Musculoskeletal Disorders and Dentistry

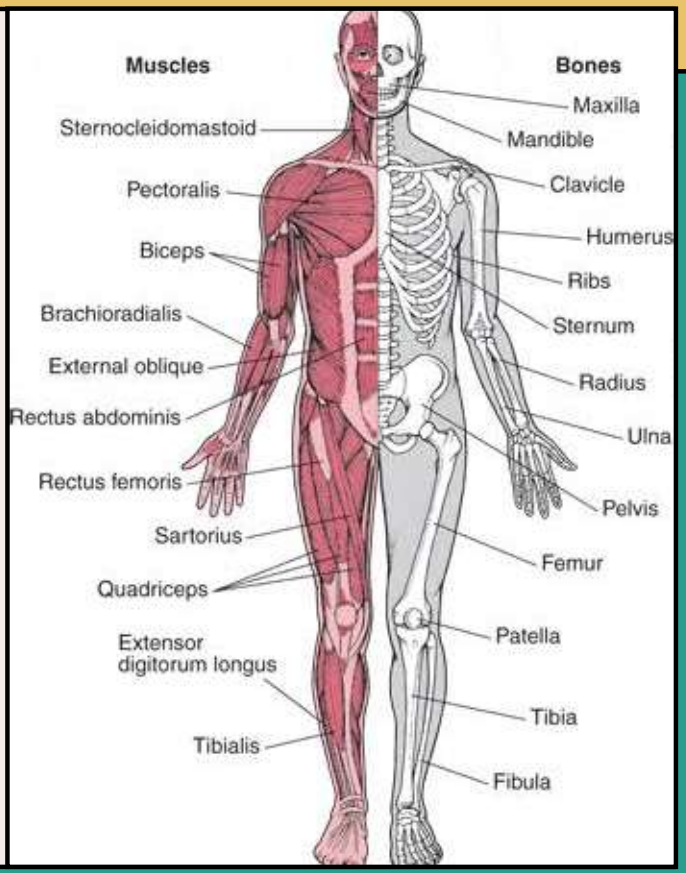
Dr Jee-Yun Leung

BDSc(Hons) MSc(SCD) DSCD(RCSEng) DClinDent(SND) MRACDS(SND) FANZASND

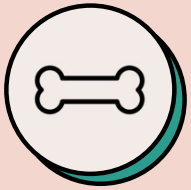
Specialist in Special Needs Dentistry

Senior Lecturer, The University of Western Australia

Consultant, Maxillofacial & Dental Dept, Fiona Stanley Hospital



Lecture Outcomes



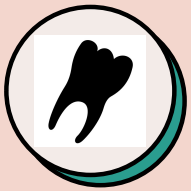
Discuss the specific characteristics and dental needs of individuals with joint (e.g. osteoarthritis, rheumatoid arthritis) and bone (e.g. osteoporosis) disorders



Perform a risk assessment and make appropriate treatment adaptations to ensure safe and effective dental care



Work a patient up prior to commencement of bone-modifying drugs (e.g. bisphosphonates, denosumab, romosozumab)



Assess MRONJ risk prior to invasive dental procedures, and institute preventive measures



Appreciate management options of MRONJ

Chronic musculoskeletal disorders

- muscles (eg sarcopenia)
- joints (eg osteoarthritis, rheumatoid arthritis)
- bones (eg osteoporosis, osteonecrosis, traumatic fractures)
- spine (eg back and neck pain)
- multiple body systems and locations (eg widespread and regional pain disorders, inflammatory or connective tissue diseases, systemic vasculitides, fibromyalgia).

Joint disorders

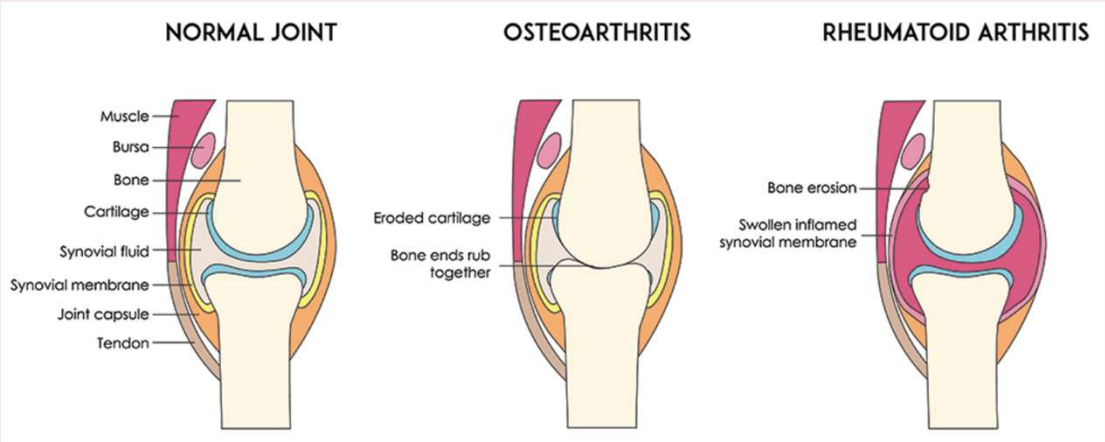
Osteoarthritis, Rheumatoid Arthritis



Arthritis

- **Osteoarthritis**: Degenerative joint disease. Key feature is degeneration of articular cartilage ("wear and tear").

- **Rheumatoid arthritis**: Systemic chronic immunologically mediated inflammatory disease affecting multiple tissues, but principally attacking the joints. Characterised by an autoantibody directed against IgG (rheumatoid factor, RF) → formation of immune complexes and activation of complement → synovial inflammation and destructive joint disease.

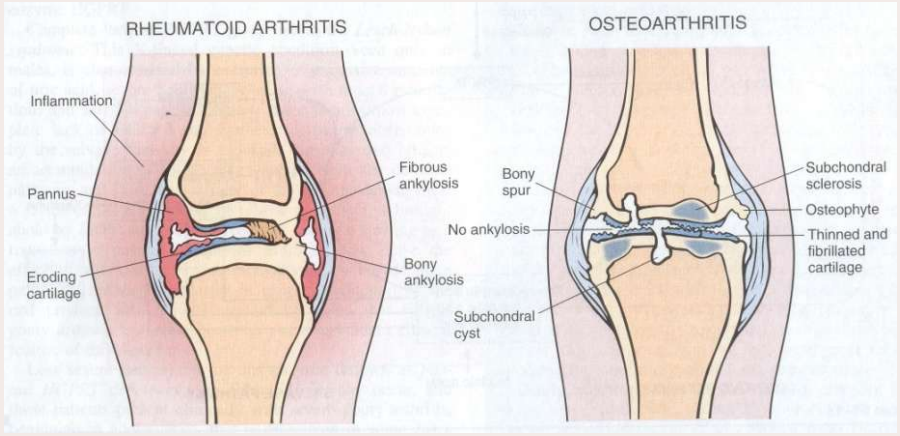


Arthritis

	Osteoarthritis	Rheumatoid Arthritis
Prevalence	Most common MSK disorder. 9% Australians	2nd most common MSK disorder (1/10 as common as OA). 1.8% Australians
Aetiology / Process	**Degenerative** Multifactorial Inflammatory result.	**Autoimmune** Immunogenetically driven Inflammatory cause.
Risk Groups	Age: >45yo M, >55yo F (onset late-middle or old age) Sex: Female (2:1) Genetic factors Obesity Joint malformation Trauma Occupation (labour, athletes) Haemochromatosis Paget disease Gout	Genetic predisposition (HLA-DR3 genotype) Sex: Female (3:1) Age: 30-40yo (onset middle age)

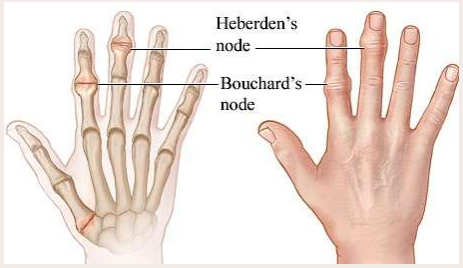
Arthritis

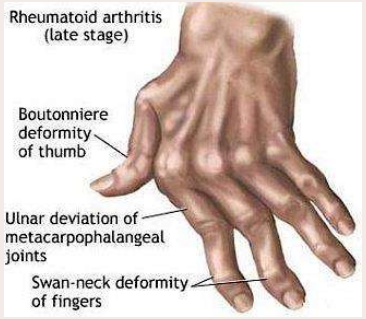
	Osteoarthritis	Rheumatoid Arthritis
Synovial joint target	Large or weight-bearing joints (hips, knees, lower back, feet) Frequently used (fingers) Traumatised joints	Small joints (hand and feet) Other joints with disease progression
Pathology	No pannus formation	Pannus formation
	No ankylosis	Bony and fibrous ankylosis
	Presenting symptoms - pain and stiffness of joints	Presenting symptoms – include malaise/fever in addition to pain and stiffness of joints
	Thinned and fibrillated cartilage	Eroded cartilage
	Bony spurs and osteophyte formation	-



Arthritis

	Osteoarthritis	Rheumatoid Arthritis
Onset	Slow, over years	Rapid, over weeks to months
Symmetry	Asymmetric	Symmetric
Pain, disability	+	++
Joint deformities	Nodes (firm / bony hard) • Heberden – DIP • Bouchard – PIP • 1st MCP joint at thumb base	Swellings (hot / tender) and deviations • Boutonniere deformity • Ulnar deviation MCP joints • Swan neck deformity fingers





Arthritis

	Osteoarthritis	Rheumatoid Arthritis
Systemic signs and symptoms	None	Malaise, fever, cervical lymphadenopathy. Obvious signs of inflammation. May be assoc with other autoimmune conditions (e.g. SLE, Sjogren's Dx).
Morning stiffness	Some	Pronounced (lasts >1hr)
Other body systems affected	None	Cardiovascular (conduction defects, myocarditis, pericarditis, valvulitis, vasculitis) Dermal/oral/para-oral (oral drug lesions, palmar erythema, Sjögren's, subcutaneous rheumatoid nodules, TMJ arthritis, vasculitis, rashes) Haematological (anaemia, leukopenia, thrombocytopenia); 1-2% have Felty's syndrome (results in neutropenia) Hepatic (abnormal liver function) Muscular (wasting, weakness) Neurological (benign trigeminal neuropathy, carpal tunnel, glove-and-stocking anaesthesia, various neuropathies) Ocular Osseous (osteoporosis) Renal (amyloidosis, nephropathy) Respiratory (bronchiolitis, fibrosis, lung nodules, pleurisy/pleural effusion) Non-specific (fatigue, fever, malaise, weight loss)

Arthritis

	Osteoarthritis	Rheumatoid Arthritis
General treatment		
Lifestyle	Exercise Weight control / diet	Exercise Weight control / diet Smoking cessation Psychosocial interventions
Physical	Appropriate footwear Walking aids Heat/cold application Topical analgesics Physiotherapy	Rest (during acute phase), exercises (between flare-ups) Splints TENS machine Thermotherapy Topical analgesics Physiotherapy
Medical	Anti-inflammatory medications (NSAIDs, COX-2 inhibitors) Glucosamine / fish oil supplementation Intra-articular corticosteroid injections	Anti-inflammatory medications (NSAIDs, COX-2 inhibitors) Glucosamine / fish oil supplementation Intra-articular corticosteroid injections *Disease-modifying anti-rheumatic drugs (DMARDs)
Surgery	Osteotomy Joint replacement (arthroplasty)	Arthrodesis Resection Synovectomy Joint replacement (arthroplasty)

Arthritis – Oral implications

Association with periodontitis: 2017 world workshop (AAP+ EFP)

- Albandar JM, Susin C, Hughes FJ. Manifestations of systemic diseases and conditions that affect the periodontal attachment apparatus: Case definitions and diagnostic considerations. J Periodontol. 2018 Jun;89 Suppl 1:S183-S203.

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Arthritis	Significant	Animal models, systematic review	Rheumatoid arthritis is an autoimmune disease; osteoarthritis is due to gradual deterioration of cartilage	• Joint pain, swelling, stiffness, redness, and limited motion • Increased risk for loss of periodontal attachment and alveolar bone	• Clinical history and physical examination for arthritis

Rheumatoid Arthritis – Drugs and oral side effects

Oral adverse effects of drugs used in RA treatment[2]	
Drug/Group	**Adverse Effects**
Antimalarials, eg. hydroxychloroquine (Plaquenil)	Lichenoid reactions Hyperpigmentation
Anti-TNF agents (most of the biological DMARDs)	Candidosis; other infections Erythema multiforme Ulceration
Corticosteroids	Candidosis
Gold	Lichenoid reactions Ulceration
Leflunomide	Candidosis Salivary swelling Taste disturbance
Methotrexate	Ulceration
NSAIDs	Lichenoid reactions Ulceration
Penicillamine (old DMARD; rarely used)	Lichenoid reactions Dysgeusia Severe ulceration

Rheumatoid Arthritis – Drugs and oral side effects

DMARDs	Conventional (1st line)	methotrexate*+; leflunomide* (Revlimid); sulfasalazine*; hydroxychloroquine (Plaquenil)
	Biological (2nd line)	abatacept* (Orencia); adalimumab*+ (Humira); certolizumab* (Cimzia); etanercept*+ (Enbrel); golimumab*+ (Simponi); infliximab*+ (Remicade); tocilizumab*+ (Actemra);
	Targeted (2nd line)	tofacitinib* (Xeljanz, Jakvinus)
Other agents		azathioprine*, cyclosporine*, gold salts

May combine with corticosteroids in induction phase

**agents causing immunocompromise*

+*Emerging case reports of MRONJ association*

↳ Associated with DMARDs

Arthritis – Dental Implications

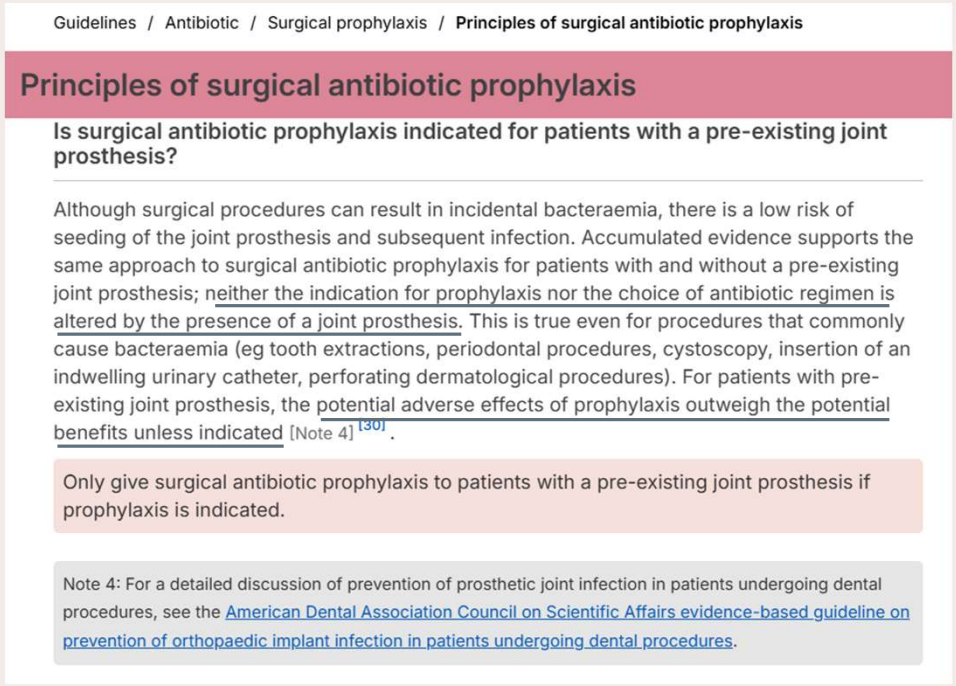
Dental implications (OA + RA)	Oral Manifestations: • Possible TMJ involvement: stiffness, trismus, often asymptomatic • Association with periodontal disease Access: • Patient positioning: Consider neck/knee/back/leg supports; Semi-supine position (if supine uncomfortable) • Timing of appointments: stiffness and pain greater in morning (book short appts in late morning or afternoon) Education: • Reduced manual dexterity: impact on oral self-care; consider TB adaptations Surgical: • Check medication list: - Bleeding implications (e.g. NSAIDs, glucosamine) - Long term corticosteroids (adrenal suppression → steroid supplementation) • Patients with prosthetic joints (see next slides)

Arthritis – Dental Implications

Additional for RA	Oral Manifestations: • Increased predisposition for Sjögren syndrome → increased dental caries and oral candidiasis risk • Severe cases: AOB, OSA • Oral adverse effects of medications (see table): e.g. stomatitis, MRONJ associations Surgery: • GA: difficult intubation, dislocation atlanto-axial joint or dens # (avoid sudden jerking extension of the neck) Spread: • Immunosuppression: increased risk oral candidiasis, treat infections aggressively, ?surgical antibiotic prophylaxis

Prosthetic joints

- Is surgical antibiotic prophylaxis indicated for patient with a pre-existing joint prosthesis?



Guidelines / Antibiotic / Surgical prophylaxis / **Principles of surgical antibiotic prophylaxis**

Principles of surgical antibiotic prophylaxis

Is surgical antibiotic prophylaxis indicated for patients with a pre-existing joint prosthesis?

Although surgical procedures can result in incidental bacteraemia, there is a low risk of seeding of the joint prosthesis and subsequent infection. Accumulated evidence supports the same approach to surgical antibiotic prophylaxis for patients with and without a pre-existing joint prosthesis; neither the indication for prophylaxis nor the choice of antibiotic regimen is altered by the presence of a joint prosthesis. This is true even for procedures that commonly cause bacteraemia (eg tooth extractions, periodontal procedures, cystoscopy, insertion of an indwelling urinary catheter, perforating dermatological procedures). For patients with pre-existing joint prosthesis, the potential adverse effects of prophylaxis outweigh the potential benefits unless indicated [Note 4] [30].

Only give surgical antibiotic prophylaxis to patients with a pre-existing joint prosthesis if prophylaxis is indicated.

Note 4: For a detailed discussion of prevention of prosthetic joint infection in patients undergoing dental procedures, see the American Dental Association Council on Scientific Affairs evidence-based guideline on prevention of orthopaedic implant infection in patients undergoing dental procedures.

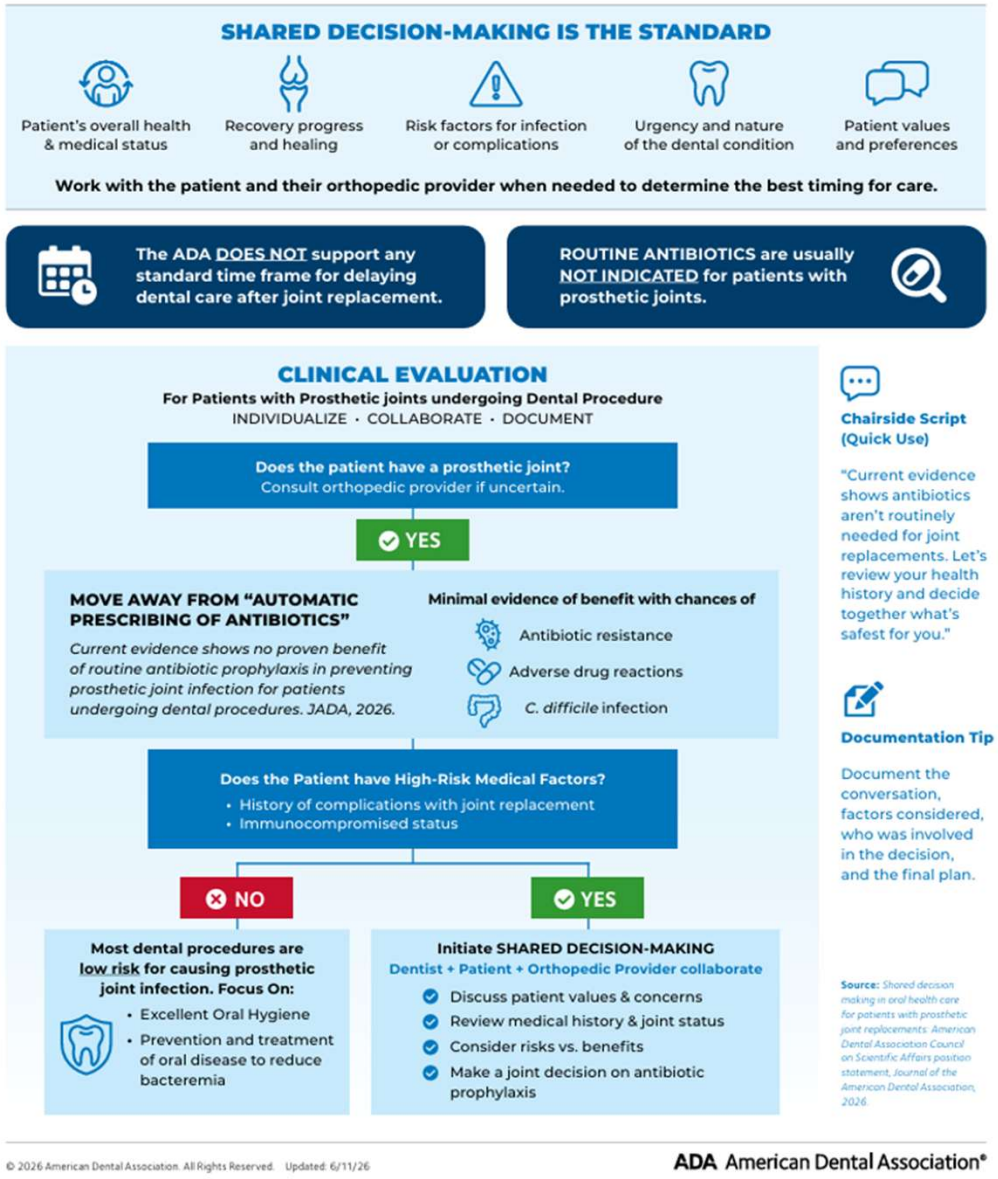
Upcoming lecture: Antibiotic Prophylaxis

Prosthetic joints

Is surgical antibiotic prophylaxis indicated for patient with a pre-existing joint prosthesis?

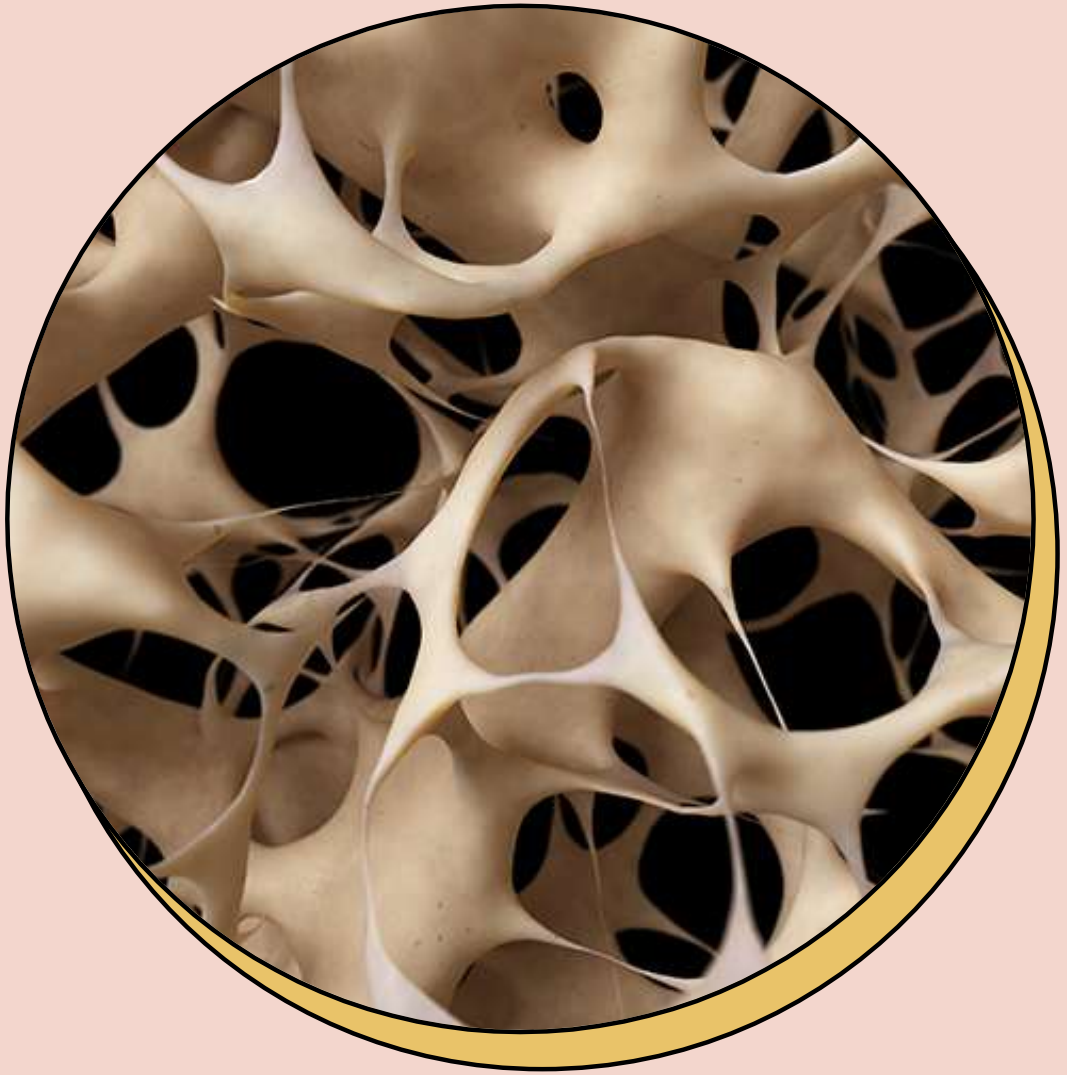
American Dental Association Council on Scientific Affairs evidence-based guideline on prevention of orthopaedic implant infection in patients undergoing dental procedures.

https://www.ada.org/resources/research/science/evidence-based-dental-research/antibiotics-to-prevent-prosthetic-joint-infection/



Bone disorders

Osteopenia, Osteoporosis

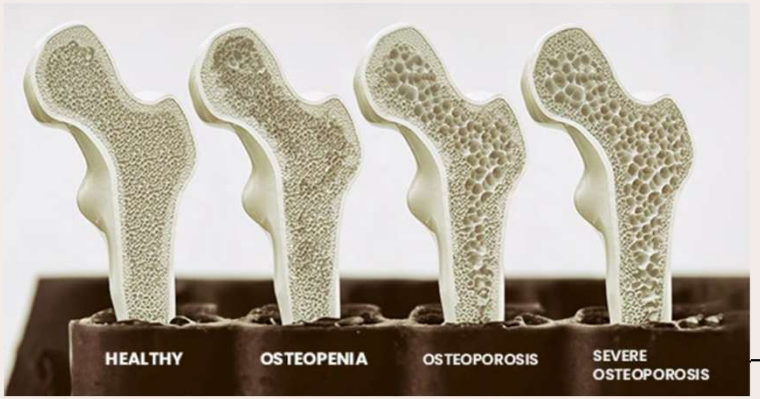


Osteopenia and Osteoporosis

Definition: Loss of bone mineral density characterised by reduced mineralised bone mass, especially common in older women.

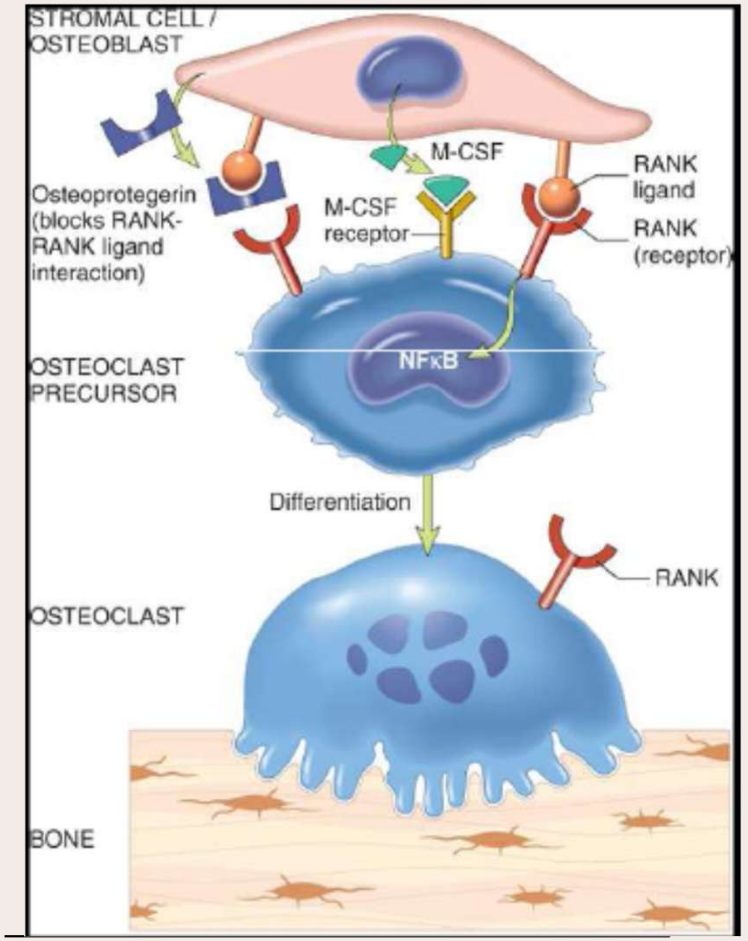
- **Osteopenia**: Bone densitometry: BMD 1 to 2.5 standard deviations (T score -1 to -2.5) below the peak bone mass of a 25yo individual.
  - precursor to osteoporosis

- **Osteoporosis**: Bone densitometry: BMD >2.5 standard deviations (T score < -2.5) below the peak bone mass of a 25yo individual.



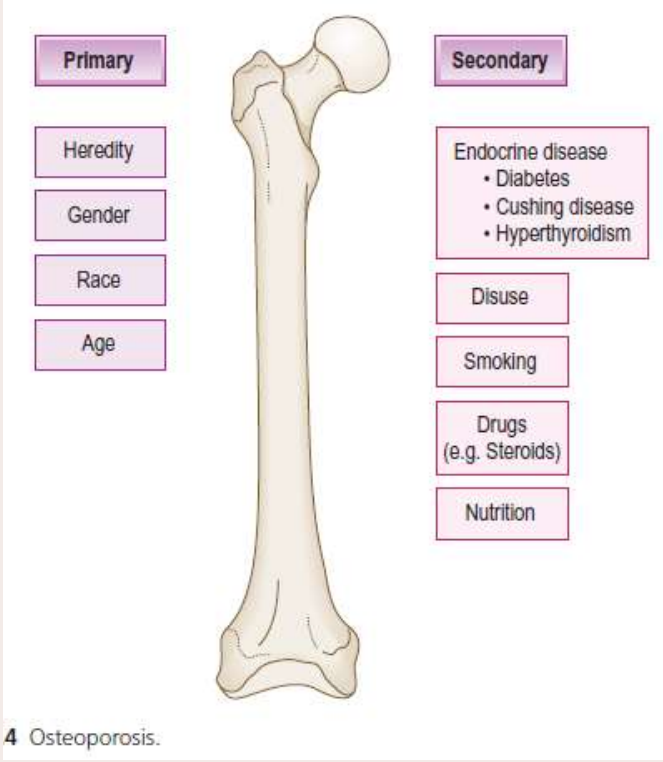
Osteoporosis - Aetiology

Metabolic bone disease that results from an imbalance in osteoblastic and osteoclastic activities.



Osteoporosis - Aetiology

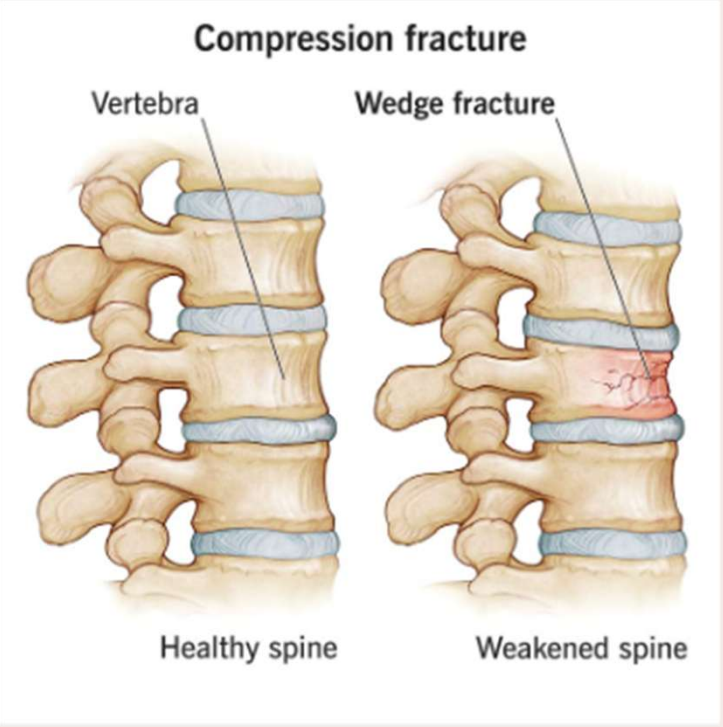
- Primary osteoporosis: androgen-oestrogen deficiency, lack of Vit D, lack of exercise
- Secondary osteoporosis: corticosteroid use, hyperparathyroidism, diabetes, chronic liver disease, malabsorption or hyperthyroidism, excessive smoking/alcohol



4 Osteoporosis.

Osteoporosis - Clinical Manifestations

- Usually asymptomatic.
- Increased bone fragility →
  - vertebral crush fractures
  - femoral neck, distal radius, humerus fractures
  - Hip fractures: 20% one-year mortality risk in older adults
- Persistent lower back pain
- Kyphosis and loss of height



Osteoporosis – General Management

Prevention

- Weight-bearing exercise
- Calcium supplementation (dairy, green veg)
- Hormone replacement therapy (HRT)
- Avoiding risk factors

Treatment

- Calcitonin
- Vitamin D
- Bisphosphonates
- Denosumab

Osteoporosis – Dental Implications

Association with periodontitis: 2017 world workshop (AAP+ EFP)

- Albandar JM, Susin C, Hughes FJ. Manifestations of systemic diseases and conditions that affect the periodontal attachment apparatus: Case definitions and diagnostic considerations. J Periodontol. 2018 Jun;89 Suppl 1:S183-S203.

Disorder	Strength of association	Quality of evidence	Biologic mechanisms	Case definitions	Diagnostic considerations
Osteoporosis	Significant	Animal models, surveys, longitudinal follow-up, case- control study, systematic reviews	Increased bone turnover leading to net bone loss, which can also be associated with other factors (such as estrogen level, vitamin D and calcium deficiency, lifestyle and behavioral factors)	• Decrease in bone mineral density and weakening of bone microarchitecture, leading to a high risk for bone fracture • Higher prevalence and severity of radio-graphic alveolar bone loss • No clear association with periodontitis (probing depth or clinical attachment loss)	• Clinical diagnosis

- Imaging: Jaws are thinned and granular. Lamina dura appears thinned. Maxillary sinus may extend between roots of molars. OPG may display spinal osteoporosis.

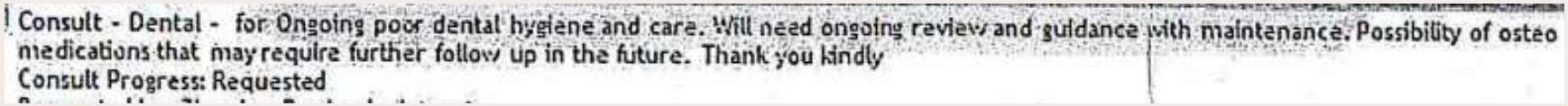
Osteoporosis – Dental Implications

- Oral Manifestation:
  - Association with periodontitis
  - Radiographic findings
- Access
  - Provide adequate mobility and positioning support (depending on severity of OP)
- Surgery
  - MRONJ risk (bone modifying drugs) – extractions, dentures, implants

Bone Modifying Drugs



A common referral to the dental clinic…


Consult - Dental - for Ongoing poor dental hygiene and care. Will need ongoing review and guidance with maintenance. Possibility of osteo medications that may require further follow up in the future. Thank you kindly
Consult Progress: Requested

Consult - Dental - for 89F from home w/ daughter, admitted for #NoF due to mechanical fall. Poor dentition. Ceased denosumab 1/52 ago. Seen by orthogeriatrics who would like to assess for suitability of resuming denosumab
Priority Level: Non-Urgent
Consult Progress: Requested

Example referrals to a SND clinic…

Reason for referral	Broken lower right second incisor - below gum line
Full medical history and diagnoses	Advanced myeloma on bisphosponates,
Medication list	Pomalidomide, Zometa, Dexamethasone, Targin, duloxetine
Dental history, including any dental treatment attempted	Dentist usually manages most care - OPG available on intelliviewre

64 YO M Admitted under Haematology [ ] for CAR T Cell Monitoring CARTITUDE10 Trial

===PMHx===
1.Multiple myeloma diagnosed November 2025.
1.1Pancytopenia, leukoerythroblastic blood film, large IgA paraprotein.
1.2 Bonemarrow shows diffuse myeloma.
1.3Compression fractures in the spine.
1.4Commenced VRd therapy (Dr Hutchinson).
1.5Consented for CARTITUDE-10 clinical trial.
2.Osteoporosis.
3. Fattyliver disease.
4.Hyperlipidaemia.
5.Ischaemic heart disease, on aspirin therapy
6. Atraumatic compression fractures T5, T7, T12, L1, L5. (fromapproximately February 2025)
6.1 Multiplepreviously vertebroplasties

On review today raised concern of loose tooth, right molar.

On examination:
Loose right upper molar
Nil petechiae
Nil jaw pain
Nil fevers
Isolated area of gum recession
Nil other loose teeth

We have requested a OPG prior to discharge and would appreciate a review from yourselves given the patients active immunotherapy and neutropaenia

Bloods
Neut 0.64
Hb 105
Lymp 0.16

MRONJ Definition

1. Current or previous treatment with **antiresorptive therapy alone** or in combination with **immune modulators or anti-angiogenic medications**
2. **Exposed bone**, or bone that can be probed through an intraoral or extraoral fistula in the **maxillofacial region** that has persisted for **more than 8 weeks**
3. **No history of radiation** therapy or **no metastatic disease** to the jaws.



(AAOMS 2022)

Clinical Presentation

Symptoms

- Jaw pain or toothache
- Halitosis
- Numbness or altered sensation (paraesthesia)





Signs

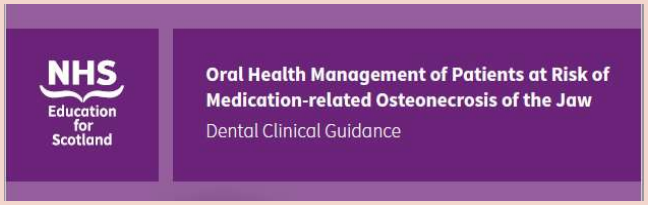
- Exposed bone in mandible or maxilla
- Localised swelling, tenderness of mucosa/gingiva
- Non healing extraction sockets
- Purulent discharge
- Pathological fracture
- Oro-cutaneous fistulae



American Association of Oral and Maxillofacial Surgeons' Position Paper on Medication-Related Osteonecrosis of the Jaws—2022 Update

Salvatore L. Ruggiero, DMD, MD, Thomas B. Dodson, DMD, MPH,† Tara Aghaloo, DDS, MD, PhD,‡ Eric R. Carlson, DMD, MD, EdM,§ Brent B. Ward, DDS, MD,‖ and Deepak Kademani, DMD, MD¶*

AAOMS 2022 Guidelines



NHS Education for Scotland

Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw

Dental Clinical Guidance

SDCEP 2017 Guidelines – Updated 2022



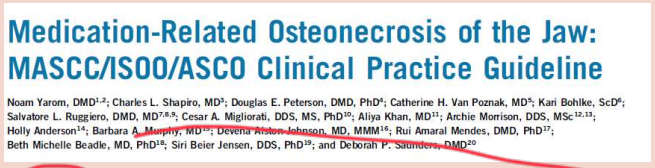
RACGP Royal Australian College of General Practitioners

HEALTHY BONES AUSTRALIA

Osteoporosis management and fracture prevention in postmenopausal women and men over 50 years of age

March 2024

RACGP 2024 Guidelines



Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline

Noam Yarom, DMD[1,2]; Charles L. Shapiro, MD[3]; Douglas E. Peterson, DMD, PhD[4]; Catherine H. Van Poznak, MD[5]; Kari Bohlke, ScD[6]; Salvatore L. Ruggiero, DMD, MD[7,8,9]; Cesar A. Migliorati, DDS, MS, PhD[10]; Aliya Khan, MD[11]; Archie Morrison, DDS, MSc[12,13]; Holly Anderson[14]; Barbara A. Murphy, MD[15]; Devena Ariston Johnson, MD, MMM[16]; Rui Amaral Mendes, DMD, PhD[17]; Beth Michelle Beadle, MD, PhD[18]; Siri Beier Jensen, DDS, PhD[19]; and Deborah P. Saunders, DMD[20]

Multinational Assoc of Supportive Care in Cancer, International Society of Oral Oncology, American Society of Clinical Oncology 2019



REVIEW

JBMR®

Diagnosis and Management of Osteonecrosis of the Jaw: A Systematic Review and International Consensus

Aliya A Khan, Archie Morrison, David A Hanley, Dieter Felsenberg, Laurie K McCauley, Felice O'Ryan, Ian R Reid, Salvatore L Ruggiero, Akira Taguchi, Sotirios Tetradis, Nelson B Watts, Maria Luisa Brandi, Edmund Peters, Teresa Guise, Richard Eastell, Angela M Cheung, Suzanne N Morin, Basel Masri, Cyrus Cooper, Sarah L Morgan, Barbara Obermayer-Pietsch, Bente L Langdahl, Rana Al Dabagh, K. Shawn Davison, David L Kendler, George K Sándor, Robert G Josse, Mohit Bhandari, Mohamed El Rabbany, Dominique D Pierroz, Riad Sulimani, Deborah P Saunders, Jacques P Brown, and Juliet Compston, on behalf of the International Task Force on Osteonecrosis of the Jaw

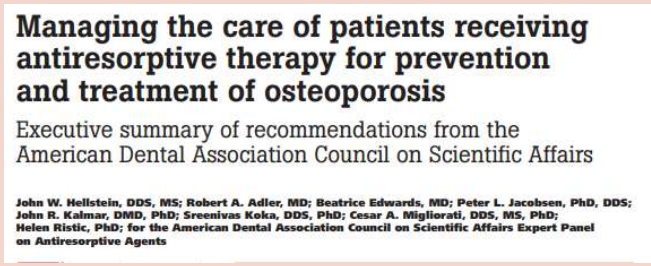
International Task Force on ONJ 2015 (ASBMR, AAOMS, CAOMS, CAOMP, ECTS, IBMS, IOF, ISCD, IAOMS, JSBMR, NOF, Osteoporosis Canada, PAOS, TES)



HEALTHY BONES AUSTRALIA | Protect Build Support

Healthy Bones Australia Consensus Statement: Medication-related Osteonecrosis of the Jaw (MRONJ) and Osteoporosis

Healthy Bones Australia 2026 ANZBMS, ADA, ESA, RHA



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

John W. Hellstein, DDS, MS; Robert A. Adler, MD; Beatrice Edwards, MD; Peter L. Jacobsen, PhD, DDS; John R. Kalmar, DMD, PhD; Sreenivas Koka, DDS, PhD; Cesar A. Migliorati, DDS, MS, PhD; Helen Ristic, PhD; for the American Dental Association Council on Scientific Affairs Expert Panel on Antiresorptive Agents

American Dental Association Council on Scientific Affairs 2011

Bone-Modifying Drugs (Anti-Resorptives – Mechanism of Action)

Bisphosphonates

- Inhibits enzymes essential to formation, recruitment and function of osteoclasts
- Binds to bone = High affinity for hydroxyapatite
- Persists in skeletal tissue for significant periods (e.g. alendronate ½ life ~10 years)

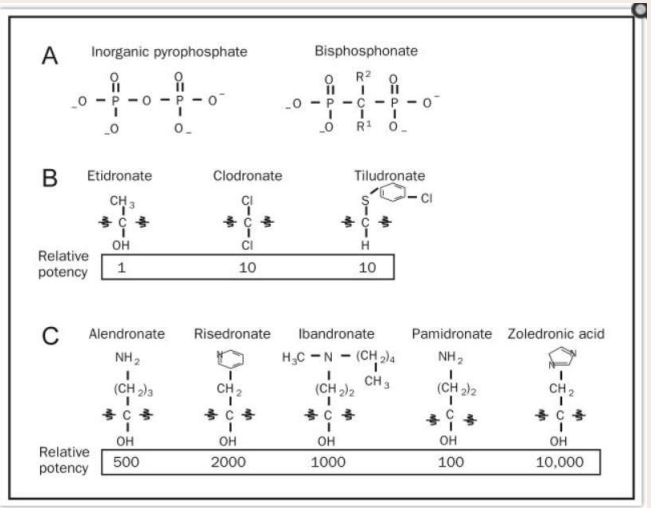
Denosumab

- Fully human monoclonal antibody which inhibits osteoclast function
- Binds to receptor activator nuclear κB factor ligand (RANKL)
- Does not bind to bone → effects on bone turnover diminish within 6 months

Romosozumab

- Monoclonal antibody
- Wnt pathway = binds to and inhibits sclerostin (produced by osteocytes)
- Potent bone anabolic agent (builds bone)
- Very high risk men and post-menopausal women of osteoporotic minimal trauma fracture

Bisphosphonates



Bisphosphonate structures and approximate relative potencies[6] for osteoclast inhibition.

Non-nitrogenous (1st gen): Direct action on osteoblastic cells to ↑ bone formation without anti-angiogenic effects
➔ NOT assoc with MRONJ

Nitrogenous (2nd 3rd gen): ↓ osteoclastic bone resorption by entering osteoclast
➔ assoc with MRONJ

Denosumab

Denosumab (Prolia®) – 6 monthly 60mg subcutaneous injection

- Osteoporosis



Denosumab (Xgeva®) – 4 weekly 120mg subcutaneous injection

- Solid cancer metastasis to bone
- Giant cell tumour of bone
- Hypercalcaemia of malignancy

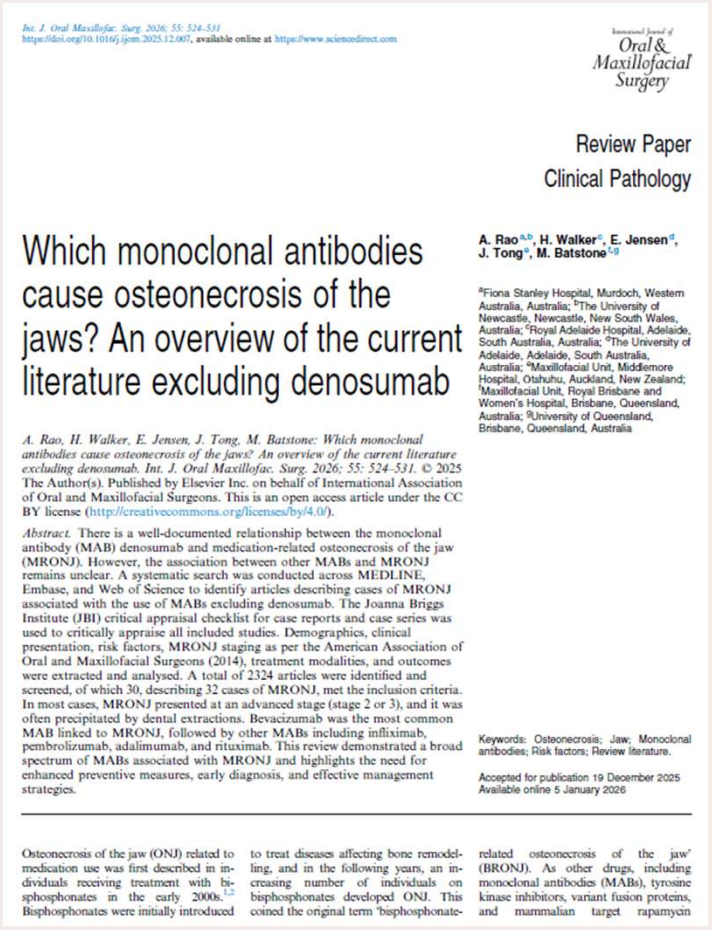


Other drugs associated with MRONJ

Well-documented	• **Antiangiogenic drugs**: bevacizumab, sunitinib, aflibercept
Possible association	• **protein kinase inhibitors**: axitinib, cabozantinib, dasatinib, everolimus, imatinib, osimertinib, pazopanib, regorafenib, sorafenib, temsirolimus • **monoclonal antibodies**: adalimumab, infliximab, ipilimumab, nivolumab, ranibizumab, rituximab, romosozumab, tocilizumab • **antimetabolites**: azacitidine, methotrexate • **tumour necrosis factor alpha inhibitor**: etanercept.

Scottish Dental Clinical Effectiveness Programme. Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw – Supplement March 2024 [Internet]. NHS Education for Scotland; 2024. Available from: https://www.sdcep.org.uk/media/d0sb4flf/sdcep-mronj-guidance-supplement_march-2024.pdf

Other drugs associated with MRONJ



Int. J. Oral Maxillofac. Surg. 2026; 55: 524–531
https://doi.org/10.1016/j.ijom.2025.12.007, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Review Paper
Clinical Pathology

Which monoclonal antibodies cause osteonecrosis of the jaws? An overview of the current literature excluding denosumab

A. Rao[a,b], H. Walker[c], E. Jensen[d], J. Tong[e], M. Batstone[f,g]

[a]Fiona Stanley Hospital, Murdoch, Western Australia, Australia; [b]The University of Newcastle, Newcastle, New South Wales, Australia; [c]Royal Adelaide Hospital, Adelaide, South Australia, Australia; [d]The University of Adelaide, Adelaide, South Australia, Australia; [e]Maxillofacial Unit, Middlemore Hospital, Otahuhu, Auckland, New Zealand; [f]Maxillofacial Unit, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia; [g]University of Queensland, Brisbane, Queensland, Australia

A. Rao, H. Walker, E. Jensen, J. Tong, M. Batstone: Which monoclonal antibodies cause osteonecrosis of the jaws? An overview of the current literature excluding denosumab. Int. J. Oral Maxillofac. Surg. 2026; 55: 524–531. © 2025 The Author(s). Published by Elsevier Inc. on behalf of International Association of Oral and Maxillofacial Surgeons. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Abstract. There is a well-documented relationship between the monoclonal antibody (MAB) denosumab and medication-related osteonecrosis of the jaw (MRONJ). However, the association between other MABs and MRONJ remains unclear. A systematic search was conducted across MEDLINE, Embase, and Web of Science to identify articles describing cases of MRONJ associated with the use of MABs excluding denosumab. The Joanna Briggs Institute (JBI) critical appraisal checklist for case reports and case series was used to critically appraise all included studies. Demographics, clinical presentation, risk factors, MRONJ staging as per the American Association of Oral and Maxillofacial Surgeons (2014), treatment modalities, and outcomes were extracted and analysed. A total of 2324 articles were identified and screened, of which 30, describing 32 cases of MRONJ, met the inclusion criteria. In most cases, MRONJ presented at an advanced stage (stage 2 or 3), and it was often precipitated by dental extractions. Bevacizumab was the most common MAB linked to MRONJ, followed by other MABs including infliximab, pembrolizumab, adalimumab, and rituximab. This review demonstrated a broad spectrum of MABs associated with MRONJ and highlights the need for enhanced preventive measures, early diagnosis, and effective management strategies.

Keywords: Osteonecrosis; Jaw; Monoclonal antibodies; Risk factors; Review literature.

Accepted for publication 19 December 2025
Available online 5 January 2026

Osteonecrosis of the jaw (ONJ) related to medication use was first described in individuals receiving treatment with bisphosphonates in the early 2000s.[1,2] Bisphosphonates were initially introduced to treat diseases affecting bone remodelling, and in the following years, an increasing number of individuals on bisphosphonates developed ONJ. This coined the original term 'bisphosphonate-related osteonecrosis of the jaw' (BRONJ). As other drugs, including monoclonal antibodies (MABs), tyrosine kinase inhibitors, variant fusion proteins, and mammalian target rapamycin

Table 1. (A) Summary of the cases from the included case reports (n = 29). (B) Summary of the cases from the included cohort study (n = 3).

	Sex, age	MAB	Indication	Jaw	MRONJ stage	Precipitating factor
1A.						
First author (Country)						
Allegra[28] (Italy)	M, 56	Rituximab	Lymphoma	MD	2	Dental extraction
Bettini[29] (Italy)	F, 57	Bevacizumab	Metastatic lung cancer	MD	2	Dental prosthesis use
Binello[31] (Italy)	M, 47	Bevacizumab	Metastatic adenocarcinoma	MD	2	None identified
Decaux[32] (Belgium)	F, 28	Pembrolizumab	Metastatic melanoma	MX	2	None identified
Disel[33] (Turkey)	M, 51	Bevacizumab	Metastatic colon cancer	MD	1	None identified
Estilo[34] (USA)	F, 51	Bevacizumab	Metastatic breast cancer	MD	1	None identified
Favia[35] (Italy)	F, 49	Infliximab	Crohn's disease	MD	3	Dental extraction
Ghosh[36] (USA)	F, 86	Golimumab	Rheumatoid arthritis	MD	3	Dental extraction
Greuter[37] (Switzerland)	F, 63	Bevacizumab	Metastatic breast cancer	MX	3	Dental extraction
Guida[38] (Italy)	F, 58	Ipilimumab	Metastatic melanoma	MD	2	Dental extraction
Hopp[39] (Brazil)	M, 58	Bevacizumab	Retinal vascular thrombosis	MD	1	None identified
Keribin[40] (France)	M, 69	Rituximab	Lymphoma	Both	1	None identified
Kolodziejwsk[41] (Brazil)	M, 53	Infliximab	Crohn's disease	MD	3	None identified
Magremanne[42] (Belgium)	M, 49	Bevacizumab	Glioblastoma multiforme	MD	3	Dental extraction
Manzie[43] (Australia)	F, 76	Trastuzumab, pertuzumab	Metastatic breast cancer	MD	2	None identified
Marotta[44] (Italy)	M, 67	Guselkumab	Psoriatic arthritis	MX	1	Dental extraction
Nisi[45] (Italy)	M, 69	Pembrolizumab	Metastatic lung cancer	MX	2	None identified
Owosho[46] (USA)	M, 52	Ipilimumab	Metastatic pancreatic cancer	MD	2	None identified
Oz[47] (Israel)	M, 79	Ranibizumab, bevacizumab	Macular degeneration	Both	2	Dental extraction
Pakosch[48] (Germany)	F, 53	Bevacizumab	Metastatic pancreatic cancer	MD	2	Dental prosthesis use
Patel[49] (UK)	M, 73	Pembrolizumab	Metastatic melanoma	MD	1	None identified
Pennings[50] (USA)	F, 44	Pembrolizumab	Lymphoma	Both	1	None identified
Pundole[51] (USA)	M, 75	Nivolumab	Metastatic melanoma	MD	3	None identified
Roh[52] (South Korea)	M, 36	Tocilizumab	COVID-19	MX	3	Odontogenic infection
Santos-Silva[53] (Brazil)	M, 61	Bevacizumab	Metastatic renal cell carcinoma	MD	1	None identified
Serra[54] (Italy)	M, 64	Bevacizumab	Metastatic lung cancer	MD	2	Dental extraction
Singh[55] (USA)	M, 59	Ramucirumab	Metastatic lung cancer	MD	1	None identified
Sisalli[56] (Italy)	F, 70	Adalimumab	Rheumatoid arthritis	MD	2	None identified
Ueda[57] (Japan)	F, 66	Bevacizumab	Metastatic breast cancer	MD	3	Failed dental implant
1B.						
Author (Country)						
Brijs[30] (Belgium)	F, 23	Infliximab, adalimumab	Crohn's disease	MX	3	Dental extraction
Brijs[30] (Belgium)	F, 57	Infliximab	Ulcerative colitis	MD	1	Dental extraction
Brijs[30] (Belgium)	M, 46	Infliximab, adalimumab	Crohn's disease	MD	2	Dental extraction

F, female; M, male; MAB, monoclonal antibody; MD, mandible; MRONJ, medication-related osteonecrosis of the jaw; MX, maxilla.

- Most common: Bevacizumab
- Followed by: infliximab, pembrolizumab, adalimumab and rituximab

Pathogenesis

- Majority: dental intervention impacting bone
  - e.g. extractions, ill-fitting dentures, sharp teeth



- May occur spontaneously



- Likely multi-factorial - current hypotheses:
  - Suppression of bone turnover
  - Inhibition of angiogenesis
  - Toxic effect on soft tissues
  - Inflammation or infection



Incidence of MRONJ

Drug	Background MRONJ Incidence	Post-extraction MRONJ Incidence
Therapy of osteoporosis		
Bisphosphonates (oral) e.g. alendronate, risedronate	0.02 – 0.05% (BP class)	0 – 0.15% (BP class)
Bisphosphonates (IV) e.g. ibandronate, pamidronate, zolendronate	<0.02% (zolendronate)	
Denosumab	0.04 – 0.3%	1%
Romosozumab	0.03 – 0.05%	Insufficient data
Therapy for multiple myeloma or metastatic bone cancer		
Bisphosphonates (IV) e.g. ibandronate, pamidronate, zolendronate	<5% (zolendronate) Range: 0 – 18%	1 – 5% (BP class) Range: 1.6 – 14.8%
Denosumab	<5% Range: 0 – 6.9%	Insufficient data
Antiangiogenic drugs e.g. TKIs (cabozantinib, lenvatinib, sunitinib), anti-VEGF monoclonal antibodies (e.g. bevacizumab)	Insufficient data to quantify. Estimated lower than BP/DMB	Insufficient data

Ruggiero SL, Dodson TB, Aghaloo T, et al. American Association of Oral and Maxillofacial Surgeons'Positon Paper on Medication-Related Osteonecrosis of the Jaws – 2022 Updates. J Oral Maxillofac Surg. 2022; 80(5): 920-943.

* Know these numbers

Incidence of MRONJ

Osteoporosis < Cancer = 0.05-1% vs <5%

Osteoporosis: bisphosphonates < denosumab (1 order higher)

- Background: <0.05% vs <0.3%
- Extractions: <0.15% vs 1%

Cancer: bisphosphonates ≈ denosumab (5%)

- Ranges up to 18% BP and 7% DMB

Risk/consequence of skeletal events > MRONJ risk

Ruggiero SL, Dodson TB, Aghaloo T, et al. American Association of Oral and Maxillofacial Surgeons'Positon Paper on Medication-Related Osteonecrosis of the Jaws – 2022 Updates. J Oral Maxillofac Surg. 2022; 80(5): 920-943.

Risk Factors

Key risk factors:

- History of MRONJ
- Cancer regimens drugs that increase MRONJ risk
- >4 years bisphosphonate therapy

Significant risk factors:

- Poor oral health / periodontal disease
- Invasive dental procedures
- Ill-fitting dentures
- Uncontrolled diabetes mellitus
- Tobacco use

Other possible risk factors:

- Chemotherapy
- Profound immunocompromise
- Corticosteroids
- Cancer site
- Renal disease / dialysis
- Erythropoietin therapy / anaemia
- Hyperthyroidism
- Gender, ethnicity, increasing age

Prevention of MRONJ

- **Medical practitioner to refer** for dental assessment prior to commencing drug

- **Dentist** should:
  - Undertake a comprehensive oral examination (including pulp tests and radiographs)
  - Eliminate dental caries (e.g. restorations, extractions)
  - Establish periodontal health (e.g. debridement, extractions)
  - Encourage good oral hygiene

- **Invasive dental procedures** should be completed prior to commencing drug
  - Osteoporosis: less ideally, complete invasive dental procedures within 6 months of the first dose

- **Regular dental review** is essential to monitor oral health

“Dentally Fit?”

“Dental Clearance”



Patients at Risk of MRONJ: Prior to Drug Therapy

Prioritise care that will reduce **mucosal trauma**, and/or may help avoid foreseeable oral surgery that may **impact bone**, and/or may risk **infection/bacteraemia**:

- Radiographs to identify possible areas of infection/pathology
- Undertake remedial dental work
- Extract any teeth of poor prognosis without delay
- Minimise periodontal / dental infection or disease
- Adjust/replace poorly fitting dentures

Potential sources of oral infection prior to urgent medical treatment

Boguslawska-Kapala et al. Oral health of adult patients undergoing hematopoietic cell transplantation. Pre-transplant assessment and care. 2017:96;1135-1145.

Table 1 Potential foci of infection and local trauma/bleeding factors within the stomatognathic system in patients undergoing HCT [12, 15–23]

Focus of infection	Advanced caries	-Cavities in which excavation may lead to pulpal exposure, -Cavities that can harbor fungal organisms, -Unrestorable carious teeth, -Compromised, large restorations
	Moderate/advanced gingivitis and periodontitis	- Furcation involvement greater than II grade, -Advanced tooth mobility, -Periodontal pockets ≥6 mm, -Advanced recession (loss of two-third bone support)
	Dental-pulp/periapical pathology	-Nonvital/inflamed dental pulp, -Chronic/acute periapical pathology
	Others	-Pericoronitis, -Sub, supra-gingival calculus, -Partially erupted teeth, -Root tips (not fully covered by bone or showing radiolucency), -Cysts, -Mucosal lesions, -Leaking crowns and fillings
Local bleeding factors		-Fractured teeth and/or restorations, -Sharp edges of teeth and/or restorations, -Ill-fitting dentures, -Orthodontic appliances, -Teeth contacting directly to the opposing mucosa

> Therefore, *if systemic conditions permit*, initiation of antiresorptive therapy should be delayed until dental health is optimized.[173,208] This decision must be made in conjunction with the treating physician and dentist and other specialists involved in the care of the patient. There is widespread consensus that optimizing dental health prior to initiating therapy is efficacious and of paramount importance.[38,185,186,209]

AAOMS 2022 MRONJ Guidelines

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;80(5):920–43.

If it's not sour

When medical condition requires prompt initiation of treatment…

TABLE 3. Descriptions of Complete, Partial, and Minimal Dental Evaluation Protocols Based on the Type of Dental and/or Periodontal Pathology[153]

Dental Pathology	Complete[154,155]	Partial[156,157]	Minimal, Incomplete, or No Clearance[154-158]
Caries	Restore all teeth	Mild/moderate caries were restored if time permitted	Intervention only if symptomatic
Severe caries/pulp involvement/ dental abscess	Root canal treatment *or* extract		
Apical periodontitis	Retreat	Symptomatic lesions and lesions ≥ 5 mm were treated	
	Apicoectomy	Asymptomatic lesions and lesions < 5 mm were observed	
	Extract		
Advanced periodontal disease	Extract teeth with:	Extract teeth with:	
	Probing depth ≥ 6 mm	Probing depth ≥ 8 mm	
	Furcation I, II, III; Mobility III	Mobility III	
	Severe inflammation	Severe inflammation	
Partially erupted third molars	Extract	Asymptomatic teeth were observed	
		Partially erupted third molars with purulence of pericoronitis were extracted	

NOTE. The proper protocol should be selected by the oncologist and dentist according to the patient's medical status.

- Yarom et al. Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. J Clin Oncol. 2019;37(25):2270-2290.
- Hong et al. A systematic review of dental disease management in cancer patients. Support Care Cancer. 2018;26:155-174.

Bone-Modifying Drugs: Work-Up

- Advise patient of MRONJ with medication they are taking, but ensure they understand the risk is small, so that they are not discouraged from taking their BMD or from undergoing dental treatment.
- Personalised preventive advice to optimise oral health (healthy diet, reduce sugar, maintain oral hygiene, fluoride, cease smoking, limit alcohol, regular dental checks)
- Ensure dentures are well-fitting

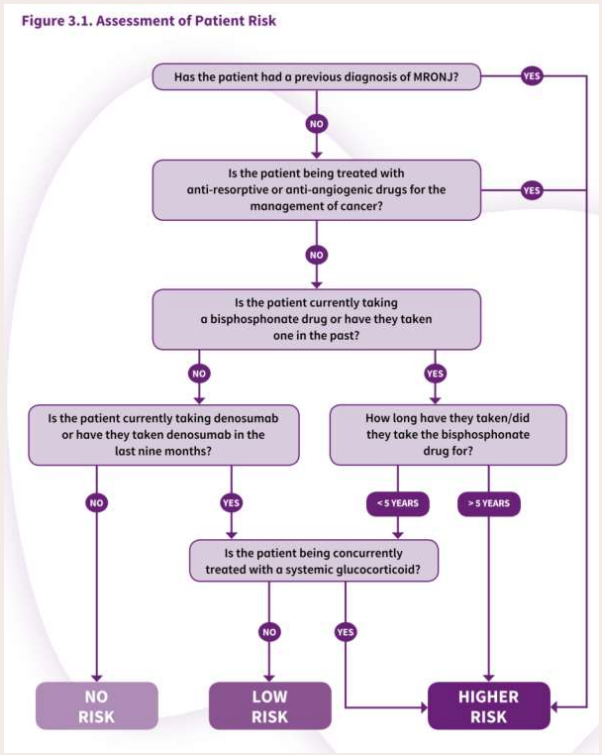
Current BMDs - Assessing MRONJ Risk prior to Invasive Dental Procedures

- Assess if patient is at low or higher risk of developing MRONJ based on their medical condition, type and duration of therapy, and any other complicating factors (eg. glucocorticoid medication and length of exposure to drugs).

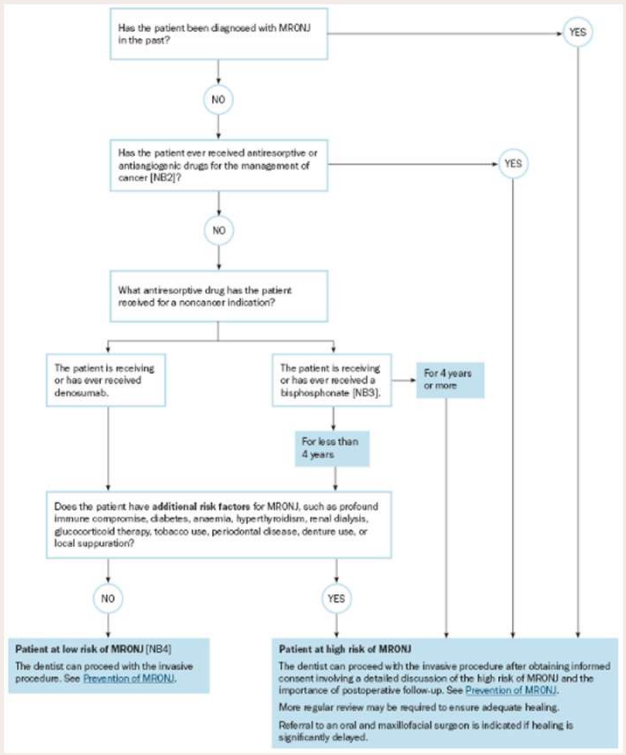
Table 3.1 Patient Risk Categories

Low Risk	Higher Risk
If any of the following is present:	If any of the following is present:
• Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget's disease) with oral bisphosphonates for **less than 5 years** who are **not** concurrently being treated with systemic glucocorticoids. • Patients being treated for osteoporosis or other non-malignant diseases of bone with quarterly or yearly infusions of intravenous bisphosphonates for **less than 5 years** who are **not** concurrently being treated with systemic glucocorticoids. • Patients being treated for osteoporosis or other non-malignant diseases of bone with denosumab who are **not** being treated with systemic glucocorticoids.	• Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget's disease) with oral bisphosphonates or quarterly or yearly infusions of intravenous bisphosphonates for **more than 5 years.** • Patients being treated for osteoporosis or other non-malignant diseases of bone with bisphosphonates or denosumab **for any length of time** who are being concurrently treated with systemic glucocorticoids. • Patients being treated with anti-resorptive or anti-angiogenic drugs (or both) as part of the management of cancer. • Patients with a previous diagnosis of MRONJ.

N.B. Patients who have taken bisphosphonate drugs at any time in the past and those who have taken denosumab in the last nine months are allocated to a risk group as if they are still taking the drug.



SDCEP 2017 Guidelines – Updated 2022



Therapeutic Guidelines – Oral & Dental v4 2026

Current BMDs – Assessing MRONJ Risk prior to Invasive Dental Procedures

Patients can undergo invasive dental procedures in general dental practice, after a discussion of the risk assessment and precautions

Figure 13.75 Precautions for managing patients at increased risk of MRONJ undergoing an invasive dental procedure

Inform the patient of the risk of medication-related osteonecrosis of the jaw and obtain informed consent for the procedure.

See advice on Drug holidays and scheduling of procedures in patients at risk of MRONJ.

Do not use antibiotic prophylaxis to reduce the risk of medication-related osteonecrosis of the jaw – there is insufficient evidence to support this practice [2]. However, an active infection should be treated.

Ensure optimal oral hygiene before and after the procedure [8].

Reduce the plaque load with mechanical debridement and pre- and postprocedural chlorhexidine mouthwash [8].

Consider root retention techniques to avoid extractions.

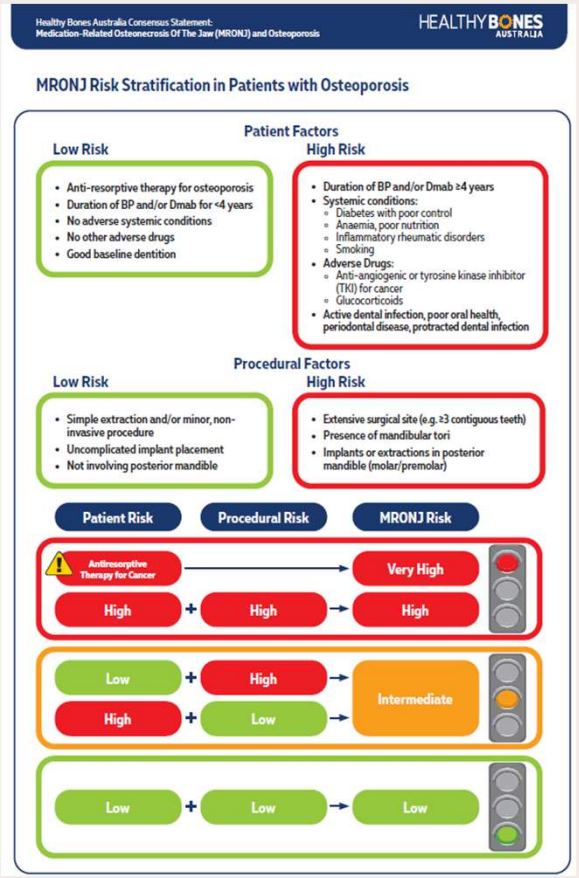
Minimise trauma and periosteum stripping, and use sutures to close any mucosal flaps that are raised.

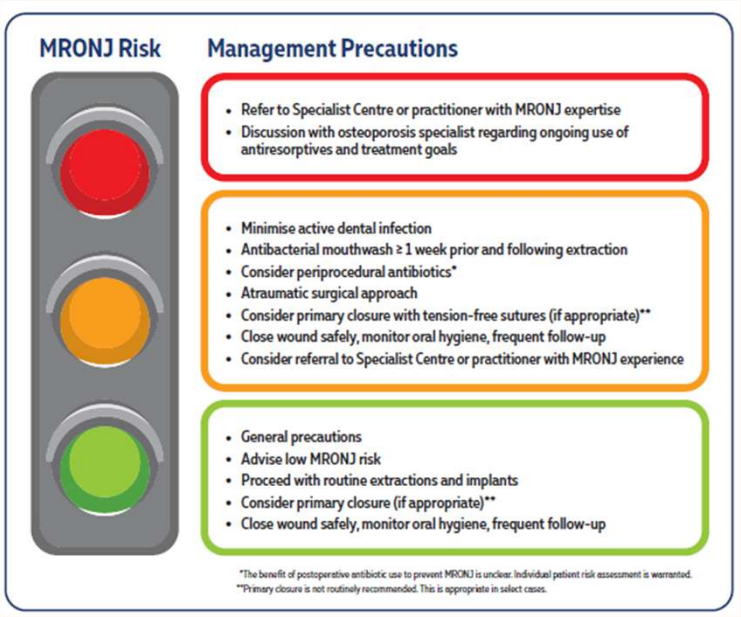
Monitor the oral wound until it heals – healing may be slow.

Do not debride nonhealing wounds.

Refer to an oral and maxillofacial surgeon if bone is still visible 8 weeks after the invasive dental procedure.

Current BMDs – Assessing MRONJ Risk prior to Invasive Dental Procedures





Current BMDs: Drug Holidays - Bisphosphonates

AAOMS 2014

Asymptomatic patients – Oral BP for osteoporosis

- **Oral BP <4 years + no risk factors** = no delays/alteration.
- **Oral BP <4 years + concomitant corticosteroids or anti-angiogenics** = consider discontinuation at least 2 months pre-op, if systemic conditions permit. Restart when osseous healing (3 months).
- **Oral BP >4 years ± concomitant medical therapy** = consider discontinuation for 2 months pre-op, if systemic conditions permit. Restart when osseous healing (3 months).

AAOMS 2022

- **Difficult to establish or refute efficacy** of drug holidays → working group evenly split
- Rarity of MRONJ in these patient populations → insufficient data for RCTs
- 2020 systematic review: variety of papers had differing conclusions
- **Factors for consideration**: disease-related risk (cancer vs OP), drug-dosing frequency, therapy duration, comorbidities, other medications (chemo, steroids, antiangiogenics), degree of infection/inflammation, extent of surgery

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;80(5):920–43.
Ottesen C, Schiodt M, Gotfredsen K. Efficacy of a high-dose antiresorptive drug holiday to reduce the risk of medication-related osteonecrosis of the jaw (MRONJ): A systematic review. Heliyon. 2020;6(4):e03795–e03795.

Current BMDs: Drug Holidays prior to Invasive Dental Procedures

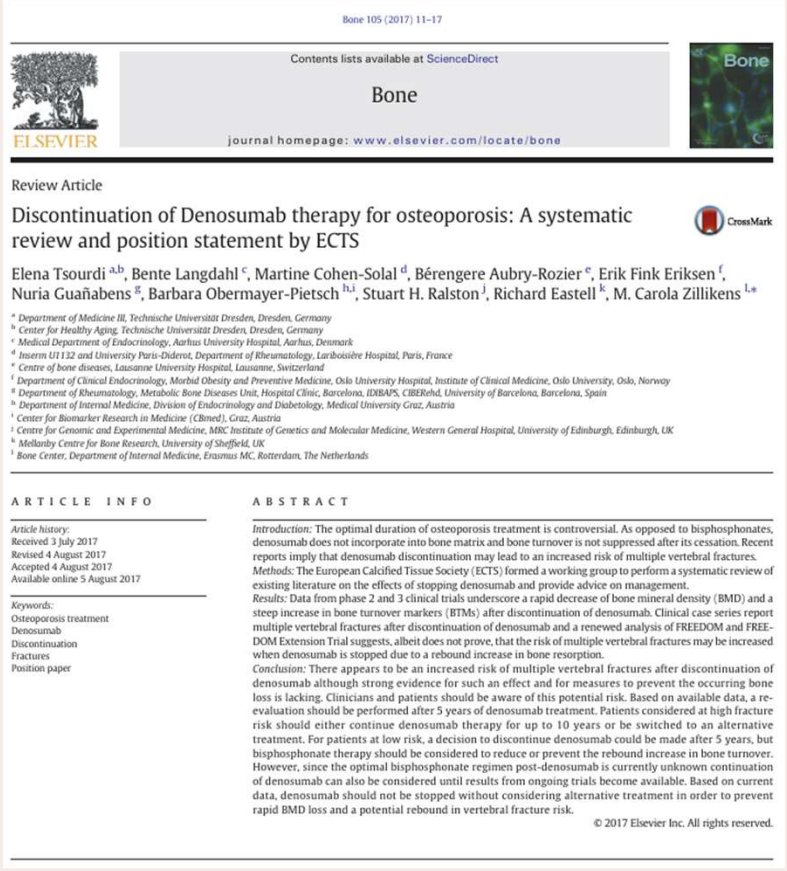
- Controversial – evidence to support or refute inconclusive
- Responsibility for drug holiday is prescribing practitioner, together with clinical judgement of the dentist, and in discussion with the patient

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;80(5):920–43.
Ottesen C, Schiodt M, Gotfredsen K. Efficacy of a high-dose antiresorptive drug holiday to reduce the risk of medication-related osteonecrosis of the jaw (MRONJ): A systematic review. Heliyon. 2020;6(4):e03795–e03795.

Yarom N, et al. Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. 2019;37(25):2270-2290

Therapeutic Guidelines: Oral & Dental version 4 2026

Current BMDs - Denosumab



Bone 105 (2017) 11–17

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review Article

Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS

Elena Tsourdi [a,b], Bente Langdahl [c], Martine Cohen-Solal [d], Bérengere Aubry-Rozier [e], Erik Fink Eriksen [f], Nuria Guañabens [g], Barbara Obermayer-Pietsch [h,i], Stuart H. Ralston [j], Richard Eastell [k], M. Carola Zillikens [l,*]

[a] Department of Medicine III, Technische Universität Dresden, Dresden, Germany
[b] Center for Healthy Aging, Technische Universität Dresden, Dresden, Germany
[c] Medical Department of Endocrinology, Aarhus University Hospital, Aarhus, Denmark
[d] Inserm U1132 and University Paris-Diderot, Department of Rheumatology, Lariboisière Hospital, Paris, France
[e] Centre of bone diseases, Lausanne University Hospital, Lausanne, Switzerland
[f] Department of Clinical Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Institute of Clinical Medicine, Oslo University, Oslo, Norway
[g] Department of Rheumatology, Metabolic Bone Diseases Unit, Hospital Clínic, Barcelona, IDIBAPS, CIBERehd, University of Barcelona, Barcelona, Spain
[h] Department of Internal Medicine, Division of Endocrinology and Diabetology, Medical University Graz, Austria
[i] Center for Biomarker Research in Medicine (CBmed), Graz, Austria
[j] Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine, Western General Hospital, University of Edinburgh, Edinburgh, UK
[k] Mellanby Centre for Bone Research, University of Sheffield, UK
[l] Bone Center, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

ARTICLE INFO

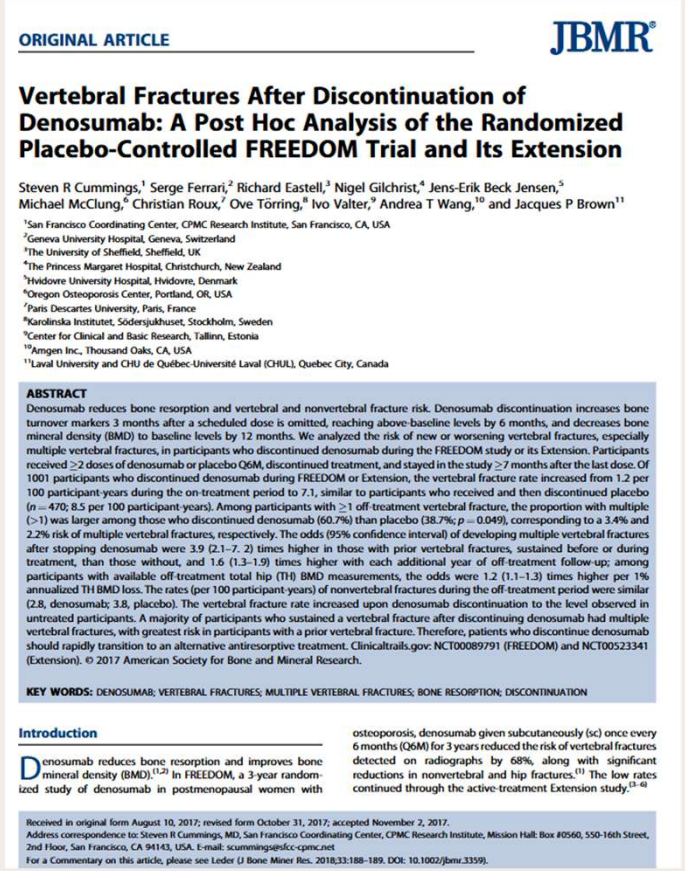
Article history:
Received 3 July 2017
Revised 4 August 2017
Accepted 4 August 2017
Available online 5 August 2017

Keywords:
Osteoporosis treatment
Denosumab
Discontinuation
Fractures
Position paper

ABSTRACT

Introduction: The optimal duration of osteoporosis treatment is controversial. As opposed to bisphosphonates, denosumab does not incorporate into bone matrix and bone turnover is not suppressed after its cessation. Recent reports imply that denosumab discontinuation may lead to an increased risk of multiple vertebral fractures.
Methods: The European Calcified Tissue Society (ECTS) formed a working group to perform a systematic review of existing literature on the effects of stopping denosumab and provide advice on management.
Results: Data from phase 2 and 3 clinical trials underscore a rapid decrease of bone mineral density (BMD) and a steep increase in bone turnover markers (BTMs) after discontinuation of denosumab. Clinical case series report multiple vertebral fractures after discontinuation of denosumab and a renewed analysis of FREEDOM and FREEDOM Extension Trial suggests, albeit does not prove, that the risk of multiple vertebral fractures may be increased when denosumab is stopped due to a rebound increase in bone resorption.
Conclusion: There appears to be an increased risk of multiple vertebral fractures after discontinuation of denosumab although strong evidence for such an effect and for measures to prevent the occurring bone loss is lacking. Clinicians and patients should be aware of this potential risk. Based on available data, a re-evaluation should be performed after 5 years of denosumab treatment. Patients considered at high fracture risk should either continue denosumab therapy for up to 10 years or be switched to an alternative treatment. For patients at low risk, a decision to discontinue denosumab could be made after 5 years, but bisphosphonate therapy should be considered to reduce or prevent the rebound increase in bone turnover. However, since the optimal bisphosphonate regimen post-denosumab is currently unknown continuation of denosumab can also be considered until results from ongoing trials become available. Based on current data, denosumab should not be stopped without considering alternative treatment in order to prevent rapid BMD loss and a potential rebound in vertebral fracture risk.

© 2017 Elsevier Inc. All rights reserved.



ORIGINAL ARTICLE

JBMR®

Vertebral Fractures After Discontinuation of Denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension

Steven R Cummings,[1] Serge Ferrari,[2] Richard Eastell,[3] Nigel Gilchrist,[4] Jens-Erik Beck Jensen,[5] Michael McClung,[6] Christian Roux,[7] Ove Törring,[8] Ivo Valter,[9] Andrea T Wang,[10] and Jacques P Brown[11]

[1]San Francisco Coordinating Center, CPMC Research Institute, San Francisco, CA, USA
[2]Geneva University Hospital, Geneva, Switzerland
[3]The University of Sheffield, Sheffield, UK
[4]The Princess Margaret Hospital, Christchurch, New Zealand
[5]Hvidovre University Hospital, Hvidovre, Denmark
[6]Oregon Osteoporosis Center, Portland, OR, USA
[7]Paris Descartes University, Paris, France
[8]Karolinska Institutet, Södersjukhuset, Stockholm, Sweden
[9]Center for Clinical and Basic Research, Tallinn, Estonia
[10]Amgen Inc., Thousand Oaks, CA, USA
[11]Laval University and CHU de Québec-Université Laval (CHUL), Quebec City, Canada

ABSTRACT

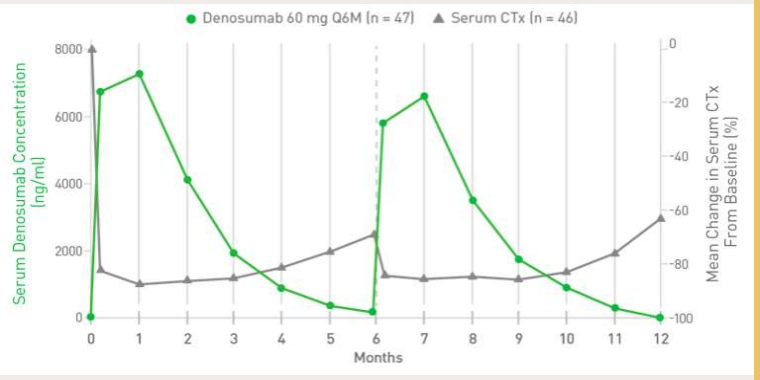
Denosumab reduces bone resorption and vertebral and nonvertebral fracture risk. Denosumab discontinuation increases bone turnover markers 3 months after a scheduled dose is omitted, reaching above-baseline levels by 6 months, and decreases bone mineral density (BMD) to baseline levels by 12 months. We analyzed the risk of new or worsening vertebral fractures, especially multiple vertebral fractures, in participants who discontinued denosumab during the FREEDOM study or its Extension. Participants received ≥2 doses of denosumab or placebo Q6M, discontinued treatment, and stayed in the study ≥7 months after the last dose. Of 1001 participants who discontinued denosumab during FREEDOM or Extension, the vertebral fracture rate increased from 1.2 per 100 participant-years during the on-treatment period to 7.1, similar to participants who received and then discontinued placebo ($n = 470$; 8.5 per 100 participant-years). Among participants with ≥1 off-treatment vertebral fracture, the proportion with multiple (>1) was larger among those who discontinued denosumab (60.7%) than placebo (38.7%; $p = 0.049$), corresponding to a 3.4% and 2.2% risk of multiple vertebral fractures, respectively. The odds (95% confidence interval) of developing multiple vertebral fractures after stopping denosumab were 3.9 (2.1–7. 2) times higher in those with prior vertebral fractures, sustained before or during treatment, than those without, and 1.6 (1.3–1.9) times higher with each additional year of off-treatment follow-up; among participants with available off-treatment total hip (TH) BMD measurements, the odds were 1.2 (1.1–1.3) times higher per 1% annualized TH BMD loss. The rates (per 100 participant-years) of nonvertebral fractures during the off-treatment period were similar (2.8, denosumab; 3.8, placebo). The vertebral fracture rate increased upon denosumab discontinuation to the level observed in untreated participants. A majority of participants who sustained a vertebral fracture after discontinuing denosumab had multiple vertebral fractures, with greatest risk in participants with a prior vertebral fracture. Therefore, patients who discontinue denosumab should rapidly transition to an alternative antiresorptive treatment. Clinicaltrails.gov: NCT00089791 (FREEDOM) and NCT00523341 (Extension). © 2017 American Society for Bone and Mineral Research.

KEY WORDS: DENOSUMAB; VERTEBRAL FRACTURES; MULTIPLE VERTEBRAL FRACTURES; BONE RESORPTION; DISCONTINUATION

Introduction

Denosumab reduces bone resorption and improves bone mineral density (BMD).[1,2] In FREEDOM, a 3-year randomized study of denosumab in postmenopausal women with osteoporosis, denosumab given subcutaneously (sc) once every 6 months (Q6M) for 3 years reduced the risk of vertebral fractures detected on radiographs by 68%, along with significant reductions in nonvertebral and hip fractures.[1] The low rates continued through the active-treatment Extension study.[3–6]

Received in original form August 10, 2017; revised form October 31, 2017; accepted November 2, 2017.
Address correspondence to: Steven R Cummings, MD, San Francisco Coordinating Center, CPMC Research Institute, Mission Hall: Box #0560, 550-16th Street, 2nd Floor, San Francisco, CA 94143, USA. E-mail: scummings@sfcc-cpmc.net
For a Commentary on this article, please see Leder (J Bone Miner Res. 2018;33:188–189. DOI: 10.1002/jbmr.3359).



Prolia® Effects on Serum CTx Levels Over the 6-month Dosing Interval.

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;80(5):920–43.

Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A Post Hoc Analysis of the Randomized Placebo-Controlled FREEDOM Trial and Its Extension. *J Bone Miner Res.* 2018;33(2):190-198

Lamy O, Stoll D, Aubrey-Rozir et al. Stopping denosumab. *Curr Osteoporos Rep.* 2019;17:8-15

Dr Jee-Yun Leung

Current BMDs - Denosumab

Osteoporotic patients with 6-monthly S.C. denosumab can delay any non-urgent invasive dental Tx in an asymptomatic tooth until 3-4 months after the last dose

This allows 6-8 weeks for healing prior to resumption of denosumab

Denosumab discontinuation → rebound risk of spontaneous vertebral fractures

- Onset of bone loss and # risk starts within 4 weeks of the missed dose
- ↑ risk occurred mostly within the first 2-6 months of discontinuation
- #s mostly occur within 6-20 months of denosumab discontinuation

risk zone

Current BMDs: Drug Holidays - Denosumab

- Denosumab discontinuation → rebound risk of multiple spontaneous vertebral fractures

- FREEDOM study and its extension (2018): risk of rebound vertebral fractures ↑ from 1.2 (on-treatment period) to 7.1 (denosumab cessation) per 100 participant-years of discontinuation.
  - ↑ occurred mostly within the first 2-6 months of discontinuation

- Lamy et al (2019):
  - Onset of bone loss and # risk starts within 4 weeks of the missed dose
  - Significant # risk occurs after 2nd dose of denosumab
  - #s mostly occur within 6-20 months of denosumab discontinuation
  - If denosumab is discontinued, bone density declines to pre-treatment levels within 12 months

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;80(5):920–43.
Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo controlled FREEDOM trial and its extension. J Bone Miner Res 2018;33(2):190–98.
Lamy O, Stoll D, Aubrey-Rozir et al. Stopping denosumab. Curr Osteoporos Rep. 2019;17:8-15

Current BMD: Drug Holidays – Therapeutic Guidelines Oral & Dental v4 2026

- *There is no evidence that drug holidays reduce risk of MRONJ.
  - If bone-invasive dental procedure cannot be avoided but is not urgent, temporary discontinuation of AR therapy, or timing procedure to coincide with a low serum drug concentration, have been suggested.
  - These practices are based on extrapolation of the drug pharmacokinetics in the serum and on bone physiology; however no available outcome evidence to support.

- *Clinical judgement of treating doctors/dentists is required to determine appropriate management of each patient.
  - Recommendations in international guidelines are inconsistent. Vary depending on indication for AR drugs, duration of therapy, and presence of additional risk factors.
  - Decision to alter AR therapy lies with practitioner responsible for managing the AR drug.

- AR drugs for **osteoporosis**:
  - Benefits of continued therapy outweigh low risk of MRONJ.
  - Bisphosphonates = Although stopping for short period unlikely to cause harm in a patient at low risk of fracture, no evidence that this reduces MRONJ risk.

- AR drugs for **cancer**:
  - Decision to alter AR therapy lies with specialist managing the cancer.

More aggressive before
more conservative after

Alternative Options for Unrestorable Teeth: RCT and tissue-level restoration

INTERNATIONAL ENDODONTIC JOURNAL
The official journal of the British Endodontic Society and the European Society of Endodontology

Original Article

Root canal treatment of compromised teeth as alternative treatment for patients receiving bisphosphonates: 60-month results of a prospective clinical study

F. Zamparini, G. A. Pelliccioni, A. Spinelli, D. B. Gissi, M. G. Gandolfi, C. Prati

First published: 09 September 2020 | https://doi.org/10.1111/iej.13405 | Citations: 2

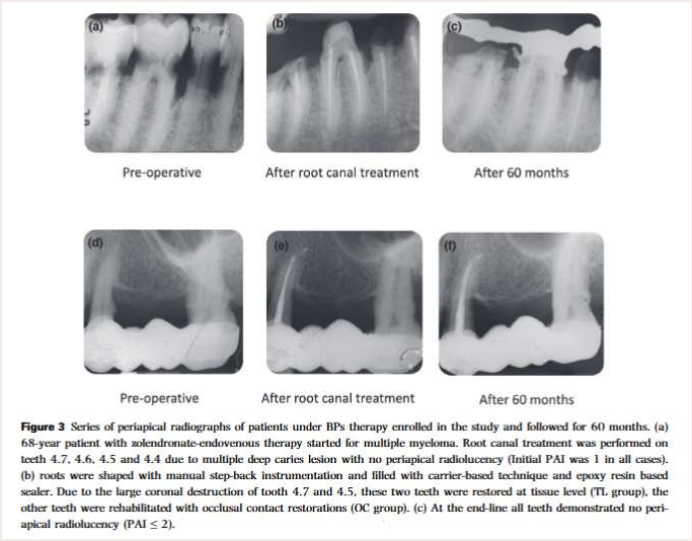


Figure 3 Series of periapical radiographs of patients under BPs therapy enrolled in the study and followed for 60 months. (a) 68-year patient with zolendronate-endovenous therapy started for multiple myeloma. Root canal treatment was performed on teeth 4.7, 4.6, 4.5 and 4.4 due to multiple deep caries lesion with no periapical radiolucency (Initial PAI was 1 in all cases). (b) roots were shaped with manual step-back instrumentation and filled with carrier-based technique and epoxy resin based sealer. Due to the large coronal destruction of tooth 4.7 and 4.5, these two teeth were restored at tissue level (TL group), the other teeth were rehabilitated with occlusal contact restorations (OC group). (c) At the end-line all teeth demonstrated no periapical radiolucency (PAI ≤ 2).

Root canal treatment of compromised teeth as alternative treatment in patients receiving bisphosphonates: 60-month results of a prospective clinical study

F Zamparini, GA Pelliccioni, A Spinelli, DB Gissi, MG Gandolfi, C Prati

Aim

This 60-month prospective study aimed to evaluate tooth survival and healing rates after root canal treatment in patients taking bisphosphonates (BPs). Secondary outcomes were complications and clinical variables observed during and after the treatment.

Methods

Root canal treatment was performed using manual K-file canal instrumentation, a carrier-based filling technique and epoxy resin–based sealer. Teeth without adequate root/crown integrity were restored by trained operators at the tissue level (TL group) to prevent occlusal/mechanical stress and to enable periapical lesion healing without the risk of root fracture. Other teeth were restored with normal occlusal contact (OC group). Healthy patients who had undergone one or more root canal treatments of the same type constituted the control group. The relationships of the following variables to survival and health status were examined (chi-squared test and multivariate analysis, p=0.05): age, gender, smoking habit, tooth location, treatment type, BPs treatment, BPs exposure, initial periapical index (PAI) and occlusal restoration. Survival curves were constructed using Kaplan–Meier analysis, with extraction serving as endpoint.

Results

In total, 65 patients with 109 root canal treated teeth who were taking BPs were included. At 60 months, data from 57 patients (52F, 5M; median-age 65.7±8.6years) who had undergone 96 root canal treatments were analysed (drop-out rate=16.9%). The survival rate was 85% and the success rate was 76%.

The control group consisted of 46 patients (21F, 25M; median-age 60.3±7.2years) who had undergone 102 root canal treatments. The survival rate was 88%, with 12 teeth lost during follow-up. The success rate was 73%. In the BPs group, 55 teeth were restored normally (OC group) and 41 teeth were restored at the tissue level (TL group). No difference in the success or survival rate was observed between the BP and control groups (p>0.05). Univariate Kaplan-Meier analysis revealed that only tooth type significantly affected survival status in the BP group. The analysis revealed the clinical relevance of smoking, tooth location and initial PAI on patients' health status (p<0.05).

Conclusion

Root canal treatments and post-endodontic restoration with tissue level filling procedures represent a safe approach for severely-damaged teeth in patients receiving bisphosphonates having comparable results to occlusal contact and control group.

Alternative Options for Unrestorable Teeth: Orthodontic Extrusion





FIGURE 3. Teeth after exfoliation of the second molar and extrusion of the first premolar.



FIGURE 4. Sockets immediately after exfoliation of both teeth.



FIGURE 5. Complete healing 2 months after exfoliation.

Regev, Lustmann, and Nashef. Extraction in Bisphosphonate-Treated Patients. J Oral Maxillofac Surg 2008.



FIGURE 6. Dentin bulge (*arrows*) preventing elastics from sliding apically.

- Regev E, Lustmann J, Nashef R. Atraumatic Teeth Extraction in Bisphosphonate-Treated Patients. Journal of oral and maxillofacial surgery. 2008;66(6):1157-61.

Alternative Options for Unrestorable Teeth: Orthodontic Extrusion



Figure 3. The roots of the first and second mandibular molars are separated during fabrication of the temporary acrylic bridge.



Figure 4. A. The distal root of the mandibular first molar is pulled toward the bridge. **B.** The erupted root. **C.** Radiograph before root eruption. **D.** Radiograph after root eruption.



Figure 6. A. Occlusal view after placement of the rubber bands. **B.** Occlusal view of the sockets. Note the appearance of the tissue around the extraction sites. **C.** The modified acrylic bridge cemented after extraction of the distal roots.

- Smidt A, Lipovetsky-Adler M, Sharon E. Forced eruption as an alternative to tooth extraction in long-term use of oral bisphosphonates Review, risks and technique. JADA. 2012;143(12):1303-12

Thinking it through… BMDs

Medical, Dental and Social Considerations

- Chemotherapy cycle and blood counts
- Long-term prognosis of tooth
- Compliance with ongoing preventive oral care
- Previous history BMD vs BMD naïve
- Concomitant oral disease (periodontal disease, periapical pathology) = infection risk factor for MRONJ
- Tobacco use

Optimal Timeframes

- Urgency to commence drug
- Prioritise care that reduces mucosal trauma or need for future oral surgery impacting on bone (e.g. poor prognosis dental extractions, poorly fitting dentures)
- Future-proof for foreseeable future
  - Bisphosphonate osteoporosis tx: 5-10 years treatment period + 10-year terminal half-life
  - Denosumab: long-term, or cessation followed by another BMD (12 months oral bisphosphonate or 1+ zolendronate infusion)
- Dental extractions just prior to 6-monthly injection
- Avoid delaying next dose = risk spontaneous vertebral fractures

Treatment Approaches

- Aggressive vs conservative
  - Typically aggressive pre-BMD, conservative options if time permits. Typically conservative post-BMD.
- Long-term medical prognosis, physiological tolerance
- Resulting QOL

) teeth only need to outlast them

Management of MRONJ

Goals: improved quality of life, disease control, prevention of secondary infection

Non-operative

Operative

* Surgical might cause more mobility

Staging

Stage 0 (non-exposed bone variant)

- No clinical evidence of necrotic bone
- Non-specific symptoms or clinical and radiographic findings
- Symptoms
  - Odontalgia unexplained by an odontogenic cause
  - Dull, aching jaw bone pain, which may radiate to the TMJ region
  - Sinus pain, inflammation and thickening of the maxillary sinus wall
  - Altered neurosensory function
- Clinical Findings
  - Loosening of teeth unexplained by chronic periodontal disease
  - Intraoral or extraoral swelling
- Radiographic Findings
  - Alveolar bone loss or resorption unattributable to chronic periodontal disease
  - Changes to trabecular pattern sclerotic bone and no new bone in extraction sockets
  - Regions of osteosclerosis involving alveolar bone and/or surrounding basilar bone
  - Thickening/obscuring of PDL

Stage 1

Exposed and necrotic bone, or fistula that probes to the bone, in asymptomatic patients without infection/inflammation

Stage 2

Exposed and necrotic bone, or fistula that probes to bone, with infection/inflammation. Patients are symptomatic.

Stage 3

Exposed and necrotic bone, or fistula that probes to bone, with infection, and one or more of:

- Exposed necrotic bone extending beyond the region of alveolar bone (i.e. mandible = inferior border and ramus; maxilla = maxillary sinus and zygoma)
- Pathologic fracture
- Extraoral fistula
- Oral antral / oral-nasal communication
- Osteolysis extending to the inferior border of the mandible or sinus floor

Treatment Strategies by Stage of MRONJ

TABLE 5. Treatment Strategies by Stage of MRONJ

Staging of MRONJ*	Treatment Strategy†
At risk: No apparent necrotic bone in patients who have been treated with oral or intravenous bone-modifying agents	No treatment indicated
	Patient education and reduction of modifiable risk factors
Increased risk: No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms	Symptomatic management, including the use of pain medication and close scrutiny and follow up
	Refer to dental specialist and follow up every 8 weeks with communication of lesion status to the oncologist
	Patient education and reduction of modifiable risk factors
Stage 1: Exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse
	Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist
	Patient education and reduction of modifiable risk factors
Stage 2: Exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics and topical antibacterial rinse
	Pain control
	Debridement to relieve soft tissue irritation and infection control
	Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist
	Patient education and reduction of modifiable risk factors
Stage 3: Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor	Symptomatic treatment with oral antibiotics and topical antibacterial rinse
	Pain control
	Surgical debridement or resection for long-term palliation of infection and pain
	Clinical follow up on an every-8-week basis by dental specialist with communication of lesion status to oncologist
	Patient education and reduction of modifiable risk factors

NOTE. Adapted from Ruggiero et al.[2]

Abbreviation: MRONJ, medication-related osteonecrosis of the jaw.

*Exposed or probable bone in the maxillofacial region without resolution for longer than 8 weeks in patients who were treated with an antiresorptive or an angiogenic inhibitor and who have not received radiation therapy to the jaws.

†Regardless of disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Extraction of symptomatic teeth within exposed necrotic bone should be considered because it is unlikely that extraction will exacerbate the established necrotic process.

Adapted from AAOMS 2014.

Source: Yarom N, et al. Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. 2019;37(25):2270-2290

Management: Non-operative

General dental practitioner

Non-operative management:

- Improve patient's oral hygiene
  - Biofilm (tooth brushing)
  - Chlorhexidine wound care: dip cotton swab or soft small toothbrush in 0.12% CHX solution, gently mechanically scrub exposed bone or fistula.
- Monitoring wound healing
- Management of generalised periodontal disease
- Adjusting dentures to alleviate pressure on non-healing area
- N/B. Stage 2 patients may struggle with local wound care and require antibiotics for symptom control

Specialist measures

- Removal of loose bone sequestra
- Adjunctive medications/treatments?
  - Teriparatide
  - Vitamin E and pentoxifylline
  - Hyperbaric oxygen
  - Ozone therapy

Management: Surgical

- Refer all patients with established MRONJ to a surgical dental specialist for assessment
- Surgery: Marginal or segmental resection (including sequestrectomy)
- Progression of MRONJ can be unpredictable
- Decision to proceed is patient-specific
  - Quality of life, symptoms, ability to clean wound to prevent infection and disease spread, morbidity of procedure, oral function, rehabilitation required after procedure

Thank you

Jeeyun.Leung@uwa.edu.au

