. *BMC Oral Health.* 2024;24:748.
- 56.** Vegh A, Vegh D, Banyai D, et al. Point-of-care HbA1c measurements in oral cancer and control patients in Hungary. *In Vivo.* 2022 Sep–Oct;36(5):2248–54.
- 57.** Vegh A, Banyai D, Ujpal M, et al. Prevalence of diabetes and impaired fasting glycemia in patients with oral cancer: a retrospective study in Hungary. *Anticancer Res.* 2022 Jan;42(1):109–13.
- 58.** Haba KS, Bencze B, Kammerhofer G, et al. Locally delivered 1% metformin gel improves periodontal parameters: a systematic review and meta-analysis. *Saudi Dent J.* 2025 Aug 20;37(7–9):40.
- 59.** Végh D, Bencze B, Banyai D, et al. Preoperative HbA1c and blood glucose measurements in diabetes mellitus before oral surgery and implantology treatments. *Int J Environ Res Public Health.* 2023 Mar 8;20(6):4745.
- 60.** Peer A, Khamaisi M. Diabetes as a risk factor for medication-related osteonecrosis of the jaw. *J Dent Res.* 2015 Feb;94(2):252–60.
- 61.** Kammerhofer G, Somogyi KS, Biczó Z, Végh D, Ujpál M, Vaszilkó MT, Bányai D, Füzes A, Végh Á, Joób-Fancsaly Á, Németh Z. A gyógyszer okozta állcsontnekrózis és

a vércukorszint kapcsolata: retrospektív epidemiológiai vizsgálat. *Orv Hetil.* 2022 Apr 10;163(15):599–605.

62. Kammerhofer G, Vegh D, Bányai D, Végh Á, Joob-Fancsaly A, Hermann P, Geczi Z, Hegedus T, Somogyi KS, Bencze B, Biczó Z, Juhász DH, Zaborszky P, Ujpál M, Vaszilkó MT, Németh Z. Association between hyperglycemia and medication-related osteonecrosis of the jaw (MRONJ). *J Clin Med.* 2023 Apr 19;12(8):2976.

63. Kammerhofer G, Vegh D, Papocsi P, Major M, Fuzes P, Vaszilko M, Ujpal M, Haba KS, Szabo G, Nemeth Z. Emergency dental care during the SARS-CoV-2 pandemic and its effect on medication-related osteonecrosis of the jaw: a retrospective study in Hungary. *Appl Sci.* 2024;14:11691.

64. Garzino Demo P, Bojino A, Roccia F, Malandrino MC, Cocis S, Ramieri G. Different presentation and outcomes in the surgical treatment of advanced MRONJ in oncological and nononcological patients taking or not taking corticosteroid therapy. *Biomed Res Int.* 2021 Aug 25;2021:7855497.

65. Kajizono M, Sada H, Sugiura Y, et al. Incidence and risk factors of osteonecrosis of the jaw in advanced cancer patients after treatment with zoledronic acid or denosumab: a retrospective cohort study. *Biol Pharm Bull.* 2015;38(12):1850–5.

66. Svejda B, Muschitz Ch, Gruber R, et al. Positionspapier zur medikamentenassoziierten Osteonekrose des Kiefers (MRONJ). *Wien Med Wochenschr.* 2016 Feb;166(1–2):68–74.

67. Belch M, Wszyńska-Pawełec G, Szuta M, et al. Analysis of potential risk factors for the development of medication-related osteonecrosis of the jaw. *Dent Med Probl.* 2025 Mar 31.

- 68.** Rahimi-Nedjat RK, Sagheb K, Pabst A, Olk L, Walter C. Diabetes mellitus and its association with the occurrence of medication-related osteonecrosis of the jaw. *Dent J (Basel)*. 2016 May 31;4(2):17.
- 69.** Park SM, Lee JH. Effects of type 2 diabetes mellitus on osteoclast differentiation, activity and cortical bone formation in postmenopausal MRONJ patients. *J Clin Med*. 2022 Apr 23;11(9):2377.
- 70.** Khamaisi M, Regev E, Yarom N, et al. Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. *J Clin Endocrinol Metab*. 2007 Mar;92(3):1172–5.
- 71.** Molcho S, Peer A, Berg T, Futerman B, Khamaisi M. Diabetes microvascular disease and the risk for bisphosphonate-related osteonecrosis of the jaw: a single-center study. *J Clin Endocrinol Metab*. 2013 Nov;98(11):E1807–12.
- 72.** Urade M. [Diabetes mellitus and bisphosphonate-related osteonecrosis of the jaws]. *Clin Calcium*. 2009 Sep;19(9):1332–8.
- 73.** Li W, Chai JL, Li Z, et al. No evidence of genetic causality between diabetes and osteonecrosis: a bidirectional two-sample Mendelian randomization analysis. *J Orthop Surg Res*. 2023 Dec 16;18(1):970.
- 74.** Zhao D, Zhang F, Wang B, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). *J Orthop Translat*. 2020 Jan 6;21:100–10.
- 75.** Migliorini F, Maffulli N, Baroncini A, Eschweiler J, Tingart M, Betsch M. Prognostic factors in the management of osteonecrosis of the femoral head: a systematic review. *Surgeon*. 2023 Apr;21(2):85–98.

- 76.** Konarski W, Poboży T, Kotela A, et al. Does diabetes mellitus increase the risk of avascular osteonecrosis? A systematic review and meta-analysis. *Int J Environ Res Public Health*. 2022 Nov 18;19(22):15219.
- 77.** Dar-Odeh N, Bobamuratova DT, Alnazzawi A, et al. Jaw-related complications in COVID-19 patients: a systematic review. *Cranio*. 2024 Sep;42(5):630–7.
- 78.** Morales A, Corral-Núñez C, Galaz C, et al. Impact of COVID-19 pandemic on quality of life of type II diabetes patients with periodontitis. *Front Oral Health*. 2021 Jun 4;2:682219.
- 79.** Vardas E, Adamo D, Canfora F, Kouri M, Delli K, Mignogna MD, Nikitakis N. Impact of COVID-19 disease on the development of osteomyelitis of jaws: a systematic review. *J Clin Med*. 2024 Jul 23;13(15):4290.
- 80.** Salve A, Gajghate A, Ansari S, Malik R, Uike S, Khetal N. Evaluation of blood glucose levels of COVID-19 patients before and after recovery regardless of their diabetic status: a retrospective cohort study. *J Datta Meghe Inst Med Sci Univ*. 2022 Aug;17(Suppl 1):S43–6.
- 81.** Roh T, Jo H, Kim JY. Maxillary bone necrosis in post-COVID-19 patients: possibility of medication-related osteonecrosis of jaws (MRONJ) induced by tocilizumab. *J Craniofac Surg*. 2024 Jul-Aug;35(5):e454–7.
- 82.** Szmironov G, Szmironova I, Nagy ÁT, Kammerhofer G, Németh Z, Zubor Z, Szabó G. Clinical outcomes associated with a propolis-based nano-formulated bioadhesive oral gel: a retrospective case series and non-randomized controlled study in patients with intellectual disabilities. *Gels*. 2026;12(6):490.
- 83.** Kammerhofer G, Nagy ÁT, Joób-Fancsaly Á, Szmironov G, Szmironova I, Végh D, Kivovics M, Szabó G, Németh Z. Clinical applications and therapeutic potential of Nano-

Bio Fusion gel in oral soft tissue therapy: a critical narrative review. Gels. 2026;12(5):429.

9. Bibliography of the candidate's publications

9.1. Publications related to the dissertation

1. Végh A, Banyai D, Ujpal M, Somogyi KS, Biczo Z, **Kammerhofer G**, Nemeth Z, Hermann P, Payer M, Vegh D. Prevalence of Diabetes and Impaired Fasting Glycemia in Patients with Oral Cancer: A Retrospective Study in Hungary. *Anticancer Research* 42(1): 109–113.

doi.org/10.21873/anticanres.15464 (2022)

IF: 2.0

2. **Kammerhofer G**, Somogyi KS, Biczó Z, Végh D, Ujpál M, Vaszilkó MT, Bányai D, Füzes A, Végh Á, Joób-Fancsaly Á, Németh Z. Relation between Medication-Related Jaw Necrosis and Blood Glucose Levels – A Retrospective Epidemiological Study. *Orvosi Hetilap* 163(15): 599–605.

doi.org/10.1556/650.2022.32445 (2022)

IF: 0.6

3. Végh A, Vegh D, Banyai D, **Kammerhofer G**, Biczo Z, Voros B, Ujpal M, Peña-Cardelles JF, Yonel Z, Joob-Fancsaly A, Hermann P, Nemeth Z. Point-of-Care HbA1c Measurements in Oral Cancer and Control Patients in Hungary. *In Vivo* 36(5): 2248–2254.

doi.org/10.21873/invivo.12952 (2022)

IF: 2.3

4. **Kammerhofer G**, Vegh D, Bányai D, Végh Á, Joob-Fancsaly A, Hermann P, Geczi Z, Hegedus T, Somogyi KS, Bencze B, Biczó Z, Juhász DH, Zaborszky P, Ujpál M, Vaszilkó MT, Németh Z. Association between Hyperglycemia and Medication-Related Osteonecrosis of the Jaw (MRONJ). *Journal of Clinical Medicine* 12(8): 2976.

doi.org/10.3390/jcm12082976 (2023)

IF: 3.0

5. Végh D, Bencze B, Banyai D, Vegh A, Rózsa N, Nagy-Dobó C, Biczó Z, **Kammerhofer G**, Ujpal M, Díaz-Agurto L, Pedrinaci I, Peña-Cardelles JF, Magrin GL, Padhye NM, Mente L, Payer M, Hermann P. Preoperative HbA1c and Blood Glucose Measurements in Diabetes Mellitus before Oral Surgery and Implantology Treatments. *International Journal of Environmental Research and Public Health* 20(6): 4745.

doi.org/10.3390/ijerph20064745 (2023)

IF: 0.0

6. **Kammerhofer G**, Vegh D, Papocsi P, Major M, Fuzes P, Vaszilko M, Ujpal M, Haba KS, Szabo G, Nemeth Z. Emergency Dental Care During the SARS-CoV-2 Pandemic and Its Effect on Medication-Related Osteonecrosis of the Jaw: A Retrospective Study in Hungary. *Applied Sciences* 14(24): 11691.

doi.org/10.3390/app142411691 (2024)

IF: 2.5

7. Haba KS, Bencze B, **Kammerhofer G**, Ujpal M, Bányai D, Hermann P, Antal S, Lipták K, Lipták L, Géczi Z, Hegedüs T, Végh Á, Haluszka D, Végh D, Alghamdi H. Locally Delivered 1% Metformin Gel Improves Periodontal Parameters: A Systematic Review and Meta-Analysis. *Saudi Dental Journal* 37(7-9): 40.

doi.org/10.1007/s44445-025-00045-8 (2025)

IF: 2.4

8. Lipták L, Lipták K, Hermann P, Rózsa NK, Somogyi KS, Végh Á, Bencze B, Kammerhofer G, Németh Z, Ujpal M, Somogyi A, Dobó Nagy C, Somogyi A, Merkely B, Moldován A, Hegedüs T, Bányai D, Kempler P, Végh D. Fogászati szűrővizsgálat fontossága a cukorbetegség ellátásában: a Semmelweis Egyetem Diabéteszes Fogászati Munkacsoportjának szerepe. *Diabetol Hung.* 2025;33(5):369–377.

doi.org/10.24121/dh.2025.28 (2025)

IF: 0.0

9. Szmirnov G, Szmirnova I, Nagy ÁT, **Kammerhofer G**, Németh Z, Zubor Z, Szabó G. Clinical outcomes associated with a propolis-based nano-formulated bioadhesive oral gel: a retrospective case series and non-randomized controlled study in patients with intellectual disabilities. Gels. 2026;12(6):490.

doi.org/10.3390/gels12060490 (2026)

IF: 6.4

10. Kammerhofer G, Nagy ÁT, Joób-Fancsaly Á, Szmirnov G, Szmirnova I, Végh D, Kivovics M, Szabó G, Németh Z. Clinical applications and therapeutic potential of Nano-Bio Fusion gel in oral soft tissue therapy: a critical narrative review. Gels. 2026;12(5):429.

doi.org/10.3390/gels12050429 (2026)

IF: 6.4

Total impact factor of original publications related to the topic of the dissertation: 25.6

9.2. Publications not related to the dissertation

1. Kammerhofer G, Bogdan S, Végh D, Ujpal M, Kiss D, Jakob NP, Fadgyas F, Szabo G, Nemeth Z. Solitary Ameloblastic Fibroma with Impacted Teeth: A Case Report. Journal of Cranio-Maxillofacial Surgery (2024) Jun 18:S1010-5182(24)00193-8.

doi.org/10.1016/j.jcms.2024.06.010 (2024)

IF: 2.1

2. Beszedics A, Koncz S, Cziriák N, **Kammerhofer G**, Bogdán S, Németh Z. A pericoronitis kezelési lehetőségei a fogászati gyakorlatban. Fogorvosi Szemle 117(1):22–25.

doi.org/10.33891/FSZ.117.1.22-25 (2024)

IF: 0.0

3. Major M, Mészáros B, Würsching T, Polyák M, **Kammerhofer G**, Németh Z, Szabó G, Nagy K. Evaluation of a Structured Light Scanner for 3D Facial Imaging: A Comparative Study with Direct Anthropometry. *Sensors (Basel)* 24(16):5286.

doi.org/10.3390/s24165286 (2024)

IF: 3.5

4. Major M, Polyák M, Würsching T, **Kammerhofer G**, Kocsis É, Németh Z, Szabó G. PRF Membranes Enhance Postoperative Recovery After Periapical Surgery: A Single-Blind Randomized Pilot Trial Using 3D Imaging. *Oral* 5(4):98.

doi.org/10.3390/oral5040098 (2025)

IF: 1.5

Total impact factor of other original publications not related to the topic of the dissertation: 7.1

9.3. Total cumulative impact factor

Total impact factor of the publications listed in the library record: 32.7

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The author takes full responsibility for the content of this dissertation.