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Prothèses et Biphosphonates

-Dental Prostheses and Bisphosphonates-

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This thesis is dedicated to my parents to whom im greatly indebted for their everlasting love, endless support and warm encouragements.

To my beloved Mother *who has always been a source of motivation and strength during moments of despair and discouragement. her motherly care and support and her valuable prayers have brought me to where I am now.*

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«No one who achieves success does so without acknowledging the help of others. The wise and confident acknowledge this help with gratitude. »

Alfred North Whitehead

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LIST OF ABBREVIATIONS:

BSUs: bone structural units.
BMUs: bone multicellular units.
PSAA: posterior superior alveolar artery.
IOA: infraorbital artery.
GPA: greater palatine artery.
SPA: sphenopalatine artery.
VA: vidian artery.
PDL: periodontal ligament.
CEJ: cementoenamel junction.
PTH: parathyroid hormone.
BMP-2: Bone morphogenetic protein-2.
IGF-I: insulin-like growth factor-I.
BPs: bisphosphonates**.**
GI: gastrointestinal**.**
SC: Subcutaneous.
BMD: bone mineral density.
HMG: hydroxymethylglutatyl.
IPP: Isopentenyl pyrophosphate.
FPPS: farnesyl diphosphate synthase.
AMP: Adenosine monophosphate.
VEGF: Vascular Endothelial Growth Factor.
FPPS: farnesyl diphosphate synthase.
TNF: Tumor necrosis factor.
HDL: High-density lipoprotein.
SERM: Selective Estrogen Receptor Modulator.
CKD: chronic kidney disease.
eGFR: estimated glomerular filtration rate.
NSAIDs: nonsteroidal anti-inflammatory drugs.
ONJ: Osteonecrosis of the jaw.
MRONJ: Medication-related osteonecrosis of the jaw.
BRONJ: bisphosphonate-related osteonecrosis of the jaw.
BIONJ: Bisphosphonate-induced osteonecrosis of the jaw.
RANK-L: receptor activator of nuclear factor-kappaB ligand.
CT : Computed tomography.
MRI: Magnetic Resonance Imaging.
STIR: Short Tau Inversion Recovery.
HIV: Human Immunodeficiency Virus.
AAOMS: American Association of Oral and Maxillofacial Surgeons.
FDP: Fixed Dental Prosthesis.
RPDP: Removable partial dental prosthesis.
CTX: Collagen Type I C-Telopeptide.
FPDs: Fixed partial dentures.
SOH: Subpontic osseous hyperplasia.
CAOMS: Canadian Association of Oral and Maxillofacial Surgeons.

Introduction

Bisphosphonates (formerly called diphosphonates) were discovered in the mid-1800s and to this day have wide commercial use as anti scaling agents because of their physical-chemical property of complexing with divalent cations. In the late 1960s, they began to be used for treatment of metabolic bone diseases as inhibitors of bone resorption.

Since that time, parallel research on the effects of bisphosphonates on bone metabolism continued, while efforts in the dental field included studies of bisphosphonate effects on dental calculus, caries, and alveolar bone loss. While some utility of this drug class in the dental field was identified, leading to their experimental use in various dentifrices formulations and in some dental applications clinically, adverse effects of bisphosphonates in the jaws have also received attention.

However, in 2003, Marx described the first cases of bisphosphonate-induced osteo-chemo necrosis called avascular maxillary necrosis whose mechanism of occurrence is not yet fully elucidated.

Bisphosphonates-related osteonecrosis of the jaws' (BRONJ) epidemiology and pathogenesis are still unclear; however, in recent years, notable progress has been made regarding its prevention by studying local risk factors in patients at risk of BRONJ and by planning dental procedures.

When it comes to edentulous patients undergoing bisphosphonates treatment, The choices available for restoration of the edentulous arch are varied. The options can be separated broadly into three categories: removable, fixed and implant prostheses.

Unfortunately, there is only little data on how to proceed with prosthodontic therapy among these patients.

Due to this lack of data, several systematic literature reviews were performed to fill this gap in favor of reducing the BRONJ occurence rates in this category.

The aim of this work is therefore to correlate the data on dentures and bis-phosphonates to determine whether it is possible to consider prosthetic therapy for patients treated with bisphosphonates by assessing the risk of developing osteonecrosis of the jaws.

CHAPTER 1 :

Anatomical and Histophysiological Reminders

1-Bone tissue:

1-1 definition:

The bone tissue also called the osseous tissue is the type of connective tissue that is hardened due to mineralization.

It is comprised of the bone matrix as well as the bone cells. The bone matrix is the extracellular matrix of the bone. It is consisted of organic and inorganic substances. The organic component of the bone matrix includes the collagen and ground substance whereas the inorganic component is the inorganic bone salts, mainly hydroxyapatite. Bone tissues consist of collagen fibers and ground substance containing calcium, magnesium, and phosphate ions that chemically combine and harden into a mineral, hydroxyapatite. The combination of hard mineral and flexible collagen makes bone harder than cartilage without being brittle.

The cellular elements of the bone include osteoblasts, osteocytes, and osteoclasts. The osteoblasts are involved in the formation and mineralization of bone tissues. The osteocytes are osteoblasts that migrated into and become trapped by the surrounding matrix. The osteoclasts are involved in the bone resorption.

There are two types of bone tissues based on the arrangement of their structure: cortical bone and cancellous bone.[1]

1-2 The histophysiological features of the bone:

1-2-1 Bone physiology:

1-2-1-1 Morphology:

Macroscopically, bone can be divided into an outer part called cortical compact bone, which makes about 80% of the total skeleton, and an inner part named cancellous, trabecular, or spongy bone. This structure, allows optimal mechanical function under customary loads.

Microscopically, woven and lamellar bone can be distinguished. Woven Bone is the type formed initially in the embryo and during growth, and characterized by an irregular array of loosely packed collagen fibrils. then replaced by lamellar bone, so that it is practically absent from adult skeleton, except under pathological conditions of rapid bone mation, such as occur in Paget's disease, fluorosis, or fracture healing. contrast, lamellar bone is the form present in the adult, both in cortical and in cancellous bone. It is made of well-ordered parallel collagen fibers, organized in a lamellar pattern.

Histologically bone formed during growth is of the woven type; in the adult it is lamellar, except in certain diseases with rapid formation.[2]

1-2-2 Bone histology:

Bone is made of basic units called bone structural units (BSUs). In cortical bone these are called osteons or Haversian systems, which represent its basic structural building blocks. These are hollow cylinders of a median length of 2 mm, but which can reach 8 mm, and 200 µm in diameter, made of concentric lamellae, between which the osteocytes are located. In the center is a canal containing the nutrient blood vessels. These anastomose with vessels from other osteons so that the various osteons are in communication with one another. The diameter of the osteon is always about 200 µm, regardless of species, the maximal distance of any part from the central vessel being no more than 100 µm, this being the largest transport distance for nutrients. Osteons are separated from one another by so-called cement lines.

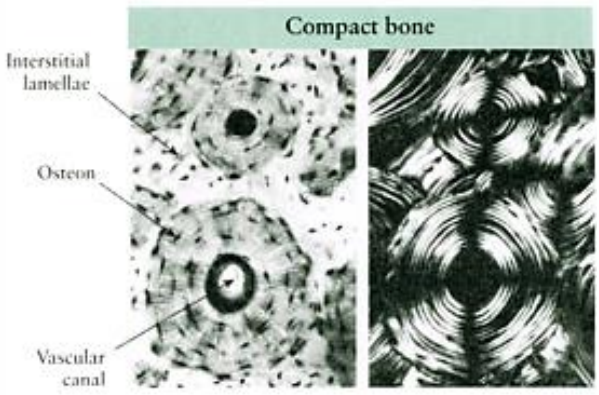


Fig 1: Cross section of compact bone showing osteons with osteocytes (left), and in polarized light with collagen lamellae (right).

The trabeculae also consist of structural units, which in this location are called packets. They are separated, as are the osteons of the cortex, by cement lines. When they are on the surface and not yet terminated, they are called bone multicellular units (BMUs). However, BMUs and packets are also found on the inner surface of the cortex, which therefore looks very much like trabecular bone. These two locations, trabeculae and inner cortex, are those that are affected predominantly by osteoporosis.

Trabeculae generally possess no vessels and are therefore nourished from the surface. This explains why they cannot become much thicker than about 2 0 0 - 3 0 0 µm, twice the distance of 100 µm over which transport of nutrients is possible.

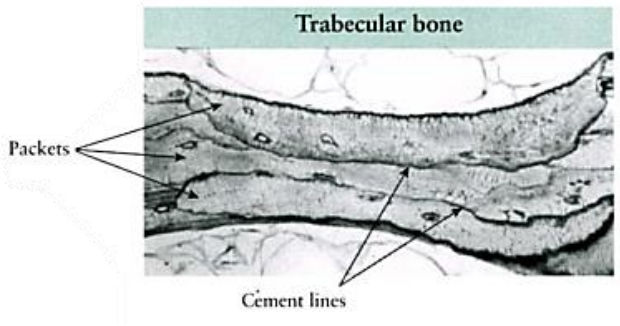


Fig2 : Trabecular bone showing individual packets separated by cement lines

1-2-2-1 bone cells:

1. Osteoprogenitor cells

These are cells of mesenchymal origin that can proliferate and convert themselves into osteoblasts whenever there is need for bone formation. They resemble fibroblasts in appearance.

2. Osteoblasts

These are bone forming cells derived from osteoprogenitor cells. They are found lining growing surfaces of bone. The cells are of varied shapes (oval, triangular, cuboidal etc.). The nucleus of these cells is ovoid and euchromatic.

These cells are responsible for laying down the organic matrix of bone including collagen fibers. They are also responsible for calcification of the matrix.

3. Osteocytes

These are the cells of mature bone. They lie in the lacunae of bone and represent osteoblasts that have been imprisoned in the bone matrix during bone formation. The main functions of osteocytes are

i) to maintain integrity of the lacunae and canaliculi and thus to open the channels for diffusion of nutrition through bone

ii) to remove or deposit matrix and calcium when required.

4. Osteoclasts

These are bone removing cells. These cells occupied pits called lacunae of Howship or resorption bays. These are very large cells (20 -100 micrometer in diameter). They have numerous nuclei – up to 20 at sites of bone resorption . Removal of bone by osteoclasts involves demineralization and removal of matrix, stimulated by factors secreted by osteoblasts and parathyroid hormone. They are derived from monocytes of blood.[3]

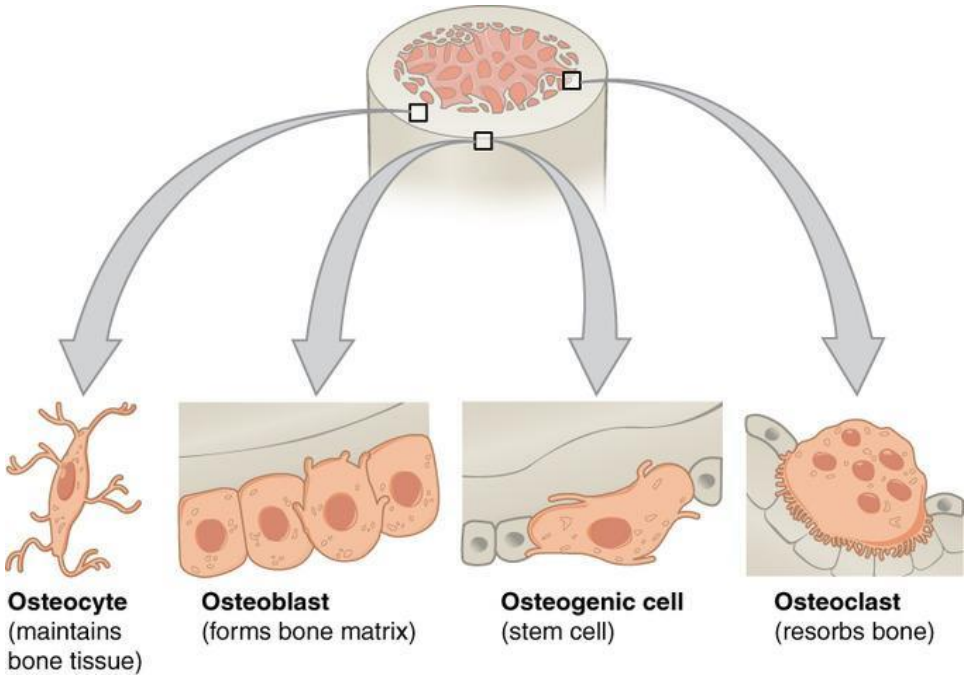


Fig3: Bone Cells. Four types of cells are found within bone tissue. Osteogenic cells are undifferentiated and develop into osteoblasts. When osteoblasts get trapped within the calcified matrix, their structure and function changes, and they become osteocytes. Osteoclasts develop from monocytes and macrophages and differ in appearance from other bone cells.

1-2-2-2 Extracellular matrix

which is made up of an organic matrix (30%) containing proteoglycans (but less than cartilage), glycosaminoglycans, glycoproteins, osteonectin (anchors bone mineral to collagen) and osteocalcin (calcium binding protein). There are collagen fibers (mostly type I (90%), with some type V). Only 25% of bone is water. Almost 70% of bone is made up of bone mineral called hydroxyapatite.[4]

2- Basal bone:

2-1 Maxillary bone:

2-1-1 Anatomical description:

The maxilla, also known as the upper jaw, is a vital viscerocranium structure of the skull. It is involved in the formation of the orbit, nose and palate, holds the upper teeth and plays an important role for mastication and communication.

This bone consists of five major parts, one being the body and four being projections named processes Bordered by several other bones of the viscerocranium, the maxilla on one side pairs with the corresponding bone on the opposite side via the intermaxillary suture.[5]

Each maxillary bone has the shape of a pyramid, it's base adjacent to the nasal cavity, its apex being the zygomatic process, and its body constituting the maxillary sinus. The maxilla connects with surrounding facial structures through four processes: alveolar, frontal, zygomatic and palatine. It articulates superiorly with the frontal bone, the zygomatic bone laterally, palatine bone posteriorly and with the upper teeth through the alveolar process inferiorly. Anteriorly, it forms the inferior and lateral borders of the pyriform aperture and articulates with the nasal bones medially at the anterior border of the frontal process.[6]

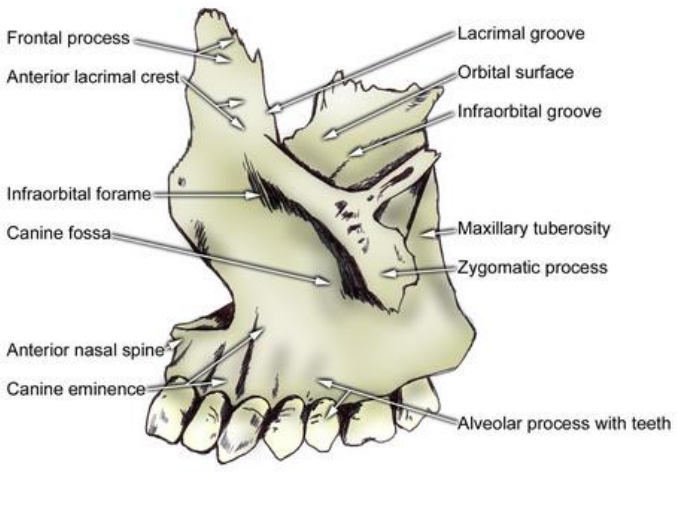


Fig 4 : Maxilla; Upper jaw, Left maxilla; Outer surface.
Contributed by Gray's Anatomy Plates

2-1-2 Blood Supply:

Blood supply to the maxilla is via branches of the maxillary artery. The maxillary artery is a terminal branch of the external carotid artery; it originates posterior to the upper portion of the mandibular ramus, runs anteriorly in the inner side of the mandibular ramus, and enters the pterygopalatine fossa to terminate with the pterygopalatine artery.[7] It has three major segments: mandibular, pterygoid, and pterygopalatine, from proximal to distal, respectively.

The pterygopalatine segment is the principal blood supply of the maxillary region. The pterygopalatine segment is in close relation to the pterygopalatine fossa from where it branches into five vessels: posterior superior alveolar artery (PSAA), infraorbital artery (IOA), greater palatine artery (GPA), sphenopalatine artery (SPA), and vidian artery (VA).[8] The VA is a recurrent branch and courses posteriorly to enter the Vidian canal, supplying the mucosa of the pterygopalatine fossa and nasopharyngeal cavity.

The PSAA runs towards the zygomatic process and has a prominent curve on its inner surface and courses towards maxillary tuberosity with branches supplying the upper molars and premolars. The IOA runs along the posterior wall of the maxillary sinus and enters the inferior orbital fissure and enters the infraorbital canal, supplying the lacrimal sac, upper incisors, canines, and mucous membrane of the maxillary sinus. The GPA emerges near the PSAA and descends through the greater palatine canal to exit through the greater palatine foramen to supply the hard palate. The SPA is the terminal branch of the pterygopalatine segment. It enters the nasal cavity posterior to the nasal turbinates to supply the nasal septum and turbinates. The posterior septal branch of the SPA courses through the incisive canal to form an anastomosis with the GPA. The PSAA, IOA, GPA, and SPA all supply the maxillary sinus walls and mucosa.[9]

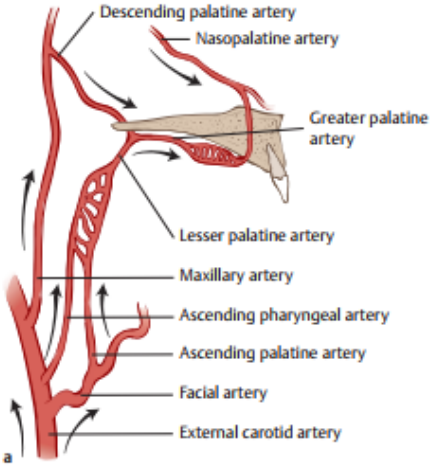


Fig 5: blood supply to the maxilla through the greater palatine artery, a branch of the descending palatine artery, and branch of the maxillary artery

2-2 Mandibular bone:

2-2-1 Anatomical description:

The mandible is a U-shaped bone. It is the only mobile bone of the facial skeleton[10], It is the largest bone in the human skull. It holds the lower teeth in place, it assists in mastication and forms the lower jawline. The mandible is composed of the body and the ramus and is located inferior to the maxilla. The body is a horizontally curved portion that creates the lower jawline. The rami are two vertical processes located on either side of the body; they join the body at the angle of the mandible. At the superior aspect of each ramus, the coronoid and condylar processes articulate

with the temporal bone to create the temporomandibular joint which permits mobility. Other than the ossicles of the ear, the mandible is the only skull bone that is mobile, allowing the bone to contribute to mastication.[11]

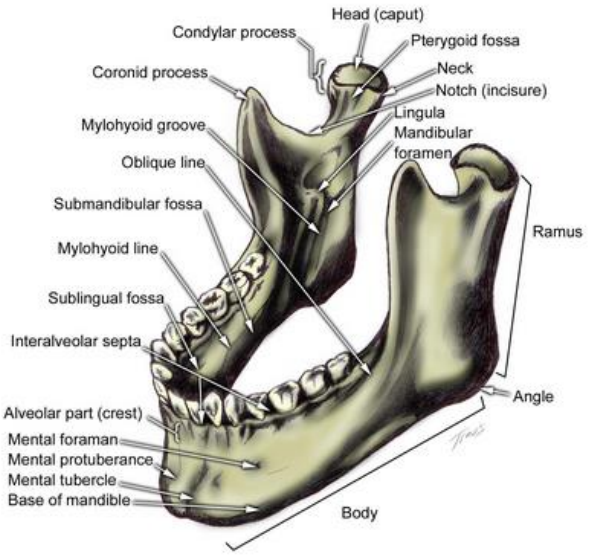


Fig6:Mandible, anterolateral superior view.

2-2-2 Blood Supply and Lymphatics

Blood supply to the mandible is via small periosteal and endosteal vessels. The periosteal vessels arise mainly from the inferior alveolar artery and supply the ramus of the mandible. The endosteal vessels arise from the peri-mandibular branches of the maxillary artery, facial artery, external carotid artery, and superficial temporal artery; these supply the body of the mandible. The mandibular teeth are supplied by dental branches from the inferior alveolar artery.

Lymphatic drainage of the mandible is primarily via the submandibular lymph nodes; however, the mandibular symphysis region drains into the submental lymph node, which subsequently drains into the submandibular nodes.[12]

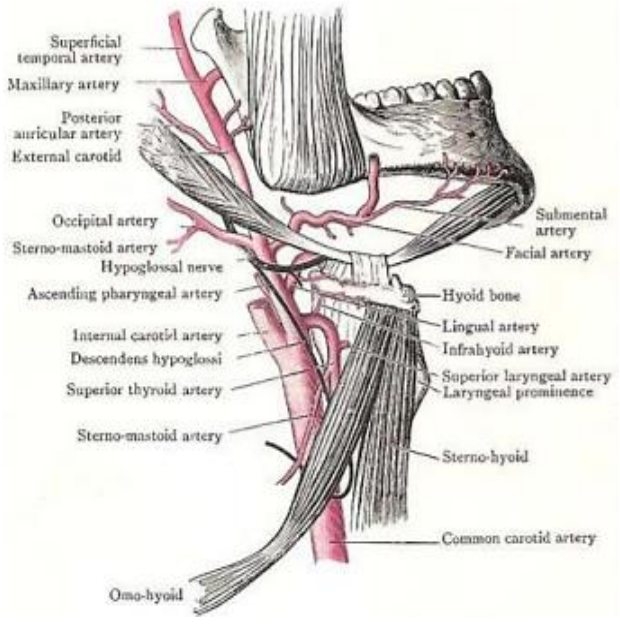


Fig7 : blood supply through the mandible via branches of the external carotid artery.

3- Alveolar bone:

3-1 Definition:

The alveolar process, which is also called the alveolar bone, is the thick ridge of bone which contains the tooth sockets. The alveolar bone is located on the jaw bones which hold the teeth. In humans, these bones that contain the teeth are the maxilla and the mandible. The curved portion of each alveolar process on the jaw is the alveolar arch.

3-2 Structure:

The alveolar bone is formed at the periphery by a compact outer layer of bone (external cortical) and an inner layer called the alveolar wall. The central portions between the cortical and alveolar walls (inter-dental and inter-radicular septa) consist of trabecular bones.

a-The cortical bone:

External cortical:

It forms the external wall of the alveolar bone. It is covered by the attached gums and is in continuity with the cortical portion of the basal portion. It's thicker on the maxilla than the mandible. Its thickness grows from the midline to the molars where it is maximum, and is higher on the lingual side compared to the vestibular side. It consists histologically of lamellar systems applied against each other and of Havers systems.

Alveolar wall:

It lines the alveolar cavity that receives the roots. It is the cell itself, also called cribriform blade or lamina dura. It consists of a portion of lamellar bone and fibrous bone where the main ligament fibres are inserted.

b-The trabecular bone:

Trabecular bone forms the body of the basal and alveolar bones. Also called spongy bone, its structure is organized into bony spans creating large cavities called medullary spaces and containing the bone marrow.
The spongy bone of the inter-dental and inter-radicular septa contains nutrient perforating channels that end at the alveolar ridge to deliver passage to the nerves and vessels.[13]

On the maxilla, the alveolar process is a ridge located on the inferior surface. On the mandible, it is a ridge located on the superior surface. It comprises of the thickest part of the maxillae.

The alveolar process includes a region of compact bone that is adjacent to the periodontal ligament (PDL). This is called the lamina dura when it is viewed on radiographs. It is the lamina dura which is attached to the cementum from the roots by the periodontal ligament. It is uniformly lighter. The integrity of the lamina dura is critical when studying radiographs for pathological lesions.

The alveolar process also has a supporting bone, both of which have the same components and includes the following: fibers, cells, intercellular substances, nerves, blood vessels and lymphatics.

The alveolar process is the lining of the tooth's socket and referred to as the alveolus. Although the alveolar process is made up of compact bone, it may also be called the cribriform plate as it contains various holes where Volkmann canals pass from the alveolar bone and into the PDL. The alveolar bone proper is also called the bundle bone because of the Sharpey fibers. A portion of the fibers of the PDL are inserted here. Similar to that of the cemental surface, Sharpey fibers located in the alveolar bone proper, are inserted at 90 degrees or at a right angle. They are also fewer in number, however, thicker in the diameter compared to those present in the cementum. Similar to the cellular cementum, Sharpey fibers are typically mineralized partially at their periphery.

The alveolar crest is the most cervical rim found in the alveolar bone proper. When it is healthy, the alveolar crest is slightly apical to the cementoenamel junction (CEJ) by about 1.5-2 mm. The alveolar crests of the adjacent teeth are also uniform in height along the jaw when they are healthy.

The supporting alveolar bone structure consists of both cortical and trabecular bone. The cortical bone, also known as cortical plates, consist of plates of compact bone found on the facial and lingual surfaces of the alveolar bone. These cortical plates are typically about 1.5-3 mm thick compared to the posterior teeth. However, the thickness varies drastically around the anterior teeth. The trabecular bone contains cancellous bone, which is located between the alveolar bone proper in addition to the plates of cortical bone. The alveolar bone is located between two neighboring teeth is the interdental septum.[14]

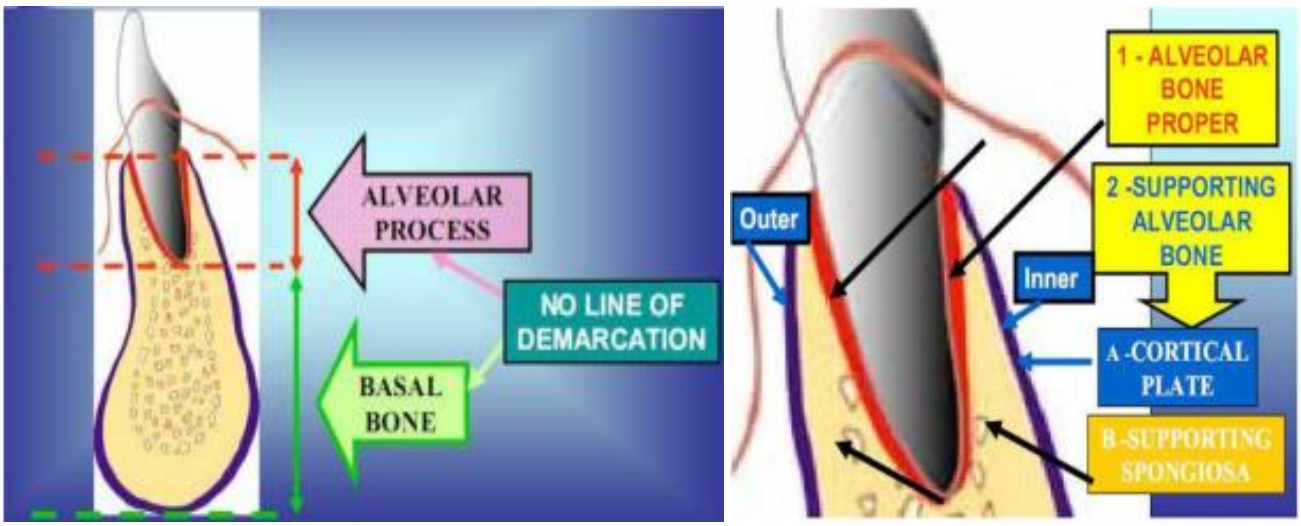


Fig8: a simplified structure of alveolar bone

3-3 Blood supply and venous drainage of the maxillary alveolar bone and teeth:

From the external carotid artery arises the **maxillary artery** which supplies both the maxillary and mandibular teeth.

The maxillary arch is supplied by a plexus of three arterial branches which include the anterior superior alveolar artery, the middle superior alveolar artery and the posterior superior alveolar artery.

- The **posterior superior alveolar artery** stems from the **third division** of the maxillary artery. It arises in the middle cranial fossa before the maxillary artery enters the pterygopalatine fossa. It continues on and enters the infratemporal surface of the maxilla to supply the maxillary sinus, the **premolars and the molars**.

- The **middle superior alveolar artery** arises from the infraorbital artery as does the anterior superior alveolar artery. Sometimes however this artery is not present. If it is, it arises within the infraorbital canal where it descends to supply the maxillary sinus and the plexus at the level of the canine.
- The **anterior superior alveolar artery** also arises at the level of the middle superior alveolar artery and runs with it to supply the **anterior portion of the maxillary arch**, the maxillary sinus and the anterior teeth.

As for the venous drainage, the posterior superior alveolar vein, the middle superior alveolar vein and the anterior superior alveolar vein drain into the **pterygoid venous plexus**.

3-4 Blood supply and venous drainage of the mandibular alveolar bone and teeth:

The maxillary artery gives rise to a single branch to supply the mandibular teeth which is known as the **inferior alveolar artery**. It descends inferiorly along with the inferior alveolar nerve and enters the bone via the mandibular foramen. At the level of the second premolar, it terminates into the branches of the **mental and incisive arteries** after it has supplied all of the mandibular teeth.

The mental and incisive arteries supply the labial gingiva of the anterior teeth and the anterior teeth themselves respectively.

The **inferior alveolar vein** is the sole collector of the blood pumped around the mandible and it drains into the **pterygoid venous plexus**.[15]

4- Bone Remodeling:

4-1 Definition:

Bone remodeling (or bone metabolism) is a lifelong process where mature bone tissue is removed from the skeleton (a process called bone resorption) and new bone tissue is formed (a process called ossification or new bone formation). These processes also control the reshaping or replacement of bone following injuries like fractures but also micro-damage, which occurs during normal activity. Remodeling responds also to functional demands of the mechanical loading.[16]

Bone remodeling performs three main functions:

- It first allows the body to regulate the mineral balance (homeostasis of calcium and phosphate).
- It then acts as a mechanism for adapting the skeleton to its mechanical environment, thereby reducing the risk of fracture.
- Finally, it is a mechanism for tissue renewal and repair of bone damage, created especially during stress.

The first of these functions is fulfilled through a redesign that does not depend on the site. To restore the mineral balance, the regulation involved is systemic and the bone tissue as a whole is

solicited until the mineral balance is restored. The other two functions, on the other hand, require a more targeted site redesign.

The alveolar bone is in constant flux. Its physiological lability is maintained by a constant balance between the phenomena of formation and resorption, ensuring the renewal of bone structures.

In the normal state, as for example during the physiological migration of the teeth, the amount of bone destroyed is equal to the amount of bone formed. In other situations, such as hypofunction or hyperfunction, the balance between resorption and formation is unbalanced.[17]

4-2 the different phases of remodeling:

This remodeling is mainly ensured by the succession of the phases of resorption and affixing.

- Osteoclasts are responsible for the destruction of old or altered bone and osteoblasts synthesize a new bone matrix.
- The metabolic activities of these two cell populations are coupled in space and time.
- The reshaping cycle, highlighted and called ARIF cycle by Baron, lasts about three months in adults, the training phase is longer than the resorption phase. This cycle consists of 5 phases:

1/Activation

2/Resorption

3/Reversal

4/Formation

5/Termination

To begin the rework cycle and enter the activation phase, the bone must be stimulated.

This stimulus, which induces the transformation of macrophages into osteoclasts and mesenchymal cells undifferentiated in osteoblasts, is attributed to different factors: variations of ionic calcium, vascular changes, or biochemical transformations.[18]

1/Activation:

Osteoclast precursor cells are recruited from the circulation and activated; the bone surface is exposed as the lining cells separate from underlying bone and form a
raised canopy over the site to be resorbed. Multiple mononuclear cells fuse to form multinucleated preosteoclasts which bind to the bone matrix to form sealing
zones around bone-resorbing compartments, thus isolating the resorption pit from surrounding bone.[19]

Initiation of bone remodeling is the first important step ensuring that, in health, remodeling only takes place when it is required. In targeted remodeling, which refers to removal of a specific area of damaged or old bone, the initiating signal originates from the osteocytes that use their extensive network of dendritic processes to signal to other cells.

Osteocyte apoptosis, induced for example by the disruption of osteocyte canaliculi caused by bone matrix microdamage, leads to release of paracrine factors that increase local angiogenesis and recruitment of osteoclast and osteoblast precursors. By contrast, nontargeted remodeling refers to remodeling in response to systemic changes in hormones such as parathyroid hormone (PTH), thus allowing access to bone calcium stores and is not directed towards a specific site.[20]

2/Resorption :(approximately two weeks)

Differentiation and activation of osteoclasts are also regulated by osteocytes. Rearrangement of the osteoclast cytoskeleton results in adherence to the bone surface, formation of a sealing zone and generation of a ruffled border that provides a greatly enhanced secretory surface area. Initially, osteoclasts pump protons, generated by Carbonic Anhydrase II, into the resorbing compartment to dissolve the bone mineral.

Specifically, the H+ATPase pumps H+ into lacunae; this is coupled to Cl transport via a chloride channel thus maintaining electroneutrality. Subsequently, the collagen-rich bone matrix is degraded by proteases such as cathepsin K and matrix metalloproteinases. The resorption phase is terminated by osteoclasts programmed cell death, ensuring that excess resorption does not occur.[21]

3/Reversal: (approximately four to five weeks)

The reversal phase, where bone resorption switches to formation, is still not well understood. However, there are thought to be two key events occurring. Firstly, the freshly resorbed bone surface is prepared for deposition of new bone matrix and further signaling occurs that couples resorption to formation, ensuring that there is no net bone loss. Preparation of the bone surface is carried out by cells of an osteoblastic lineage which remove unmineralized collagen matrix, and a non-collagenous mineralized matrix ‘cement-line’ is then deposited to enhance osteoblastic adherence.[22]

The exact signal that couples bone resorption to subsequent formation is not yet fully understood. However, it is likely that the cells of the reversal phase are involved in sending or receiving these signals. It has been postulated that osteoclasts may be the source of the coupling factor, either secreting cytokines such as interleukin 6 (IL-6), or via a regulatory receptor on their surface such as the Ephrin receptor family and their membrane bound ligand, Ephrins, present on osteoblasts. Other signaling pathways may include matrix-derived factors such as BMP-2, transforming growth factor β and insulin-like growth factor.[23]

4/Formation: (approximately four months)

New bone formation can be divided into two parts.

Firstly, osteoblasts synthesize and secrete a type 1collagen-rich osteoid matrix.

Secondly, osteoblasts play a part in regulating osteoid mineralization.60 The process of bone mineralization, whereby hydroxyapatite crystals are deposited amongst collagen fibrils, is complex and its regulation is incompletely understood. Control is exerted by systemic regulation of calcium and phosphate concentrations, local concentration of calcium and phosphate within extracellular matrix vesicles and by local inhibitors of mineralization, including pyrophosphate and non-collagenous proteins such as osteopontin.

The ratio of inorganic pyrophosphate to phosphate is a critical regulator of mineralization, and the relative activities of tissue nonspecific alkaline phosphatase and ectonucleotide pyrophosphatase are the key determinants of this ratio.[24]

5/Termination:

Once mineralization is complete, osteoblasts undergo apoptosis, change into bone-lining cells or become entombed within the bone matrix and terminally differentiate into osteocytes. Osteocytes play a key role in signaling the end of remodeling via secretion of antagonists to osteogenesis.[25]

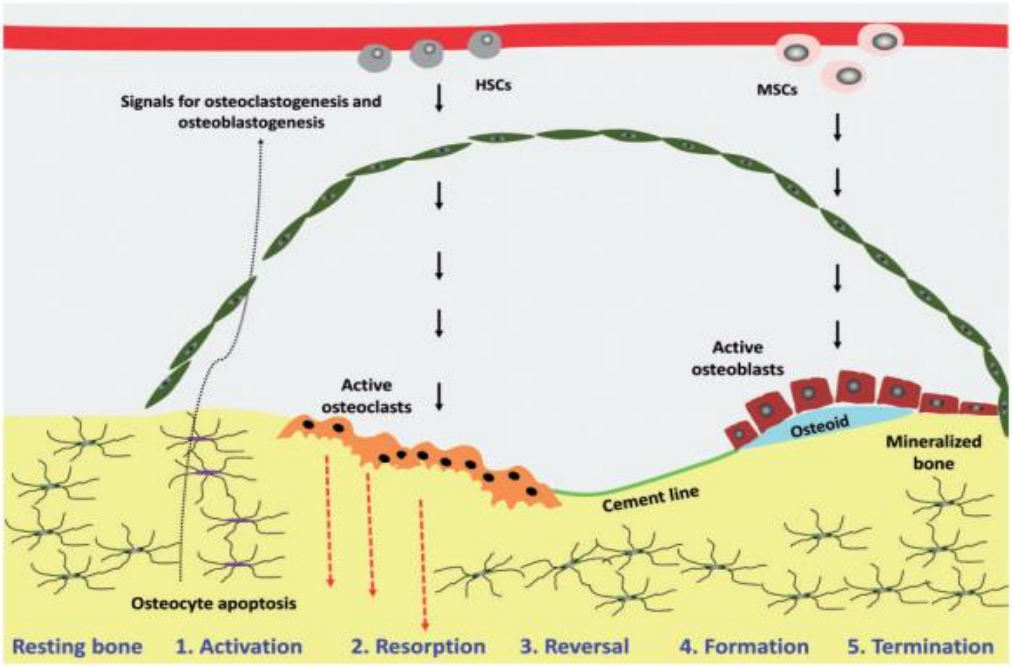


Fig 9 : BMU at different phases of the bone remodeling cycle.

4-3 REGULATORY FACTORS IN BONE REMODELING

The balance between bone resorption and formation is influenced by such interrelated factors as genetic, mechanical, vascular, nutritional, hormonal and local.

4-3-1 Genetic factors:

These are important in determining the maximum bone mass, since between 60 and 80% of this is genetically determined. Thus, Black people have a greater bone mass than Whites, who in turn have a higher mass than Asians. Bone mass is a characteristic transmitted from parents to children, which is why daughters of mothers with osteoporosis are more predisposed to having this condition themselves.[26]

4-3-2 Mechanical factors

Physical activity is essential for the correct development of bone. It is believed that muscular action transmits tension to the bone, which is detected by the osteocyte network within the osseous fluid. These osteocytes produce regulators such as prostaglandins, nitric oxide and IGF-I, which stimulate both their own and the osteoblast activity, increased bone formation. On the other hand, the absence of muscular activity, rest or weightlessness has an adverse effect on bone, accelerating resorption.[27]

4-3-3 Vascular/nerve factors

From studies by Trueta, it is known that vascularization is fundamental for normal bone development, supplying blood cells, oxygen, minerals, ions, glucose, hormones and growth factors. Vascularization constitutes the first phase in ossification: the blood vessels invade the cartilage and later produce resorption via the osteoclasts originating from the nearby vessels. In the same way, vascular neoformation is the first event in the repair of fractures or bone regeneration, since the supply of oxygen is fundamental to the production of the restitutio ad integrum rather than fibrous tissue. Ham described this phenomenon in 1952, observing that the osteocytes die when they are at some distance from a capillary vessel (the maximum distance being 0.1 mm). Innervation is necessary for normal bone physiology. The bone is innervated by the autonomous nervous system and by sensorial nerve fibers. Autonomous fibers have been found in periosteum, endosteum, cortical bone and associated with the blood vessels of the Volkmann conduit, and likewise neuropeptides and their receptors in bone. Examples of the importance of innervation in bone physiology are found in osteopenia and the bone fragility present in patients with neurological disorders, and also in the decreased bone density in de-nerved mandibles.[28]

4-3-4 Nutritional factors

This factor is interesting because it can be modified. A minimum amount of calcium is needed for mineralization, which the majority of authors put at 1,200 mg per day to the age of 25, not less than 1g per day from 25 to 45, and following menopause should be at least 1,500 mg per day. Likewise, it is known that toxic habits such as smoking, caffeine, alcohol and excess salt constitute risk factors for osteopenia.[29]

4-3-5 Hormonal factors

The metabolic functions of the skeleton are served in large part by two major calcium-regulating hormones, parathyroid hormone (PTH)1 and 1,25-dihydroxy vitamin D. A third hormone, calcitonin, which can inhibit bone resorption, may be important in skeletal development but appears to play little role in physiologic calcium regulation in adult humans. It is a potent inhibitor of bone resorption and is used clinically in the treatment of osteoporosis.

PTH regulates serum calcium concentration. It is a potent stimulator of bone resorption and has biphasic effects on bone formation. There is an acute inhibition of collagen synthesis with high concentrations of PTH, but prolonged intermittent administration of this hormone produces increased bone formation, a property for which it is being explored clinically as an anabolic agent. Plasma PTH tends to increase with age, and this may produce an increase in bone turnover and a loss of bone mass, particularly of cortical bone. 1,25-Dihydroxy vitamin D has its greatest effect on intestinal calcium and phosphate absorption, but it may also have direct effects on bone and other

tissues. It is probably critical for the differentiation of both osteoblasts and osteoclasts and can stimulate bone resorption and formation under some experimental conditions.

Other systemic hormones are important in regulating skeletal growth. Growth hormone, acting through both systemic and local insulin-like growth factor (IGF) production, can stimulate bone formation and resorption. Glucocorticoids are necessary for bone cell differentiation during development, but their greatest postnatal effect is to inhibit bone formation. This is the major pathogenetic mechanism in glucocorticoid-induced osteoporosis. Indirect effects of glucocorticoids on calcium absorption and sex hormone production may, however, increase bone resorption. Thyroid hormones can also stimulate bone resorption and formation and are critical for maintenance of normal bone remodeling.

Probably the most important systemic hormone in maintaining normal bone turnover is estrogen. Estrogen deficiency leads to an increase in bone remodeling in which resorption outstrips formation and bone mass decreases. This can be observed not only in postmenopausal women, but also in men with defects either in the estrogen receptor or in the synthesis of estrogen from testosterone. The mechanisms by which estrogen regulates bone turnover are still not well understood, although studies in animals suggest that estrogen acts by altering either the production or activity of local factors that regulate osteoblast and osteoclast precursors. Estrogen treatment produces a decrease in both formation and resorption of bone associated with decreased remodeling but increases bone mass. This increase may simply be a result of the filling in of the resorption space. Alternatively, estrogen may inhibit local factors that impair bone formation or enhance local factors that stimulate bone formation.[30]

4-3-6 Local factors

Bone remodeling is also regulated by local factors, among which principally growth factors and cytokines, and recently the bone matrix proteins have been implicated as modulators of other local factors. Bone cells also play an important role in the production of prostaglandins and nitric oxide, as well as cytokines and growth factors.[31]

CHAPTER 2 :

BISPHOSPHONATES

1- Structure and classification of bisphosphonates:

1-1 Definition:

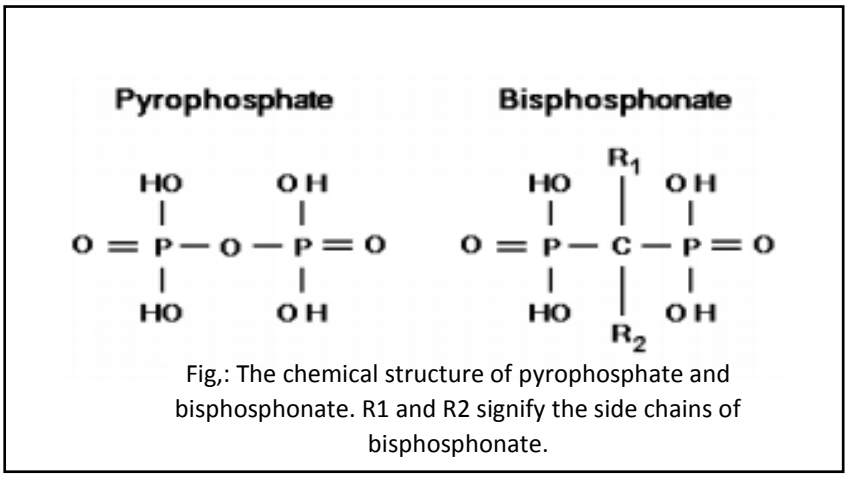
Bisphosphonates are anti-resorptive drugs that act specifically on osteoclasts, thereby maintaining bone density and strength[32]. Bisphosphonates are used in many clinical settings, including prevention and treatment of primary and secondary osteoporosis, Paget's disease of bone, hypercalcemia, multiple myeloma and osteolysis associated with bone metastases of malignant tumors[33]. They may directly inhibit the bone-resorbing activity of osteoclasts by mechanisms that can lead to osteoclast apoptosis.

Moreover, a study by Sahni et al [34] suggested that part of the inhibitory action of bisphosphonates on the osteoclasts is mediated through an action on the osteoblasts. However, it is not yet known whether this plays any important role *in vivo.*

1-2 Structure:

Bisphosphonates are synthetic pyrophosphate analogs with a P-C-P bond instead of the P-O-P bond of inorganic pyrophosphates, which are used as anti-tarter agents in toothpastes and as a bone-specific radionuclide in technetium 99m methylene diphosphonate (Tc 99m MDP) bone scans. Unlike pyrophosphates, bisphosphonates are resistant to breakdown by enzymatic hydrolysis, which explains their accumulation in the bone matrix and their extremely long half-life. The P-C-P structure allows a great number of possible variations, especially by changing the two lateral chains (R1 and R2) in the carbon atom. The two phosphate groups are essential for binding to bone mineral such as hydroxyapatite and together with the R1 side chain they act as a "bone hook". A hydroxyl (OH) group or an amino group at the R1 position increases the affinity for calcium and thus for bone mineral.

The structure and three-dimensional conformation of the R2 side chain determine the anti-resorptive potency and the enhanced binding to hydroxyapatite [35].



Fig,: The chemical structure of pyrophosphate and bisphosphonate. R1 and R2 signify the side chains of bisphosphonate.

1-3 Classification:

The newer classification differentiates bisphosphonates into the following groups: Nitrogen containing and non-nitrogen containing. It is based on the nature of the lateral chain and includes:

-No Nitrogen containing bisphosphonates that are now rarely used, they include **the first-generation BPs** with alkyl lateral chain ex: clodronate, etidronate, tiludronate

-Nitrogen containing bisphosphonates: are more widely used as they are extremely bone selective, they include the **second-generation BPs** with an amine-terminal side chain ex: paramidronate and alendronate and **the third-generation BPs** with cyclic lateral chain: zoledronate, risedronate.

Although the mechanisms of action are different, these molecules result in the inactivation and then apoptosis of osteoclasts. Zoledronate also has the ability to suppress pre-osteoclasts and thus inhibits osteogenesis and angiogenesis.

The fourth-generation BPs where the nitrogen atom is directly bound to the central carbon are being studied. In addition to their anti-osteoporotic activity, they possess antimicrobial and antiparasitic properties: incadronate or incadronic acid is already marketed in some countries[36]

Generation	Type	Examples
First generation	Non-nitrogen containing BPs	Etidronate (Didronel® Norwich Pharmaceuticals, Inc. North Norwich Clodronate (Bonefos® Bayer PLC, UK) Tiludronate (Skelid® Sanofi-Aventis Australia Pty Ltd)
Second generation	Alkyl-amino nitrogen containing BPs	Pamidronate (Aredia®, Novartis International AG, Basel, Switzerland) Alendronate (Fosamax®, Merck & Co., Inc. Kenilworth, New Jersey, USA) Ibandronate (Boniva®Roche and GlaxoSmithKline Brentford, London,UK) Olpadronate (Olpadronate Sodium®, PharmaChem USA)
Third generation	Heterocyclic nitrogen containing BPs	Risedronate (Actonel®, Sanofi S.A. Gentilly, France) Zoledronate (Reclast® Novartis Pharma AG, Switzerland)

Table: generations and types of Bps

2- Pharmacokinetics of Bisphosphonates:

Pharmacokinetics is the activity of drugs in the body over a period of time, including the process by which drugs are absorbed, distributed in the body, localized in the tissue ,and excreted.[37]

Bisphosphonates are a unique class of drugs. As a family, they are characterized pharmacologically by their ability to inhibit bone resorption, whereas, pharmacokinetically, they are classified by their similarity in absorption, distribution, and elimination. Although all bisphosphonates have similar physicochemical properties, their antiresorbing activities differ substantially. Activity is dramatically increased when the amino group is contained in the aliphatic carbon chain. For example, alendronate, an aminobisphosphonate, is approximately 700-fold more potent than etidronate, both in vitro and in vivo.[38]

2-1 Administration routes of Bisphosphonates:

A number of BPs have been approved for clinical use in Paget's disease, hypercalcemia of malignancy, and osteoporosis. The major disadvantage of the clinically utilized BPs is their poor oral absorption from the GI tract, typically less than 1% is absorbed. In addition, the BPs have been associated with adverse gastrointestinal effects in humans. The challenge for novel drug delivery systems is to achieve improved bioavailability and safety. Dosage form strategies reviewed include the use of particular formulations for increasing oral absorption as well as decreasing adverse gastrointestinal effects, absorption enhancers, BP compounds and the solubility of their calcium complex/salts, and the prodrug approach. Because of the poor GI absorption, attempts have been made to enhance the bioavailability of BPs by several parenteral routes other than i.v. injections. Description of nasal administration, s.c. and i.m. injections are reviewed.[39]

2-1-1 Oral administration:

Orally administered medications can cross the gastrointestinal epithelium by either the transcellular route or the paracellular route depending on their physiochemical properties.

Bisphosphonates are a large, hydrophilic molecule that cannot cross the gastrointestinal epithelium via the transcellular route and inefficiently utilize the paracellular route of absorption due to their large size and negative charge: the brush-border membrane is negatively charged and will often repel the negatively charged phosphate groups on the bisphosphonate from the epithelium and tight junctions. Finally, these negative charges also give bisphosphonates the tendency to bind with cations such as calcium and magnesium present in the intestinal lumen. In relation to this, the opening and closing of tight junctions has been linked to shifts in intracellular and extracellular movements of calcium. This additional supply of calcium ions may also interfere with the movement of the bisphosphonate through these junctions.

This will lead to lowering absorption and oral bioavailability.[40] Therefore , Oral administration of bisphosphonates is complicated by poor bioavailability (generally <5%) and poor gastrointestinal tolerability. First-generation bisphosphonates, such as clodronate (Bonefos; Anthra Pharmaceuticals; Princeton, NJ), must be administered at high oral doses (1,600-3,200 mg/day) to achieve therapeutic effects, which leads to poor tolerability and compliance with oral dosing regimens.[41]

2-1-2 Intravenous administration:

Bisphosphonate injections are given as a drip (infusion) into the vein. The infusion will take between 20 minutes and two hours depending on the type of bisphosphonate being given and the condition being treated.

Bisphosphonate infusions may be given once a year or up every two-three years or every three months depending on the type prescribed and the condition being treated.

Bisphosphonate injections come in different doses. The dose and how often it is given will depend on the type of bisphosphonate being used and the condition being treated.[42]

Intravenous therapy has gained a high degree of compliance, especially with patients who are already taking a number of other drugs. Additional advances are 100% bioavailability and no gastrointestinal side effects. Moreover, the effect on bone density and fracture rate are comparable to dose of oral therapy. Therefore, intravenous BPs formulations by long dosing interval and infrequent upper digestive tract adverse events, appear a logical alternative to oral preparations.

However, there are some concerns regarding potent intravenous bisphosphonates including: zoledronic acid, ibandronate and pamidronate with respect to tolerability, mainly the acute phase response and to safety, mainly a theoretical risk of over suppression of bone turnover, renal toxicity and osteonecrosis of the jaw.[43]

2-1-3 Nasal administration:

Apart from intravenous and oral routes for the administration of bisphosphonates, a nasal route has also been reported. The nose offers access to mucosal surfaces suitable for the delivery of vaccines and bioactive agents. This route offers several advantages: it provides a direct route for drugs into the blood stream; it protects the drugs from enzymatic attack that is common with oral administration of drugs resulting in enhanced bioavailability; the rate of absorption and plasma concentration is better than the subcutaneous routes; it is convenience, easy and painless.[44]

2-1-4 Subcutaneous injection:

Subcutaneous (SC) injection of BP's is associated with considerable cutaneous toxicity. The tolerability of SC BP with recombinant human hyaluronidase (rHuPH20), an enzyme that increases the absorption of locally injected drugs by degrading hyaluronan (HA) in the skin interstitium was therefore explored.[45]

2-1-5 Intramuscular injection:

the bisphosphonate clodronate is also available via the intramuscular (i.m.) route of administration, and the present study was performed to test its efficacy.

Random patients were given intramuscular clodronate. We noticed an increase in BMD, though a substantial pain at the site of injection.
These results indicate that intermittent i.m. clodronate administration can provide clinically relevant benefits to bone density, but the in-situ pain may limit its extensive use.[46]

2-2 Absorbtion of Bisphosphonates:

Absorbtion is the movement of drugs into the bloodstream after administration. It affects bioavailability—how quickly and how much of a drug reaches its intended target of action.[47]

2-2-1 Intestinal Absorbtion:

In general, bisphosphonates are poorly absorbed from the gastrointestinal tract (between 1% or less and 10% of the amount ingested) as a result of their poor lipophilicity.[48]

Nitrogen containing bisphosphonates, alendronate, risendronate and ibandronate, have an absorption value (F) of 0.7%, whereas non-nitrogen containing bisphosphonates, clodronate and etidronate have a higher F of 2.0-2.5%.

The bisphosphonates studied up to now, such as etidronate, clodronate, pamidronate, and alendronate, are absorbed, stored, and excreted unaltered. The intestinal absorption of the bisphosphonates is low. The newer bisphosphonates are at the lower end of the scale.[49]

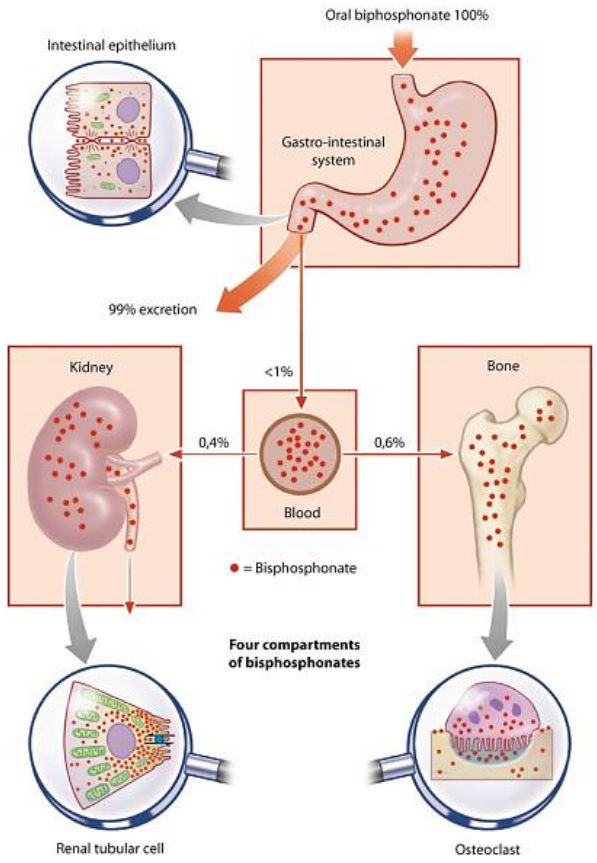


Fig10 : Diagrammatic representation of the four compartments of bisphosphonate absorption and excretion: Gastro-intestinal tract, blood, bone and kidney

2-3 Distribution half-life :

Bisphosphonates are bound to albumin in the blood. There are big differences in the strength of the albumin bonds (from 22% for Zoledronate to 87 for ibandronate) and therefore in the time it takes for the bisphosphonate to be eliminated from the plasma.

The half-life of the Zoledronate in the plasma Is only 1-2 hours, while that of ibandronate is 10-16 hours.but the half life in the bone is much longer, it lasts for several years.

Bisphosphonates in the plasma are actively bound to the surface of the bones, especially in the resorption lacunae where they are attached to calcium. The amount of deposition depends on the extent of resorption surface of bone available.[50]

- **Affinity to Bone :**

By binding to hydroxyapatite, bisphosphonates accumulate at sites of bone resorption and are selectively internalized by actively resorbing osteoclasts. The different bisphosphonates have different affinities for hydroxyapatite crystals.

These differences in binding affinities and effects on mineral surface properties are likely to be reflected in the clinical differences among these bisphosphonates: uptake and retention on the skeleton, diffusion of the drug within the bone, release of absorbed drug from the bone, potential recycling of the desorbed drug back onto bone surface, effects on mineral dynamics, and affects on bone cellular function.[50]

2-4 Elimination of Bisphosphonates:

Bisphosphonates are eliminated without prior metabolism via the kidneys. This renal clearance of bisphosphonates is accomplished by glomerular filtration as well as active tubular excretion. Bisphosphonates are passively bourne by the blood stream to the kidneys; the quantity depends on the concentration gradient of the bisphosphonate in the blood. Bisphosphonates released from the surface of the bone (T½ 150–200 h) also reach the kidneys by way of the blood stream and are actively eliminated by the proximal tubules.

Consequently, excretion of bisphosphonates given by intravenous infusion is multiphasic – a fast biphasic elimination from the blood stream, followed by a lengthier phase with a final elimination half-life of several days. Even after administration of a number of doses, accumulation in the plasma does not occur.

About half of the amount of bisphosphonate given at any time is excreted unchanged by the kidneys within 24 h. The half-life time of the bisphosphonates in renal tissue is very variable. It is clear that these differences are responsible for differences in toxicity to the kidney, particularly if and when administration is repeated. Therefore, when dealing with patients with impaired renal function, precautionary measures have to be applied.[50]

3- Pharmacodynamics of Bisphosphonates:

Pharmacodynamics is the study of the mechanisms by which a drug affects an organism at different levels. The cellular and molecular targets of bisphosphonates are multiple. The action resulting is a pharmacological inhibition of bone resorption. Their mechanism is complex.

3-1 At the tissue level:

Bisphosphonate improvement of mechanical strength, reflected in a reduction in fracture risk, is caused by an increase in bone mass, as well as by an improvement in architecture, which is attributable to a reduction in bone turnover. A higher number of bone-remodeling sites, where excessive osteoclastic destruction of bone takes place, leads to formation of areas of stress concentration and, thus, increased risk of fracture.

By reducing turnover, bisphosphonates reverse this condition. Decreased bone turnover also explains the overall prevention of bone loss.

The initial rise in bone mass is caused by the continued rebuilding of basic multicellular units (BMU) that were initiated before bisphosphonate treatment. Bisphosphonates also reduce the number of new BMUs and, at individual BMUs, they act by decreasing the depth of resorption and possibly increasing wall width during the formation phase [51].

Another mechanism for increased bone strength is the increase in mineralization associated with lower bone turnover. Lower turnover lengthens the life span of the BMU, thus permitting it to mineralize more completely and increase mineral content. [52,53,54]

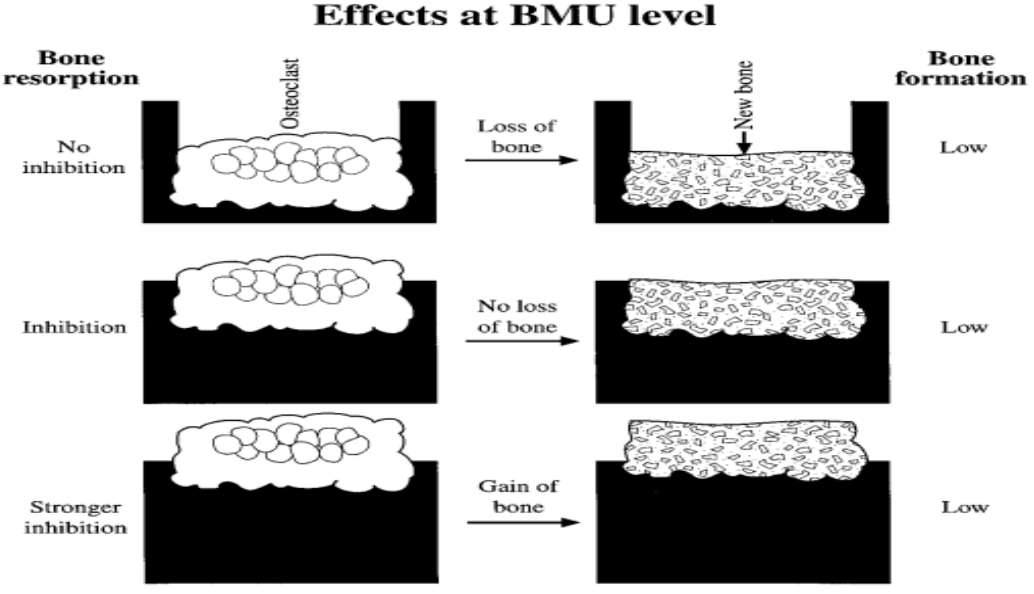


Fig 11: Possible effects of bisphosphonates at the level of the individual BMU.

3-2 At the Cellular level:

At the cellular level, there is general agreement that the final target of bisphosphonate action is the osteoclast. Bisphosphonates could reduce osteoclastic bone resorption through:

(a) alteration of the bone or bone mineral in ways which reduce, by a pure physicochemical and not a cellular mechanism, the rate of its dissolution.
(b) inhibition of osteoclast activity on the bone surface;
(c) inhibition of osteoclast recruitment to the bone surface;
(d) shortening of the osteoclast lifespan;

These effects could be due to direct action on the osteoclast, or indirectly via action on cells which modulate the osteoclast.

(a) Alteration of bone mineral:

The earliest hypothesis for bisphosphonate action on bone proposed physical effects on mineral dissolution. Although bisphosphonates, like pyrophosphate, could affect this process, it is now obvious that the low concentration of bisphosphonates, and especially of the newer more potent ones necessary to produce a pharmacological effect, has no significant impact on mineral dissolution and that their action is therefore cellular.

(b) Inhibition of osteoclast activity on the bone surface:(**Direct action on osteoclasts):**

BPs are mostly taken up by bone tissue, and selectively bind to the hydroxyapatite crystal structure of the mineral phase of bone tissue at active sites of resorption.

In the bone resorption phase, the proton pump of the brush border of the osteoclast acidifies the medium.

Acidification of the medium triggers the secondary release of BPs and their concentration under the osteoclastic cells.

The bisphosphonate molecules are then internalized in the cell by endocytosis, where they act on glycolysis, enzymatic activity, protein synthesis and decrease in acid production.

This direct action at the level of the osteoclastic cell is revealed by the disappearance of the brush border of the osteoclasts and changes in the cytoskeleton, a sign of the disruption of cell activity. There is a decrease in both the activity of osteoclasts and their number (death by apoptosis). [55]

(c) Inhibition of osteoclast recruitment to the bone surface: (indirect action on osteoclasts)

the effect on osteoclastic precursors, or by the induction of the production by osteoblasts of a factor inhibiting recruitment and / or decreasing the lifespan of osteoclasts [56,57] .

- **Action on Osteoclastic precursors:**

Mononuclear osteoclastic precursors present in the bone marrow differentiate into mature multinucleated osteoclasts on the bone surface. Certain bisphosphonates have been shown in vitro to act indirectly by inhibiting the synthesis of osteoclastic precursors and their processing.

This action results in a decrease in the recruitment of active osteoclasts and therefore a decrease in bone remodeling sites. [58]

- **Action on osteoblasts :**

BPs stimulate the production by osteoblasts of factors that inhibit osteoclast formation. This factor is thought to act on osteoclastic precursors and prevent the formation of mature osteoclasts. This results in the inhibition of bone resorption activity.

(d) Shortening of the osteoclast lifespan:

The life span of osteoclast nuclei has been estimated from histomorphometric studies at 2 weeks [59]. However, bisphosphonates can shorten their lifespan inducing their apoptosis and this is due to a toxic accumulation of bisphosphonates within the cell.

3-3 At the molecular level:

At this level, bisphosphonates interfere with the **mevalonate** pathway by inhibiting formation of the lipid chains of prenylated proteins and thus also with metabolism of steroids.

Bisphosphonates inhibit the formation of lipid chains of prenylated proteins, while statins effect the synthesis of mevalonic acid by inhibition of **HMG-CoA-reductase**, the bisphosphonates interfere with the earlier phases of prenylation and of steroid synthesis [60]. The following steps in the process of mevalonic acid synthesis are clinically relevant and are targets of the bisphosphonates:

1. The first-generation bisphosphonates (non nitrogen- containing bisphosphonates) together with adenosine monophosphate, they form an **ATP** analogue which cannot be hydrolyzed and thereby withholds the energy required for the synthesis of isopentenyl pyrophosphate.

2. The second-generation bisphosphonates (nitrogen-containing) – these prevent the enzymatic switch of *Dimethylallyl pyrophosphate* to *geranyl pyrophosphate*.

3. The third-generation bisphosphonates (nitrogen- containing) – these additionally block the next step in the enzymatic reaction, *conversion of geranyl pyrophosphate to farnesyl pyrophosphate or to geranylgeranyl pyrophosphate* [61] .

Consequently, the cells become *inactive*, lose their membrane-specific properties, and eventually induce programmed cell death, *apoptosis.*

Initially, this blockage takes place in the osteoclasts, due to their uptake of bisphosphonates from the osseous surface. Within osteoclasts, bisphosphonates cause many changes that affect their ability to resorb bone, such as loss of the ruffled border, disruption of the cytoskeleton, and inability to migrate or bind to bone [61].

Because of the inhibitory effect of nitrogen containing bisphosphonates, there is an increase in the concentration of **IPP**, which in turn results in the formation of isopentenyl ATP by means of its reaction with AMP. This combination triggers the excretion of **caspases** (intracellular proteolytic enzymes that mediates apoptosis) and thereby programmed cell death .

It should be stressed that the same process occurs in all cells in which bisphosphonates accumulate and it is responsible for the (desired) effects as well as the (unwanted) side effects of the bisphosphonates.

Nowadays, mainly nitrogen containing bisphosphonates (second and third generation) are widely used in clinical practice. Their activity is strongly dependent on local pH values. In acidic milieus nitrogen-containing bisphosphonates are released and activated and exert their therapeutical effects as well as their side effects[61].

In summary, inhibition of osteoclastic resorption is accomplished by means of three different mechanisms corresponding to the three generations of bisphosphonates [61].

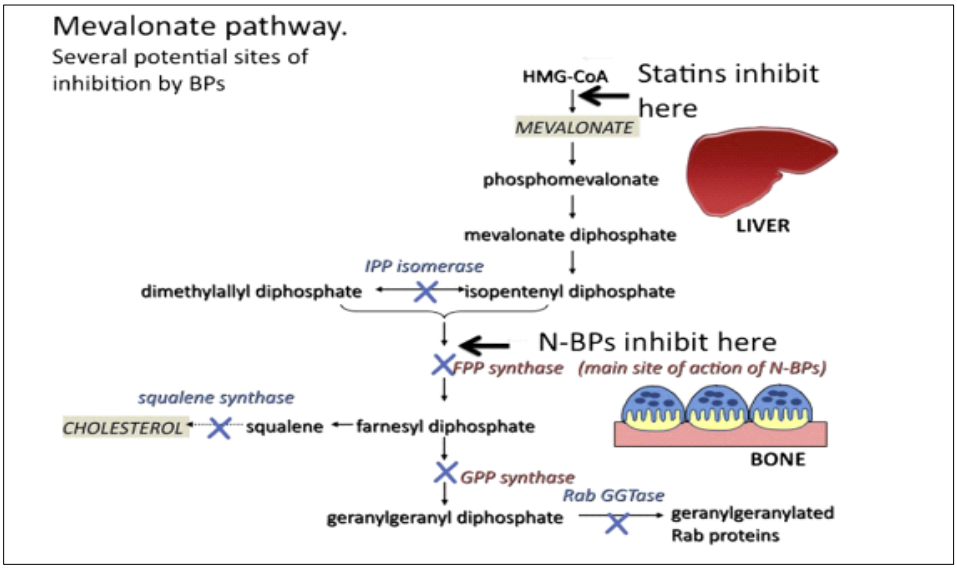


Fig12: The different effects of statins and BPs in the mevalonate pathway, indicating how tissue selectivity of uptake determines their pharmacological specificity [62].

4- The biological effects and mechanisms of action of Bisphosphonates:

The bisphosphonates have two fundamental biological effects: inhibition of calcification, when given at high doses, and inhibition of bone resorption[63].

4-1- Inhibition of calcification:

The mechanism of action is physico-chemical: bisphosphonates have a very strong affinity for calcium phosphate crystals; they bind to calcium by chemisorption and prevent both dissolution and growth of crystals.

Bisphosphonates have a regulatory property on endogenous calcium metabolism which enables them to prevent ectopic calcifications in vivo. This prevention of extra osseous calcifications is obtained by their action on the mineral tissue but also by their effects on cholesterol, elastin, and the collagen of the arterial walls. They prevent the build-up of lipoproteins in macrophages, which is the first phase in the process of atherosclerosis. Bisphosphonates have a beneficial effect in arterial calcifications, they have proven their effects in the treatment of certain calcifying conditions such as myositis ossifying for more than three decades and they have recently been used in the treatment of intracerebral calcifications.[64]

4-2- Inhibition of bone resorption:

In vitro and in vivo studies have shown that inhibition of bone resorption is the main effect of Bps, which are potent inhibitors of osteoclastic activity; they reduce bone remodeling, `` turn-over '', by binding strongly to the bone, they are not metabolized and remain accumulated in the bone until the area, in which they are trapped, is degraded again.

This effect is seen in healthy subjects as well as in subjects with osteolytic disease.

- At the tissue level: Their major effect is a strong inhibition of bone remodeling.
- At the cellular level: Bps inhibit the activity and differentiation of osteoclasts.

4-3- Anti-tumor effect:

Several studies have demonstrated the capacity of certain amino-bisphosphonates to reduce the proliferation and viability of tumor cell lines in vitro. Experiments in animal models have also shown that they can reduce tumor burden and slow the progression of bone lesions [65] .

Bisphosphonates act by various mechanisms:

- Indirect mechanisms: By reducing osteolysis and the local release of growth factors they would make the bone less favorable for the growth of tumor cells, and they could also inhibit their adhesion to the bone extracellular matrix [64].

  In addition, bisphosphonates could make tumor cells more sensitive to cytotoxic

  T lymphocytes and increase this cell population up to 50 times.

- Direct mechanism: bisphosphonates appear to be able to directly induce apoptosis in tumor cell lines.

Since the cellular absorption of bisphosphonates is quite poor, research is now focused on the development of prodrugs which, by intracellular activation, could release bisphosphonates inside cancer cells [66].

4-4- Anti-angiogenic effect:

Bisphosphonates would have anti-angiogenic activity: they would be able to oppose the formation of new vessels by reducing the proliferation of endothelial cells and increasing their apoptosis, by reducing the formation of capillaries as well as the circulating level of VEGF (Vascular Endothelial Growth Factor).

Zoledronate and ibandronate have thus shown their ability in vitro to inhibit the proliferation of endothelial cells.

A decrease in the Vascular Endothelial Growth Factor has also been observed in patients treated with pamidronate.

The anti-angiogenic effect of these drugs could therefore be compared to the effect of radiotherapy which alters bone metabolism by associating hypovascularization, hypocellularity and hypoxia.

The importance of this anti-angiogenic activity, however, needs to be confirmed in human clinics [67].

4-5- Effect on bone formation:

Studies have suggested that Bps may have a direct effect on bone formation: [64]

- An increase in bone formation has been observed in BMUs
- Icadronate administered orally at a toxic dose for 13 weeks caused intramembranous bone formation in the intramedullary area
- In vitro bisphosphonates caused proliferation of osteoblasts and cartilage cells as well as increased production of collagen and osteocalcin by bone cells and proteoglycan by cartilage cells.

Very recently, a study showed that zoledronate and ibandronate were able to enhance the expression of gènes for osteoblast differentiation markers when present at a certain concentration. On the other hand, at lower concentrations, they would lead to a decrease in the expression of these genes. Non-nitrogenous. bisphosphonates would have less influence [68] .

4-6- Pro-inflammatory effect:

Inhibition of farnesyl diphosphate synthase (FPPS) causes the accumulation of isopentenyl pyrophosphate (IPP) which will activate T lymphocytes. They then release TNF-α, which initiates an inflammatory phase.

This pro-inflammatory effect is particularly well demonstrated by the frequent occurrence of a flu-like syndrome during IV administration of bisphosphonates [69].

4-7- Effects on uncalcified tissue:

At very high doses (and probably not at a therapeutic dose), bisphosphonates have shown multiple effects which are still poorly understood: effects on the immune system, increase in HDL, inhibition of the growth of protozoan parasites (Entamoeba, Plasmodies, Trypanosomes, Toxoplasma, Cryptosporidia, and Leishmania), action on the gastric mucosa...etc[70]

In vitro, bisphosphonates bound to a bone surface have also been show to be able to inhibit the growth of adjacent epithelial cells. [68]

5- Therapeutic Indications :

5-1 Non-malignant pathologies :

5-1-1 Osteoporosis :

Osteoporosis is a skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [71].

The treatments used in the management of osteoporosis are calcium and vitamin D preparations, biphosphonates, SERM (Selective Estrogen Receptor Modulator) such as Raloxifene, anabolic substances, calcitonin and monoclonal antibodies (Denosumab). Currently BPs used in the treatment of osteoporosis are often administered orally, but sometimes also intravenously [72]. Women receiving bisphosphonates present decreased bone turnover and serum markers of bone turnover, such as cross-linked C-telopeptides of collagen type 1[73].

5-1-2 Paget's disease:

This pathology is characterized by an abnormality of bone remodelling that results in excessive osteoclast activity (resulting in the resorption of the bone), and an increase in the filling of resorby spaces, by osteoblasts. The result is an abnormally fragile bone because the neoformed bone is disorganized [74].

Bisphosphonates allow the return to physiological bone remodelling, with reconstruction of a histologically normal bone. They stabilize the disease and reduce pain and fractures[75]. The most commonly used bisphosphonates are: Tiludroante (Skelid®), Pamidronate (Aredia®). Risedronate (Actonel®) and Zoledronate (Aclasta®) [76].

5-1-3 The imperfect osteogenesis:

Imperfect osteogenesis is inherited congenital osteoporosis, autosomal dominant inheritance. Bisphosphonate therapy has altered the natural derogatory course of the disease especially in growing children. The procedure for administration of bisphosphonates remains to be specified in order to obtain the minimum therapeutic dose with the minimum of long-term. side effects. The treatment of this disease is interdisciplinary: medical, surgical and rehabilitation [77].

5-1-4 Other Indications:

Glucocorticoid-induced osteoporosis is an important indication for bisphosphonate use in various diseases. As an example, **Crohn's disease** and its therapy affect bone health and result in a high prevalence of low bone mineral density disease such as osteoporosis and osteopenia, which may be ameliorated by bisphosphonate therapy [78].

Apart from their antiresorptive activity, bisphosphonates may also have specific analgesic or anti-inflammatory effects. Thus, **rheumatic diseases** associated with systemic and sometimes focal bone loss, such as **rheumatoid arthritis**, **spondylarthritis**, or **SAPHO** (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome, are candidates for bisphosphonate therapy. Also, non-inflammatory rheumatic diseases, such **as aseptic osteonecrosis**, **neuropathic osteoarthropathy**, **algoneurodystrophy**, and **fibrous dysplasia**, are associated with pain and increased focal bone remodeling.

The Bps have been used in some **periodontal treatments** to limit bone resorption. Lane et al. have shown that their use improved the level of the clinical attachment, decreased the depth of the pockets and sulcular bleeding. Their studies show that treatment with bisphosphonates prevents bone resorptions and maintains bone volume. However, clinical regression remains very insufficient[79].

5-2 Malignant pathologies:

5-2-1 Multiple Myeloma :

Multiple myeloma patients are often affected by pathological fractures early in their disease course but still have a long survival compared to other patients with bone metastases. Due to early and massive bone affection, potent intravenous bisphosphonate regimens are the preferred treatment strategy in multiple myeloma patients. However, the prolonged intravenous bisphosphonate use is probably the reason for a high incidence of bisphosphonate-related osteonecrosis of the jaw (up to 23 %)[80] in these patients. Data clearly demonstrating the superiority of zoledronic acid compared to ibandronate in multiple myeloma patients is missing; however, ibandronate is not approved for use in multiple myeloma patients, although the incidence of bisphosphonate-related osteonecrosis of the jaw seems to be lower than with zoledronate treatment [83] . Thus, to date, intravenous zoledronate is the preferred bisphosphonate regimen for multiple myeloma patients.

5-2-2 Breast Cancer:

Breast cancer is the most frequently diagnosed cancer in women not only in Western countries but also in Algeria, and bone loss is common throughout the disease course. About 70 % of patients with advanced breast cancer develop bone metastases, a complication that is often painful and potentially leads to debilitating skeletal-related events. In early breast cancer, accelerated bone mineral density loss frequently occurs in the wake of adjuvant therapy. Rate and extent of chemotherapy or endocrine cancer therapy-induced bone loss are often greater than decreases in bone mineral density during menopause. Bisphosphonates such as zoledronic acid are indicated for the treatment of breast cancer bone metastases and reduce the fracture risk by a third [81].

Zoledronate has been shown to also prevent cancer therapy-induced bone loss and improve bone mineral density in premenopausal women receiving adjuvant endocrine or chemotherapy for breast cancer [82].The benefits of bisphosphonate therapy in breast cancer go beyond maintaining bone health and include potential anticancer effects [85].

5-2-3 Prostate Cancer and Other Genitourinary Malignancies:

In men, prostate cancer is the most frequent malignancy and the second most common cause of cancer death. Skeletal complications are numerous, either due to bone metastases or as a consequence of androgen deprivation therapy. Complications of bone metastases include bone pain, pathologic fractures, and spinal cord compression [83]. Less common genitourinary malignancies also have a predilection for metastases to the bone. Preclinical studies in models of genitourinary cancers have shown that bisphosphonates can inhibit overall tumor progression, proliferation, invasion, and angiogenesis; activate the immune response against cancer cells; and produce synergistic anticancer effects with cytotoxic agents. Compared to other bisphosphonates, zoledronate demonstrated especially profound direct anticancer activity and synergy with cytotoxic chemotherapy in preclinical studies with prostate cancer cells [84].

5-2-4 Malignant hypercalcemia:

The two main causes of hypercalcemia are primary hyperparathyroidism and malignant hypercalcemia in breast and lung cancers [85]. It occurs when osteolysis is severe, and renal excretion capacities are exceeded [86]. Bisphosphonates normalize calcemia, reduce pain and fractures, and significantly decrease the development of osteolytic lesions [87].

6- Contraindications of Bisphosphonates :

- Oral bisphosphonates should not be used as initial therapy in patients with **esophageal disorders** (eg: **achalasia**, **esophageal stricture**, **esophageal varices**, **Barrett's esophagus**) or with an inability to follow the dosing requirements (eg: stay upright for at least 30 minutes).
- Oral bisphosphonates should also be avoided after certain types of **bariatric surgery** in which surgical anastomoses are present in the GI tract (eg, Roux-en-Y gastric bypass).
- Oral and IV bisphosphonates should not be used routinely in patients with **chronic kidney disease (CKD)** and an estimated glomerular filtration rate (eGFR) <30 to 35 mL/min.
- Oral and IV bisphosphonates should not be used routinely in patients with **hypocalcemia**, **vitamin D deficiency**, and **renal impairment**, their correction is necessary prior to administration.[87]

7- Adverse effects of Bisphosphonates :

7-1 Gastrointestinal adverse effects :

All oral bisphosphonates have correlations with upper gastrointestinal adverse effects, including gastrointestinal reflux, esophagitis, esophageal/gastric ulcers, and gastritis. Gastrointestinal side effects are the most common reason for discontinuation of oral bisphosphonates. The risk increases in patients who take concomitant NSAIDs.[88]

Proper administration of oral bisphosphonates may help to reduce the risk of these gastrointestinal adverse effects. Clinicians should avoid oral bisphosphonates in patients who are at a higher risk of these gastrointestinal adverse effects including those who are not able to sit upright for at least 30 minutes after taking the bisphosphonate, and patients with esophageal disorders such as achalasia, esophageal stricture, Barrett's esophagus, and esophageal varices and patients who have undergone Roux-en-Y gastric bypass. The risk of upper gastrointestinal adverse effects may be slightly lower with risedronate compared to alendronate. Other gastrointestinal adverse effects include abdominal pain, diarrhea, and constipation, which can occur in up to 5% of patients.

7-2 Infusion reaction:

Intravenous bisphosphonates have associations with an infusion/acute phase reaction characterized by flu-like symptoms, fevers, myalgias, arthralgias, and headaches within 1 to 3 days of the infusion. The symptoms usually respond to acetaminophen or NSAIDs and resolve within a few days. The risk of the acute phase reaction is highest with the 1st infusion of the intravenous bisphosphonate (up to 30%), and the risk declines significantly with further dosing (less than 7%). This infusion/acute phase reaction is usually mild and self-limiting and does not necessitate discontinuation of the intravenous bisphosphonate therapy.

7-3 Hypocalcemia:

Transient hypocalcemia is a common issue secondary to bisphosphonate use, and the incidence may be as high as 18%. Severe hypocalcemia, however, is rare. Hypocalcemia is more common, secondary to intravenous bisphosphonates, and in patients who have an underlying untreated vitamin-D deficiency, hypocalcemia, poor calcium intake, and hypoparathyroidism. [89,90] Calcium and vitamin-D deficiency require correction before initiating bisphosphonates, especially intravenous bisphosphonates.

7-4 Arthralgia and Myalgia:

Bone, joint, and muscle pain can occur secondary to bisphosphonates. The symptoms are rare, with an incidence of less than 5%. Symptoms are usually mild, although there have been reports of severe pain. Musculo-skeletal pain can have onset within days two years after starting bisphosphonates and may not always resolve entirely after discontinuation of bisphosphonates. [91]

7-5 Ocular adverse effects.

Rare ocular adverse effects, including uveitis, conjunctivitis, and scleritis, have been reported with all bisphosphonates. The incidence is infrequent [92].

7-6 Atypical femur fractures.

7-7 Osteonecrosis of the jaw. (Check the next chapter)

CHAPTER 3 :

OSTEONECROSIS OF THE JAWS

1- Osteonecrosis of the jaw:

1-1 Definition:

Osteonecrosis of the jaw (ONJ) is classically considered as a disruption of vascular supply or avascular necrosis with exposure of the jaw bones. It can be caused by radiation, high-dose steroid therapy, and medications that disrupt vascular supply or bone turnover in the jaws.[93]

1-2 Pathophysiology

The pathophysiology of ONJ is not well understood and appears to be multifactorial. Suppression of bone remodelling may contribute to the development of osteonecrosis and result in inadequate osteoclast activity to allow healing of the extraction socket.

Infection is a major factor in the development of ONJ. Polymorphonuclear leukocytes and aggregates of bacteria are almost always seen in the ONJ tissue. Bacteria stimulate bone resorption and contribute to bone necrosis.

Bacteria can increase bone resorption through the production of local cytokines, resulting in osteolysis locally. The damaged oral mucosa can contribute to infection, and infection can contribute to further mucosal damage. Bisphosphonates may also activate the gamma delta T-cells and impair the immune response to infection.

Denosumab may impact monocyte function and this may also be a contributing factor to the development of ONJ. Bisphosphonates may have antiangiogenic effects; in addition, treatment of cancer with tyrosine kinase inhibitors and monoclonal antibodies to vascular endothelial growth factor has also been associated with the development of ONJ alone or in combination with bisphosphonates and denosumab therapy.

Lastly, genetic predisposition may enhance the risk of ONJ in certain individuals who have polymorphisms in the farnesyl pyrophosphate synthase gene or cytochrome P450 CYP2C8 genes.[94]

1-3 Risk factors:

1-3-1 Local factors:

1-3-1-1 Dentoalveolar surgery:

-Extractions

-Dental implants

-Periapical surgery

-Periodontal surgery

-Cancer patients treated with IV bisphosphonates and who underwent dentoalveolar procedures had more risk of MRONJ than cancer patients who were treated with IV bisphosphonates and who did not undergo dentoalveolar procedures [95].

1-3-1-2 Local anatomy :

Mandibula:

-Lingual torus

-Mylohyoid line

Maxilla:

-Palatine Torus

* These areas are composed of a mature cortical and trabecular bone with minimal osteoblast activity. The mucous membrane covering it is thin and less vascularized, making them more sensitive [96]

*The lesions are located with a higher frequency on the mandible than on the superior maxilla and more frequently in areas with thin mucosa that cover bone protrusions, such as the torus, bone exostosis and the mylohyoid edge [97] [98].

1-3-1-3 Concomitant oral diseases: Dental or periodontal abscesses [99].

1-3-2 Systemic and demographic factors:

-Age: Advanced age is related to a higher prevalence of MRONJ.

-Sex: This factor has not been statistically related to a higher risk of osteonecrosis.

-Race: Caucasians have a higher risk of MRONJ compared to the black race [100].

-Cancer diagnosis, with or without osteoporosis: The type of malignancy is not statistically related to a higher risk of MRONJ, although the presence of bone metastasis presents a correlation, according to Wessel's article [101]. It is related with a higher risk of osteonecrosis in the coadjuvant treatments in these patients, such as chemotherapeutic agents (cyclophosphamide), erythropoietin and steroids [102] [103].

-Tobacco and alcohol: There is a possible correlation with smoking but not with drinking, according to the study published by Wessel et al. [101].

-Genetic factors: It has been proven that polymorphism in the farnesyl pyrophosphate synthase or the cytochrome of gene P450 CYP2C8 increase the risk of MRONJ in patients treated with IV bisphosphonates. [104] [105]

-Others: Dialysis, low hemoglobin, obesity and diabetes are variables related to MRONJ[106].

1-2-3 Drug-related factors:

-Bisphosphonate potency: IV bisphosphonates present higher power than oral ones [95].

-Duration of the treatment: The longer the duration of the treatment, higher the risk of MRONJ [95].

1-4 Signs and symptoms:

Patients diagnosed with MRONJ are defined by the following characteristics [107]:

-Prior treatment with antiresorptive and antiangiogenic drugs.

-Presence of bone exposure or intra or extraoral fistula for over 8 weeks, without remission.

-Patients who have not been treated with radiotherapy nor have metastasizing diseases in the jaws.

With the intention of standardizing all the signs and symptoms present in the patients affected by osteonecrosis of the jaws, a protocol for MRONJ diagnosis was proposed in 2010 [108.]

2-Bisphosphonates related osteonecrosis of the jaw:

2-1 Pathophysiology:

Initially, when the condition was called bisphosphonate-related osteonecrosis of the jaw (BRONJ), its similarities with radiation-induced osteonecrosis led to the assumption that the condition started with sterile necrosis of the jaw bone. Therefore, the term osteonecrosis was used otherwise reserved for sterile bone death usually because of impaired blood supply. At that time, it was speculated that BPs could cause osteonecrosis through effects on blood vessels in bone, possibly by inhibition of vascular endothelial growth[109].

Later, it has been suggested that the condition does not begin as a form of classical osteonecrosis but in fact osteomyelitis from the start.

Bacterial contamination with Actinomyces and Staphylococcus may play a role in maintaining osteomylitic wounds and because maxillofacial bone tissue containing BPs will resorb slowly, it is conceivable that contaminated bone cannot be removed fast enough to prevent the development of chronic osteomyelitis. This view is supported by the fact that similar lesions appear after treatment with anti-RANK-L antibodies that reduces osteoclast recruitment. Thus, it appears that reduced resorptive activity is a key factor behind the impaired healing capacity of these lesions.[110]

The antiangiogenic role of bisphosphonate is still unclear and ONJ proceeds despite the use of antibiotics in some cases. One explanation could be the fact that bacterial contamination maintains chronic osteomyelitis of the jaws. Another explanation is perhaps the reduced microcirculation of the gingiva causing the soft tissue unable to heal.[111]

Corticosteroids and chemotherapeutics have been suggested as factors that can predispose to ONJ or increase the risk of developing ONJ; the duration of BP therapy also appears to be related to the likelihood of developing necrosis with longer treatment regimens associated with a greater risk. The time to develop osteonecrosis after IV zoledronate treatment was in mean 1.8 years, after IV pamidronate 2.8 years and after oral BPs therapy, like alendronate, the mean time was 4.6 years.

Numerous studies have explored the toxic effect of BPs on a variety of epithelial cells. There is clear documentation of bisphosphonate toxicity to gastrointestinal epithelia. It has been suggested that high concentrations of bisphosphonate in the oral cavity (bone tissue) disrupt the oral mucosa. Failure of healing of the soft tissue may cause secondary infection of the underlying bone.[112]

2-2 Clinical aspects:

The clinical findings in BIONJ patients include the exposure of non-vital, whiteyellowish bone tissue surrounded by an inflamed and edematous mucosa in the mouth. This situation can be anticipated in patients describing a vague sensation of pain or discomfort in the affected area.
As previously described, osteonecrosis generally develops after procedures that cause trauma to the jaw (e.g: dental extractions). Episodes of spontaneous onset have been reported and documented and are more likely to occur close to palatal and mandibular tori and in partially or completely edentulous patients .
The early signs and symptoms of BIONJ are the same as in any odontogenous infection (halitosis, pain, edema and ulceration of the mucosa, dental mobility). In an advanced stage of the disease, there may be inflammatory and infectious foci (suppurative osteomyelitis), pathological fractures, skin fistulas, as well as oral and nasal antral fistulas, all of which contribute to worsen the symptomatology. Patients at risk for or with established BIONJ may also present with other common clinical conditions, including alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathology, and temporomandibular joint disorders [113].

Diagnosis is based on clinical findings rather than on histological or radiographic evidence. Radiographically, the condition has a normal appearance or it may resemble bacterial osteomyelitis or osteoradionecrosis. The clinical appearance and history are sufficient to distinguish ONJ from other delayed bone and wound-healing pathologies.[114]

The area of exposed bone is typically surrounded by inflamed erythematous soft tissue. Purulent discharge at the site of the exposed bone will be present when these sites become secondarily infected.

Fig 13: Exposed, necrotic bone at an extraction site in a patient exposed to five years of weekly oral bisphosphonate therapy for osteoporosis.

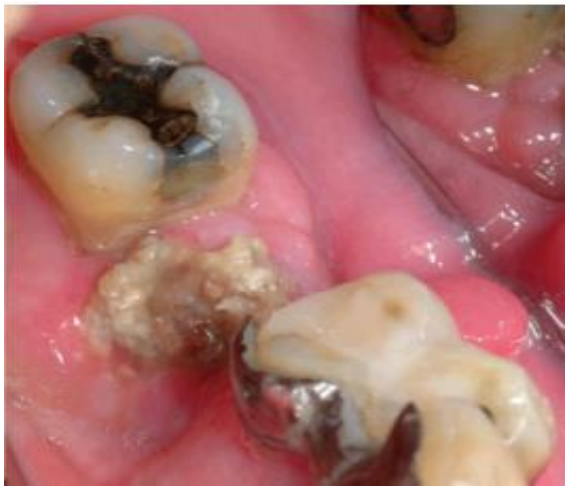
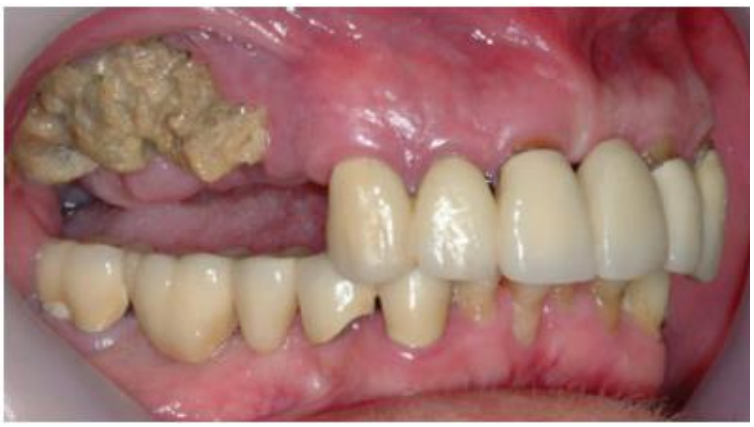


Fig 14: Large segment of necrosis localized to the right maxilla. The patient had received three years of intravenous zolendronic acid for the treatment of metastatic breast cancer



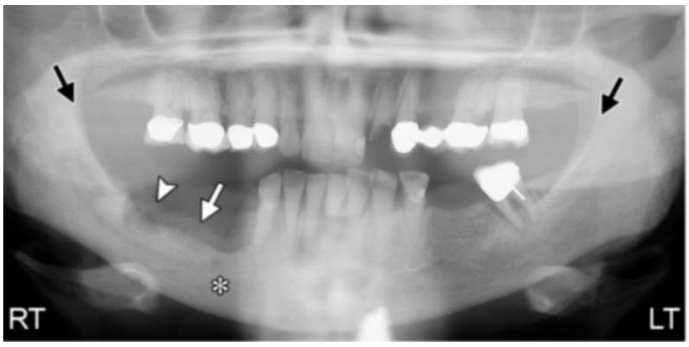
2-3 Radiological aspects:

2-3-1 Panoramic radiography:

Ortho Pantographs serve as the initial radiologic screening of patients who present for evaluation of BRONJ. In all symptomatic patients, the radiographic imaging shows that areas of bone destruction are present in correspondence with the regions of clinical involvement. The radiolucent areas are patchy, with occasional evidence of radiopaque sequestra of necrotic bone and little evidence of healing. The border between the necrotic and normal bone is not sharply defined and subperiosteal new bone formation is not usually evident. The radiographic imaging of the asymptomatic patient shows a radiolucent lesion corresponding to an empty socket.

Fig 15 : The appearance of ONJ on panoramic radiograph

Panoramic radiograph view of ONJ shows alveolar bone reaction at the area of the empty socket of previously extracted teeth (arrowhead and white arrow), and loss of cortication on the right side compared to the left (black arrows)

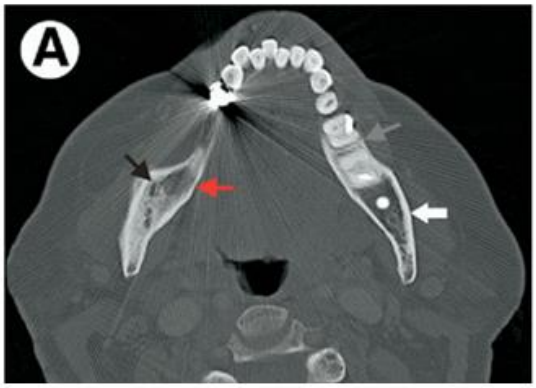


2-3-2 Computed Tomography :

CT scans will help to identify findings difficult to discern on plain films and also provide three-dimensional information and better delineation of the extent of the lesions.

Imaging evaluation of CT scan disclose abnormalities in all symptomatic patients. The images show a moderate irregularity of the cortical margins and, in all symptomatic patients, destruction of cortical bone are noticed. Both clear areas of osteolysis and osteosclerosis are noticed too. The CT scan doesn't add significant data to the panoramic radiograph of the asymptomatic subject.

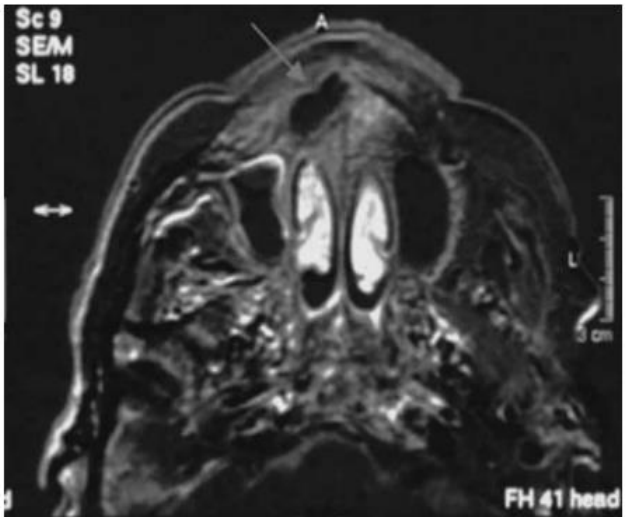
FIG : Radiographic views of a 70-year-old woman being treated for metastatic breast cancer with a history of alendronate and zoledronic acid use. Axial CT scans without contrast displaying trabecular alteration with more radiolucent appearance (asterisk), cortical bone erosion (red arrow), sequestrum formation (black arrow), thickened lamina dura surrounding teeth (gray arrow), and new osteosclerotic periosteal bone (thick white arrow).



2-3-3 Magnetic Resonance Imaging:

MRI enables even more accurate assessment of the extent of lesions and infections
associated. In all cases, it was possible to identify the involvement of the cancellous bone, which produced low signal intensity on T1 weighted images and a mild hyperintensity on T2 weighted and T-STIR images. A mild and irregular enhancement of the lytic areas is noticed after injection of the contrast agent. Where the bone sequestrum is evident, it presents as a well-defined dark area. In patients with evident swelling, an area of oedema of soft tissues is clearly visible on T-STIR images as high signal intensity.

Fig 16 :MRI showing bone sequestrum in the right maxilla



2-3-4 Scintigraphy:

Bone scintigraphy can highlight areas where bone turnover is high by detecting the radiation emitted by a transmitter (bisphosphonate marked with radioactive technetium 99m) with a camera.
It is a very sensitive method but not very specific, it does not always differentiate malignant processes from inflammatory processes.
Bone scintigraphy is the most effective way to identify the earliest stages of BIONJ.[115 116]

- **Imaging Characteristics of BRONJ :**

Imaging Modalities	Imaging Characteristics
Radiography, CT	Osteolysis, sclerotic lesions, periosteal reaction, narrowing of the marrow space, involvement of the inferior alveolar canal, fractures
MR imaging	
T1-weighted	Typically decreased signal intensity
T2-weighted	Variable: intermediate or slightly increased signal intensity in early disease; increased or decreased signal intensity in later stages of disease
Contrast material–enhanced	Variable: may correlate with the degree of signal intensity decrease on T1-weighted images; typically spares the low T2 signal bony sequestrum
Technetium 99m bone scintigraphy	Areas of decreased uptake may be present in early disease; in later stages of disease, there is increased uptake with possible decreased central uptake

2-4 Histopathological and Microbiological Aspects:

2-4-1 Histopathological aspects:

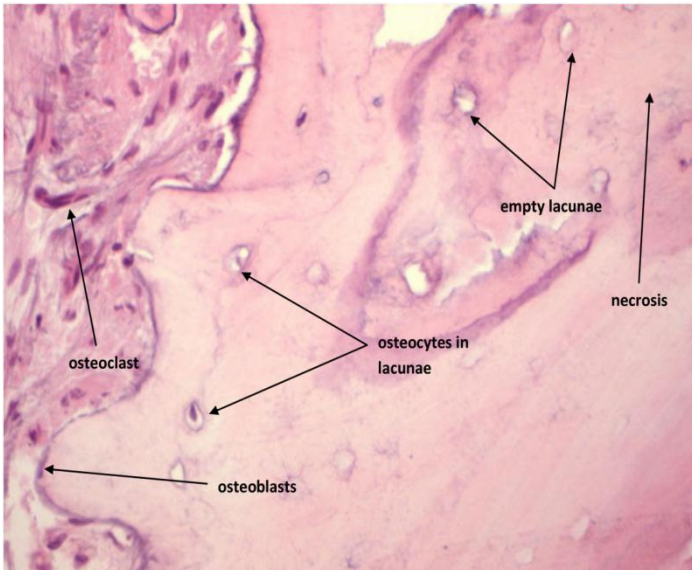
Histopathological examination most often shows bone necrosis with bacterial debris and granulation tissue.[117]

Necrotic bone appears to be virtually devoid of bone cells and vessels and none evidence of active remodelling is detectable. This is called “frozen bone”.

Usually there are many osteoresorption gaps indicating a strong anterior osteoclast activity.

It is probable that the disappearance of osteoclast can be explained by the action of bisphosphonates, promoting their apoptosis, while that of other bone cells. could be caused secondarily by the phenomenon of necrosis. Signs of chronic inflammation are associated with this acellular necrotic bone performing a mixed inflammatory infiltrate (neutrophil polynuclear, lymphocytes, plasmocytes).[118]

Fig 17: BRONJ Empty lacunae are seen in the centre of the bone while towards the surface some lacunae display their osteocytes



2-4-2 Microbiological aspects:

The presence of microbes, such as Actinomyces is found with a frequency estimated at 90% in patients with Osteonecrosis of the jaws. It is a Gram-positive anaerobic bacillus. The rupture of the mucous barrier (due for example to a dental extraction) would allow the implantation of Actinomyces within the damaged tissues.[119]

According to the authors, their presence may be an aggravating factor, triggering or simply be a secondary infection of necrotic tissue [120] . Indeed, in case of infection. bone repair needs have increased, but BPs inhibit this repair, hence septic necrosis. Bacterial colonization would also result in modification, from the bone surface preventing proper fixation of the osteoblasts and resulting in exposure to devitalized bone [121].

To sum up, Actinomyces are an underrecognized agent in pathogenesis, and timely actinomycosis-specific treatment may improve outcome.

Other germs are also found in tissue biopsies, such as. Veillonella (Gram-negative cocci, anaerobic), Eikenella (Gram-negative bacillus, anaerobic) and Moraxella (Gram-negative bacterium, aerobic). Further down, in the necrotic surface, sulfur granules may be present, which justifies the diagnosis of an actinomycosis.

2-5 Differential Diagnosis:

Differential diagnosis of BRONJ includes [122] :

- Malignancies - differentiation is through histopathological analysis.
- Osteoradionecrosis if jaws were exposed to prior radiation.
- Osteomyelitis in which, unlike bisphosphonate-associated osteonecrosis, necrotic bone is surrounded by vital bone, which reacts with a violent inflammatory reaction, thus limiting necrosis.
- Osteopetrosis - an extremely rare congenital condition;
- Bone necrosis in HIV-positive patients.
- Others : [123]

  -necrotic ulcerative gingivitis

  - Sinusitis

  - Dry socket

  - Dental periapical pathologies

  - Prosthetic trauma

2-6 Classification:

The classification or staging system currently proposed by the AAOMS [124], and which is correlated to therapeutic strategies specific of each stage, is as follows:

❖ **<u>At risk:</u>** Patients subjected to antiresorptive or antiangiogenic treatment via the oral or intravenous route, and with no symptoms or apparent bone necrosis.

❖ **<u>Stage 0:</u>** (disease variant without bone exposure): No clinical evidence of necrotic bone, though with clinical findings, radiographic changes and nonspecific symptoms.

Among the symptoms :

- Tooth pain in the absence of a dental cause.
- Maxillary bone pain that may irradiate to the region of the temporomandibular joint.
- Pain of the maxillary sinuses that may be associated to inflammation and thickening of the sinus walls.
- Neurosensory function.

Among the clinical findings :

- Tooth mobility that cannot be explained by periodontitis.
- Periapical or periodontal fistulas not associated to pulp necrosis secondary to trauma, caries or restorations.

Among the radiographic findings :

- Loss or reabsorption of alveolar bone that cannot be explained by periodontitis.
- Changes in trabecular-dense bone pattern, with no formation of new bone in extraction sockets.
- Zones of osteosclerosis in alveolar bone or around the basal layer.
- Thickening or opacification of the periodontal ligament (thickening of the lamina dura, sclerosis, and reduction of the periodontal ligament space).

❖ **Stage 1:** Exposed bone or intra- or extraoral fistulization in the maxillofacial region penetrating to the bone, in asymptomatic patients without evidence of infection.

In addition, radiographic findings such as those described in stage 0 may be observed in alveolar bone.

❖ **Stage 2:** Exposed bone or intra- or extraoral fistulization in the maxillofacial region penetrating to the bone, with infection evidenced by pain and erythema in the region or exposed bone with suppuration. In addition, radiographic findings such as those described in stage 0 may be observed in alveolar bone.

❖ **Stage 3:** Exposed bone or intra- or extraoral fistulization in the maxillofacial region penetrating to the bone, with pain, infection and at least one of the following signs:

- Necrotic bone extending beyond the alveolar bone (inferior margin or ramus of the mandible, maxillary sinus and zygoma)
- Pathological fracture
- Extraoral fistula
- Oroantral or oronasal communication
- Osteolysis extending to the inferior margin of the mandible or sinus floor

As can be seen, no unified classification or staging system has yet been established for use by all professionals – though most studies are based on the classification of the AAOMS.

Furthermore, it would be advisable to establish the diagnosis not only on the basis of the clinical data but also on the findings of the CT scan, since the latter technique offers greater information on the extent and severity of the disorder.

2-7 Treatment of BRONJ

The treatment of BRONJ based on the consensus of a panel discussion from AAOMS, is described in the table below:

Table: Clinical staging of BRONJ and treatment guideline

Stages	Treatments guidelines
At risk category: no apparent exposed/necrotic bone in patients treated with either oral or iv bisphosphonates	No treatment indicated Patients education
Stage 1: exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse Clinical follow-up every 4 months
Stage 2: exposed/necrotic bone associated with infection. Presence of pain and erythema in the lesional area with or without purulent drainage	Treatment with broad-spectrum oral antibiotics Antibacterial mouth rinse Pain control Superficial debridement to relieve soft tissue irritation
Stage 3: exposed/necrotic bone in patients with infection and pain. Presence of one or more of the following: pathologic fractures, extraoral fistula, or osteolysis extending to the inferior border	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain

3- Why does BRONJ only affect the Jaws :

- The turnover rate of jaws, especially alveolar bones, is so rapid

The remodeling rates of the cortical bone in the jaw are 10–20 times higher than in the cortex of iliac crest in humans.

- Jaws have teeth and gum that may become an easy entrance for bacterial infection
    - Vulnerability of the jaw to bacterial infection: Jaw seems to be the most liable to bacterial infection since mucosa covering the alveolar bone is very thin and vulnerable, and infection caused by mucosal injury spreads to the jawbone beneath it.
    - The teeth easily become a pathway for bacteria from the outside into the bone.
    - The jawbone is exposed to the oral cavity following invasive dental treatments including tooth extraction, leading to infection, in addition of undergoing constant masticatory forces causing microtraumas that don’t heal properly and set the satge for BRONJ.[125]

CHAPTER 4 :

DENTAL PROSTHESES AND BISPHOSPHONATES

A- Dental Prostheses:

1- Definition:

An artificial replacement for one or more natural teeth or part of a tooth, or associated structures, ranging from a portion of a tooth to a complete denture. The dental prosthesis is used for cosmetic or functional reasons, or both. Dentures and specific types of dental prosthesis are also available.[126]

2- Benefits of Dental Prosthetics:

- **Reduced Bone Loss**

Loss of teeth results in oral bone loss. This is especially common in cases where the tooth is not replaced, and more so in cases where multiple teeth are lost. Dentures, whether partial or full, do not help in minimizing bone loss, because, as compared with natural teeth, they exert a very small amount of chewing pressure. Unlike dentures, fixed dental prosthetics give the jawbone a replacement tooth, which exerts pressure similar to natural teeth. As a result, bone loss is decreased by a large extent.

- **Effective oral rehabilitation and maintenance solution**

To date, there is essentially no other restorative dental procedure that is as efficient and effective as prosthetic dentistry. As this treatment uses advanced technologies like electron microscopy, 3D imaging and nanotechnology-based implants, it gives patients the best results in minimal time. Thus, along with better treatment, patients have a low maintenance solution for all of their oral woes.

- **Improved aesthetic**

Dental Prosthesis functions to restore aesthetics, mastication and speech.

-Aesthetics: dental prosthesis should restore the lost facial contours, vertical dimension...etc Artefacts like stains can be incorporated in order to improve the aesthetics.

-Mastication: dental prosthesis should have proper balanced functionnal occlusion in order to enhance the stability of the denture.

-Phonetics: One of the most important functions of a dental prosthesis is to restore the speech of the patient.

- **objectives of dental prosthesis:**

1-rehabilitation is the key or overriding objective.

2- comfort; physical and mental; is the first sub-objective, for such qualities are intimately tied in with all denture values.

3-esthetics, or a natural, youthful, and pleasing dentofacial appearance, statically and functionally are the second sub-objective.

4- restoration of functions, communication and speech are the third sub-objective.[127]

3- Diffrent types of dental prostheses: [128]

3-1 Fixed Prosthesis:

A damaged tooth can be rebuilt with fixed dentures. There are several types used as needed.

The denture crown replaces the entire visible part of the tooth. It covers the entire tooth and consolidates it.

The inlay is used to replace a small internal part of the tooth. Onlay, which is a partial dental crown, can also be used on the outer part of the tooth.

If one or more teeth are missing, they can be replaced with a bridge (or dental bridge) attached to the adjacent teeth by an onlay or crown.

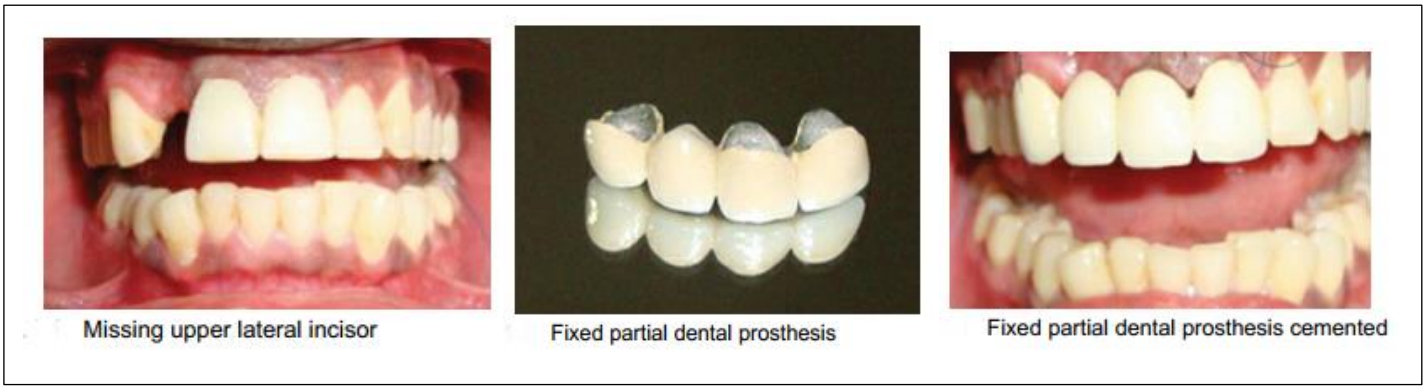


Fig18: Cement retained dental prosthesis

3-1-1 Indications for Fixed Dental Prosthesis FDP:

- One or two adjacent teeth are missing in the same arch (short span edentulous area)
- When the supportive tissues are healthy.
- Suitable abutment teeth are present.
- The patient is in good health and desires to have the prosthesis placed.
- The patient has the skills and motivation to maintain good oral hygiene
- Patients preference
- Good oral hygiene

3-1-2 Contraindications for a Fixed Dental Prosthesis:

- Lack of supporting tissue and alveolar bone
- Presence of periodontal disease
- Excessive mobility of abutment teeth
- Patients with poor oral hygiene
- Patients who cannot afford treatment. [129]

3-2 Removable Prosthesis:

The removable prosthesis reproduces the colour of the neighbouring teeth and the shape of the missing ones.

Removable dentures can be removed as desired. Especially for their daily maintenance. They can be partial or total depending on the patient's needs and the number of teeth to be replaced.

A partial removable denture only replaces one or more teeth. It rests on the gums and the remaining teeth with hooks.

The complete removable denture will replace all the teeth in the jaw; it simply leans on the gums.

3-2-1 Removable partial dental prosthesis RPDP:

The prosthesis that replaces some teeth in a partially edentulous arch and that can be removed from the mouth by the patient. It can be a simple removable partial denture fabricated in acrylic resin called as temporary partial denture. A removable partial denture fabricated in cast metal alloy and acrylic resin is called cast partial denture.

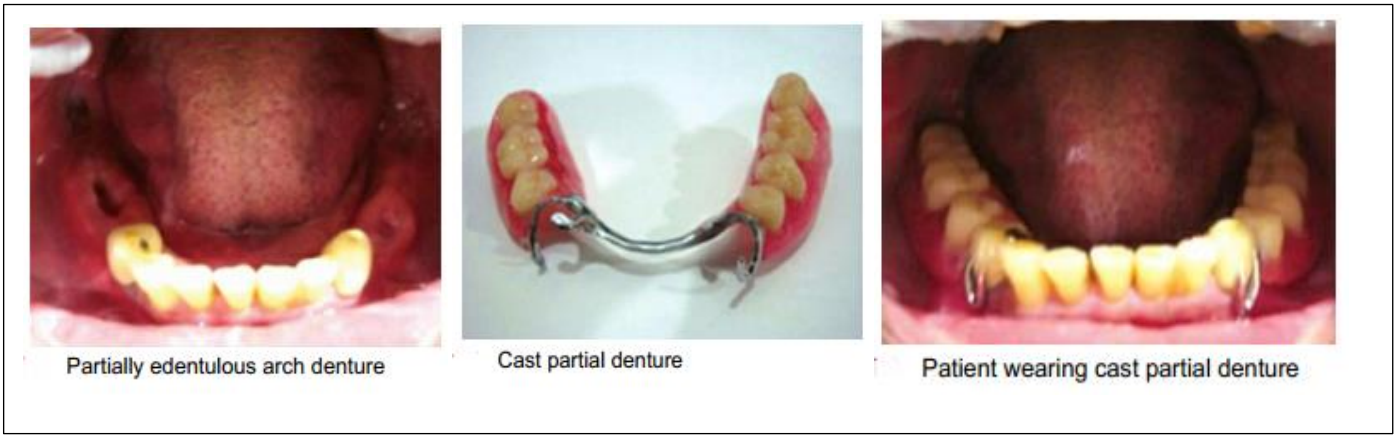


Fig19: cast partial denture

Fig20: removable temporary denture

3-2-2 Indications for a Removable Partial Denture:

- To replace several teeth in the same quadrant or in both quadrants of the same arch.
- To replace missing teeth for patients who do not want a fixed bridge or implants.
- For the patient who finds it easier to maintain good oral hygiene.
- To serve as a splint to support periodontally involved teeth.

3-2-3 Contraindications for a Removable Partial Denture:

- A lack of suitable teeth in the arch to support, stabilize, and retain the removable prosthesis.
- Rampant caries or severe periodontal conditions that threaten the remaining teeth in the arch.
- A lack of patient acceptance for esthetic reasons.
- Chronic poor oral hygiene.[130]

3-3 Removable Complete dental prosthesis:

Complete dentures are full-coverage oral prosthetic devices that replace a complete arch of missing teeth.

Fig 21: removable complete denture

3-3-1 Indications:

- A full arch of missing teeth
- Dental implants that have been deemed inappropriate by patient and/or doctor because of financial constraints, a medically compromised status that contraindicates surgery, or inevitable damage to vital structures such as maxillary sinuses, nerves, and vessels
- Intraoral cancer that has caused a loss of gross intraoral tissue, resulting in an edentulous dental arch; the complete denture prosthesis would then not only replace teeth but also fill in the portion of missing tissue (eg: nasopharynx, hard palate)

3-3-2 Contraindications:

Definitive contraindications to complete dentures have not been reported. However, the following factors should prompt a dentist to reconsider the use of a complete denture:

- Patient does not desire to have a removable appliance to replace missing teeth
- Patient has an allergy to the acrylic used in the fabrication of the complete denture
- Patient has a severe gag reflex (although this could be controlled with gag reflex desensitization)
- Patient has severely resorbed dental alveolar ridges, which would compromise retention with a complete denture alone. [131]

3-4 Combined Prosthesis:

A combined prosthesis consists a fixed part and a removable part. The removable part on the metal plate, replacing the missing tooth(s), is connected to the remaining teeth by means of an anchoring element – attachment, hook, telescopic crown...

These prostheses are generally used in patients for whom implantation cannot be carried out or who cannot afford implant procedures.

3-5 Implant Prosthesis:

There are two types of implant prostheses that can be offered to the patient: fixed prostheses which are dental crowns or bridges directly screwed or sealed on dental implants.

And the so-called removable prostheses on implants: they are partial or complete removable prostheses, stabilized by implants by means of fastening systems that often resemble small snap buttons.

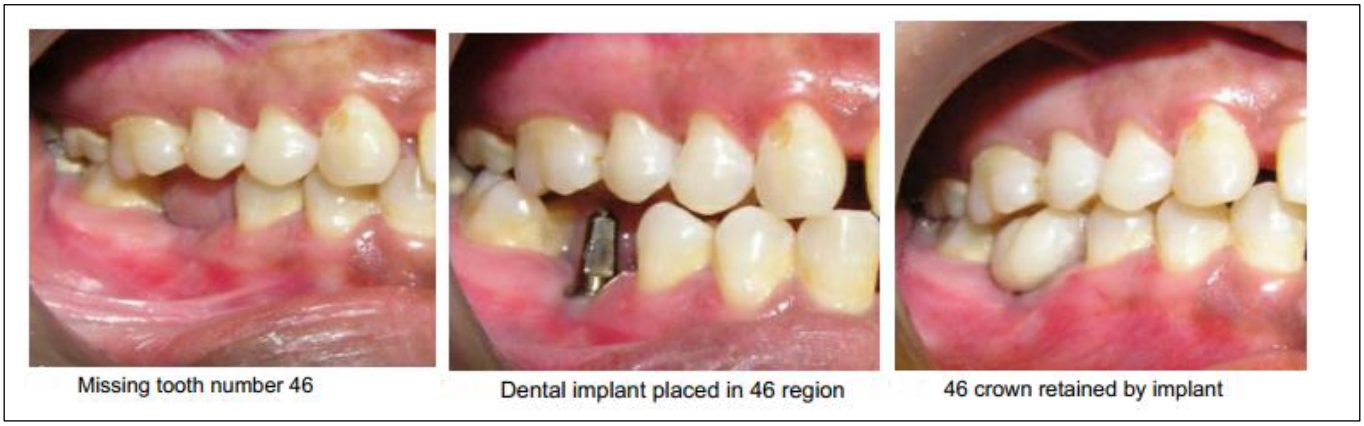


Fig22: dental implant on the lower molar

3-5-1 Indications:

Candidates for dental implants and mini-implants include partially and totally edentulous patients with proper bone height and width for implant placement.

An implant should have at least 1.5-2 mm of bone between the body of the implant and an adjacent tooth. At least 3 mm should separate two implants. If there is not enough bone height or width, bone grafting to the site can be considered.

3-5-2 Contraindications:

Absolute contraindications (medical-local) include the following:

- Poor oral hygiene and patient compliance
- Active chemotherapy
- Active infection or other pathology at the implant site
- Medical conditions that prevent safe surgery

Relative contraindications (medical-local) are as follows:

- Type 2 diabetes mellitus (not well controlled)
- Significant tobacco consumption
- Severely resorbed ridges
- History of radiation to implant site
- Inferior alveolar nerve and maxillary sinus position
- Active periodontal disease
- Parafunctional dental habits
- Unbalanced jaw relationship. [132]

B- Dental Prosthetic Therapy for Patients Undergoing Bisphosphonates treatment:

1- The removable prosthesis:

1-1 Effects of bisphosphononate on removable prosthesis:

Removable prosthesis like that of complete denture or removable partial denture all rest on mucosa and underlying bony tissue. It is now clear that patients who have been exposed to nitrogen containing BPs therapeutic agents are at risk for Osteonecrosis of jaw when dental treatment or trauma violates the integrity of the oral epithelium. [133] [134]

Landesburg et al published a landmark study showing the effect of nitrogen containing BPS on oral mucosa cells and the inhibition of oral keratinocyte migration. Following an intraoral traumatic event to mucosa, bisphosphonates inhibit normal epithelial wound healing and keratinocyte migration, resulting in a prolonged exposure of underlying bone to oral micro flora, thereby allowing secondary bone infection to ensue.

Many experimental and clinical studies show that BPs conserve bone architecture and strength.

However there have been concerns about whether use of prolonged high doses of BPs may impair bone turnover to such an extent that bone strength is impaired. It has been suggested that BPs might prevent naturally occurring microscopic cracks in bone from healing, which in turn leads to accumulation of micro damage. [135]

Chances of developing BRONJ increase many folds if patient is having other factors like in immune compromised patients. [136]

1-2 Precautions and management:[137]

Since in residual alveolar ridge is not meant to bear direct occlusal loads and also the mucosa covering the ridge is also compromised in patients taking bisphosphonates, following prosthodontic considerations which should be considered.

- ✓ The main function of denture should be for esthetics and speech and should provide either no or very limited functionality for mastication depending on the type of bisphosphonate drug patient is taking, route of administration, time span of administration and any previous history of BRONJ.
- ✓ Removable prosthesis should be stable and should be relined or rebased time to time, as unstable dentures are tending to injure the epithelium as well as demand for more residual ridge resorption.
- ✓ Removable prosthesis should not engage into any undercut or tori if present.
- ✓ If a patient requires any kind of pre prosthetic surgery then CTX test should be carried out and accordingly "drug holiday" should be taken into consideration.
- ✓ If a removable prosthesis is planned, forces on the basal seat should be reduced with minimal pressure impressions and functional placement of the borders to provide the “snowshoe effect,” reducing the force per unit area while providing retention and stability. Preprosthetic surgery could ensure removal of bony spikes and spicules, which act as foci of stress concentration in specific conditions, under the denture in function.
  Gross bony defects created by scalloping to remove necrotic bone mass (in case of BRONJ) must be evaluated prior to impression-making.
- ✓ Preliminary impressions in such cases may be made in i**rreversible hydrocolloid** and definitive impressions in **light-body silicones** in a pressure-less fashion. For less-stress transference to the remnant bone and reduction of undesirable horizontal forces, **acrylic cuspless/monoplane** teeth are indicated.
- ✓ Decreasing the occlusal table and reducing vertical overlap of prosthetic teeth within functional limits may also be advocated. **Heat-cured soft liner** materials could be used to line the intaglio surface of dentures to dissipate and distribute forces by their cushioning effect, and to improve patient compliance and treatment prognosis.
- ✓ Finally, after prosthodontic treatment, the patient should be recalled at intervals of at least 2 to 3 months to monitor health of the denture-bearing tissues, clinically and radiographically. Advice on keeping the prostheses out of the mouth for at least 12 hours daily should be given.

1-3 Influence of dentures in the initial occurrence site on the BRONJ:

the oral cavity is highly prone to infections because of the abundant resident flora, and the antiangiogenic action of BPs delays wound healing; as a result, the frequency of BRONJ increases. In a study that determined the association between wearing dentures and the initial occurrence site of BRONJ, Kyrgidis et al.[138] stated that wearing dentures is the most important risk factor for BRONJ. Sedghizadehet al.[139] reported that development of osteonecrosis of the jaw is strongly related to denture trauma. Furthermore, Vahtsevanos et al.[140] observed that the frequency of BRONJ in patients with cancer using intravenous BPs was approximately double in patients wearing dentures.
The results revealed that patients wearing dentures had a significantly shorter duration to onset than patients not wearing dentures. Therefore, because patients on high doses of BPs or prolonged use of BPs are at a high risk of developing BRONJ.

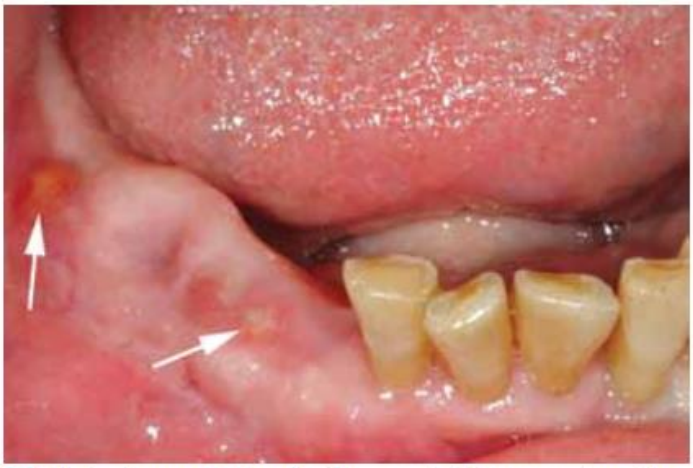
When they wear dentures, regular check-ups and denture adjustments are important.
The findings show that the incidence of BRONJ increased in the following order: **anterior teeth < premolar <molar and upper jaw < lower jaw.** In addition, remission in the areas of the lower premolars and lower canine was difficult when wearing a denture. The lingual side of the lower premolar is a common site for bone torus and the lining mucosa is thin; as a result, pressure from the denture leaves it constantly irritated and inhibits healing. On the other hand, the results showed that the lower second molar region obtained remission significantly with denture wearing. This may be because the buccolingual width of bone in the mandibular molar part is wide and the change in pressure exerted by the denture was small, leading to better blood circulation to the tissue and faster remission than in other locations.[141]

2- The Fixed Prosthesis:

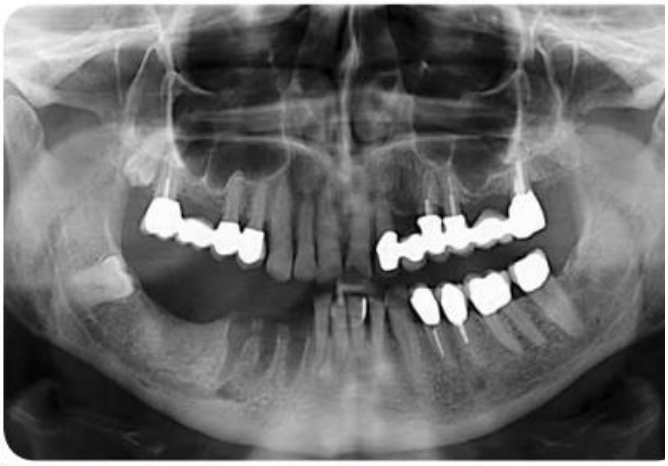
For a patient undergoing bisphosphonates treatment and getting fixed prosthesis, maintenance of oral hygiene status becomes an important step towards good prognosis. Margins during crown preparation should always be kept **supra-gingival** for following reasons:

- ✓ To place margins sub gingival, sulcus epithelium can get traumatized in the process which can latter lead to delayed healing and thus chances of developing BON are there.
- ✓ Also since the loss of alveolar bone in periodontitis is a regular immune response of body towards the microorganisms, inhibiting or modulating host response by bisphosphonate drugs can actually lead to BON. A study conducted by Aghaloo TL et al, demonstrate that bisphosphonates can attenuate alveolar bone loss caused by an on-going periodontal disease. These indicate that margins for crown preparation should be supragingival in patients taking bisphosphonates.

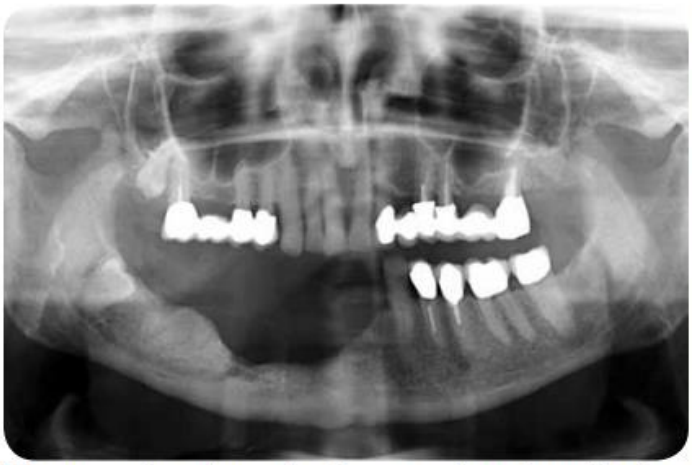
2-1 A case of prosthodontic treatment of a patient with BIONJ using a combined dental prosthesis with a heat-polymerized resilient liner:



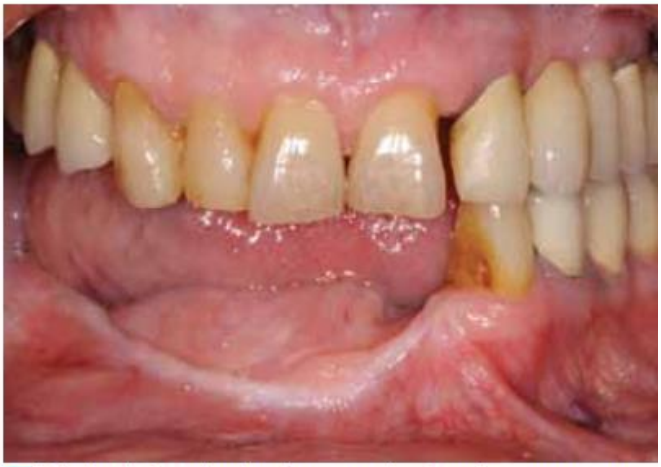
1 Clinical presentation before surgical intervention. Note swelling of mucosa on right buccal vestibule and 2 ulcerated lesions (white arrows) at alveolar mucosa.



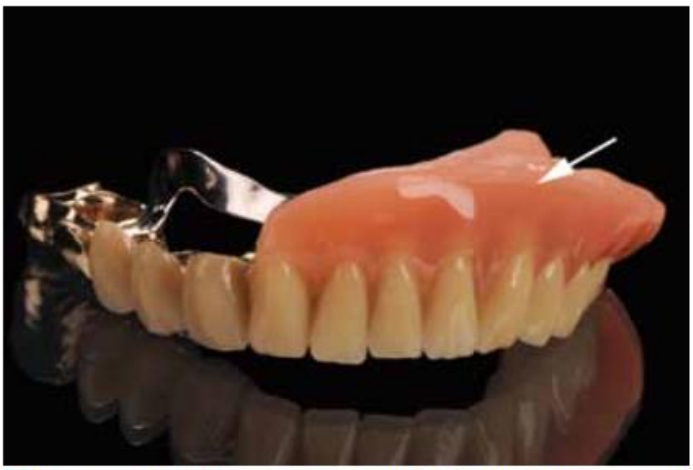
2 Panoramic radiograph before surgical intervention.



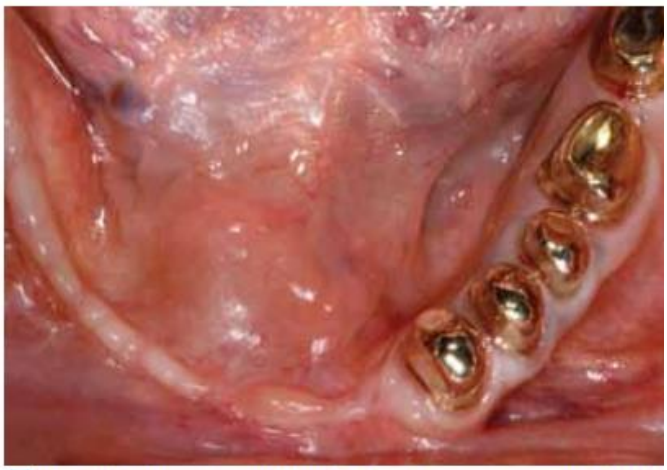
3 Panoramic radiograph after extraction of mandibular incisors and resection of infected necrotic bone.



4 Clinical situation before prosthodontic treatment.



5 Removable dental prosthesis with laboratory-processed resilient liner after fabrication. Note interface line (white arrow) between resilient liner and acrylic resin base.



6 Mandibular view of residual ridge and cemented telescopic crowns.

2-1-1 Description of the clinical case and the adopted approach:

In this clinical report, treatment of a patient who received a telescopic overdenture with a resilient, laboratory-processed silicone liner is described. Prior to prosthodontic treatment, the patient had recurrent BONJ after extraction of teeth without administration of preextraction antibiotics. The patient received BP treatment for a metastatic bone lesion in the pelvic bone following treatment for breast cancer.
The patient described was treated with pamidronate (60 mg/month).
Pamidronate is a highly effective nitrogen-containing BP that is administered intravenously. As described in the scientific literature, use of pamidronate can result in BONJ, either spontaneously or after dental treatment. in the present report, the patient received intravenous pamidronate monthly, starting 14 months before tooth extraction and the appearance of BONJ.

For the patient described here, a single-dose antibiotic, clindamycin (ClindaHEXAL, 600 mg; Hexal AG), was administered before oral preparation and impressions to minimize the risk of infection. Subsequently, good oral hygiene was ensured by monitoring the patient's oral health at frequent recalls. Patients with a removable dental prosthesis need frequent recalls to examine lesions of the mucosal barrier. If the prosthesis is ill fitting or highly mobile, the mucosa can be injured, thus permitting entry of oral flora into the bone.

A partial combined removable dental prosthesis with 5 telescoping crowns on the mandibular left canine, first and second premolar, and first and second molar was planned Telescopic primer crowns were cast with high noble metal alloy allows for a rigid connection between the abutment and prosthesis and may reduce the risk of mobility compared to a partial removable dental prosthesis retained by clasps. There tends to be less displacement of the denture base when the denture is designed with a rigid connection to the retainer and with cross-arch stabilization.

In the present situation, the distribution of the remaining abutments was disadvantageous for the kinematics of the prosthesis and distribution of the abutment support. To reduce the unavoidable pressure on oral structures, a heat-polymerized silicone resilient liner was selected for the tissue-interface area of the prosthesis.
Lesions of the oral mucosa are often associated with mechanical injury by dentures with nonresilient liners. Nonuniform loading of hard denture bases can cause traumatic ulcers that destroy the mucosal barrier, resulting in bacterial invasion and, finally, infection of the bone.Thus, a resilient liner can act as a cushion to reduce pressure; this allows the soft tissue to heal and bone remodeling to proceed without complications.
One disadvantage of resilient liners compared to hard acrylic resin materials is the greater risk of bacterial and fungal contamination.To prevent denture-related stomatitis, the prosthesis must be cleaned with a 5.25% sodium hypochloride solution. The authors recommend this cleaning solution be used at 3-month intervals.

A second potential issue with a resilient liner is long-term reduction of tensile strength and shear bond strength between the resilient lining materials and the heat-polymerized denture base acrylic resin; this can limit the longevity of the device.
While it was an inherent risk to incorporate a tissue-borne prosthesis on a tissue base that required recurrent surgical management, it is noteworthy that no prosthodontic induced complications occurred after insertion of the dental prosthesis. Although the mental foramen on the affected side was at the ridge crest after neurolysis and resection of the necrotic bone, the patient reported no pain or paresthesia induced by the denture base. Clinical trials are needed to confirm the benefits of prostheses with laboratory heat-processed resilient lining materials and rigid attachment elements for prevention of BONJ in patients taking BPs or with a history of BONJ.[142]

2-2 A Case of Bisphosphonate-Related Osteonecrosis of the Jaw in a Patient with Subpontic Osseous Hyperplasia:

Fixed partial dentures (FPDs) with pontics are commonly used to replace missing teeth. Osteoblastic deformation occurring under pontics was first introduced as subpontic osseous hyperplasia (SOH) by Calman et al. in 1971.

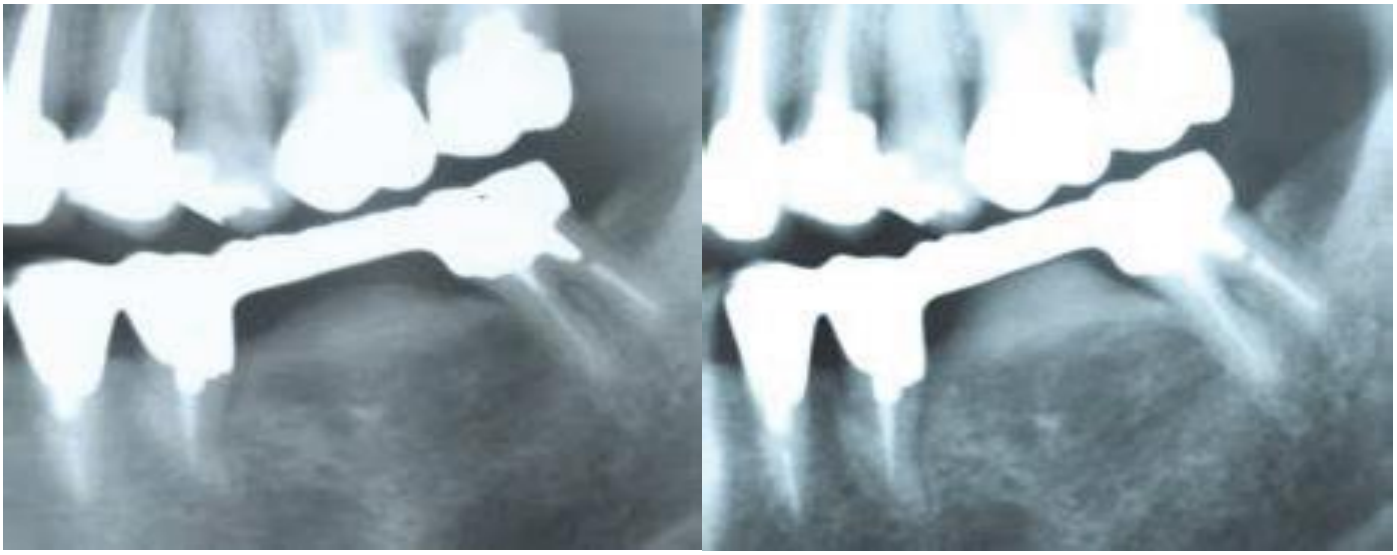
Since then, many studies have investigated SOH. The condition is normally discovered when individuals wearing FPDs for several years undergo simple radiography because of discomfort and pain at FPD sites. Many patients with SOH undergo surgical resection because the spontaneous detachment of hyperplastic bone has not been reported previously.

Subpontic osseous hyperplasia (SOH) is a growth of bone occurring on the edentulous ridge beneath the pontics of fixed partial dentures (FPDs).

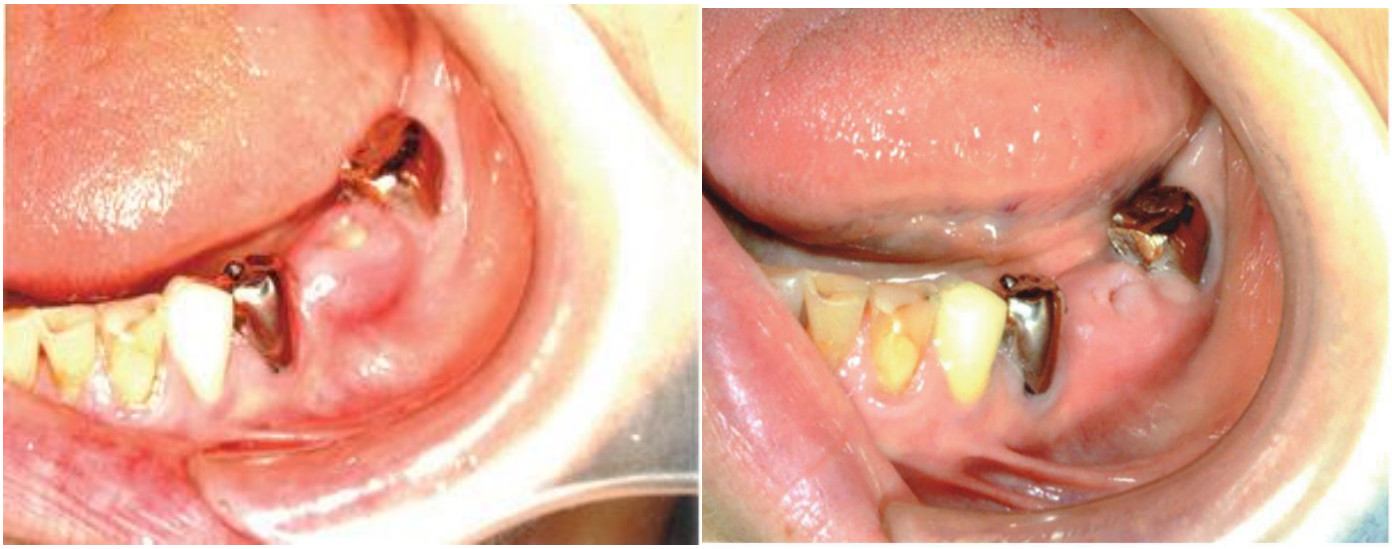
This report describes a case of bisphosphonate related osteonecrosis of the jaw (BRONJ) in a SOH patient followed by deciduation of the bony lesion.

A 73-year-old woman visited a dental clinic after experiencing pain and swelling beneath the pontics of a FPD that had been inserted 15 years ago. The pontics were removed, but the symptoms persisted and she was referred to the hospital of Nagoya-Japan. There was an osseous bulge and gum swelling around the edentulous ridge of teeth 18 and 19, as well as bone exposure. As she had been taking an oral BP for 6 years, we diagnosed this case as stage 2 BRONJ.

Following BP withdrawal, the bony lesion detached from the mandible. The tissue was diagnosed as sequestrum based on the histopathological findings. Two months after deciduation, epithelialization over the area of exposed bone was achieved and no recurrence has been observed.[143]



Panoramic radiographic images. (a) Image taken in October 2002 (before starting the oral bisphosphonate [BP])(b) Image taken in September 2011 (5 years and 4 months after starting the oral BP). These images show chronological changes in the subpontic bone formation.



(c)Intraoral photographic image taken in the first examination. The bone is exposed from the alveolar crest of the lower left teeth 6 and 7, with swelling and redness in the surrounding gingiva.

(d)Intraoral photographic image after detachment of detachment of the sequestrum. Epithelialization was underway with no exposed bone.

Fig 23: A Case of Bisphosphonate-Related Osteonecrosis of the Jaw in a Patient with SOH

3- The Implant Prosthesis:

3-1 Risk factors:

Given the widespread use of bisphosphonates for several conditions and the large use of dental implants, as well as the increasing of cases of bisphosphonate related osteonecrosis of the jaw, it is important to evaluate the relation between these topics to find out the risks for the osseointegration process and BRONJ appearance.

- **Intravenous Bps:** Javed and Almas [144] showed that the incidence of implant failure was minimal in patients using oral and intravenous bisphosphonates, and concluded that dental implants in patients undergoing BPs therapy can osseointegrate and remain functionally stable. On the other hand, Mínguez-Serra et al[145]. suggested the avoidance of dental implant procedures in patients that have been receiving intravenous BPs. This is in accordance with the results of the present review on where one hundred percent of the studies which related combined use of oral and intravenous BPs, have shown cases of osteonecrosis. In the case of administration via oral route, caution is required, avoiding these procedures, or indicating them only when absolutely necessary.
- **Sex:** The study of Yip et al.[146] indicates that women with implant failure had increased odds of implant failure. These findings suggest that dental practitioners should be aware of the increased risk of implant failure associated with oral bisphosphonate use in certain patient populations.
  Their conclusion is in agreement with the recommendation for discontinuation of oral bisphosphonate therapy in long-term oral bisphosphonate users for 4-6 months prior to implant insertion, and several months after, to allow for the recovery of bone remodeling [147]
- **Malignant diseases:** The most of the studies [148] with cases of osteonecrosis enrolled patients with underlying disease such as malignant diseases, osteoarthritis and polymyalgia rheumatic as indication, whereas the majority [149]of the studies with no cases of osteonecrosis, presented only osteoporosis as indication for BPs therapy. This information suggests that general health status of the patients might also have contributed with the development of BRONJ.
- **Dentoalveolar surgery** is considered as a great risk factor for the MRONJ. It is reported that among patients with MRONJ 52 to 61% of patients report tooth extraction as the precipitating event. Above all, it is important to be aware of the great destructive potential of osteonecrosis of the jaws. [150]
- **others:** The literature reviewed say that patients who take oral bisphosphonates, can be submitted to dental implant surgery, on the condition that the risks are thoroughly assessed. The evaluation of the risks associated to the patients comprises: type of agent, dose, and duration of BPs treatment (determinant); female gender, age greater than 65 years, comorbidities such as diabetes or obesity diabetes, steroids use, hypertension , tobacco abuse, concomitant treatment such as corticotherapy, chemotherapy, immunosuppressive therapy, mandibular localization, posterior area, bone diseases such as exostosis, or tori, harboring a badly fitted prosthesis (potentially aggravating), and periodontal disease, bad oral and dental hygiene (aggravating).

3-2 The Dental Approach:

3-2-1 patients with implants and candidates to BPS treatment:

All professional recommendations agree that the patient must be informed of the risks associated with BPs treatment and must have a healthy dental condition, before initiating treatment, if his medical condition allows it.

According to these recommendations, when the indication of treatment with BPs is made, the prescriber must inform his patient of the risks and benefits associated with the chosen molecule and the need to consult an oral cavity professional to make an oral assessment dental and receive appropriate care prior to initiation of treatment with BPs, if medical condition permits.

At the end of this consultation, the patient must be aware of the risks of ONJ and must contact the oral cavity professional. The prescriber should also inform the professional of the oral cavity being treated, the type of treatment prescribed, its potential duration, the risk factors for ONJ and the foreseeable course of the pathology that motivated the treatment with BPs.

Before starting BPS treatment, the professional recommendations recommend that a complete oral assessment (clinical and radiological) be carried out by the oral cavity professional; teeth and soft tissues as well as prostheses (mucosal injuries that may pose a risk of ONj will be carefully examined. [151]

Since a dental extraction is a risk factor for ONJ, it is recommended to wait for tissue scarring before initiating treatment, if the patient's medical condition permits it [152]. When treatment cannot be delayed, the most invasive act will be done first, as the risk of ONj increases with the duration of treatment with BPS. As regards implants already integrated, there is no justification for removing them. [153]

The oral cavity professional should inform his patient that periodic oral monitoring and rigorous hygiene measures are essential during all treatment with BPs. The patient will also be informed that he must report any dental mobility or inflammation of the gingival mucosa (pain, swelling, heat, redness).

3-2-2 Patients undergoing BPS treatment and candidates for dental implant:

- **Patient Information Prior to Implant Placement**

The patient should be informed of the risks associated with implant placement: The risk of developing ONJ is low and can be minimized by periodic oral monitoring and rigorous hygiene measures; however, it cannot be completely ruled out and cannot be predicted by validated diagnostic methods. This risk increases even more as the duration of treatment is longer than 2 years [154], the potential discontinuance of treatment and its health consequences (for example risk of fracture) should be discussed with the BPs prescriber.

- **Should discontinuation of treatment be considered prior to implant?**

AAOMS recommended discontinuation of treatment, 3 months before surgery for patients on oral BPs for less than 3 years and with concomitant corticosteroid treatment and for patients on oral BPs for more than 3 years, with or without associated corticosteroid, and this until complete tissue scarring. Similarly, recommendations from the CAOMS recommended that, in the absence of an emergency, a shutdown of the BPs, 3 to 6 months before the intervention and during the healing period, is recommended. [155]

However, there is no consensus on the positions on the temporary cessation of the BPs and its duration. In the absence of forward-looking data and the fact that the half-life of the BPs can reach several years, some authors believe that it is impossible to state, on the one hand, that discontinuation of treatment eliminates or reduces the risk of an BONJ and, on the other, discontinuation of treatment has a negative effect on the patient's bone state.

Thus, in the absence of data based on sufficient levels of evidence, recent occupational recommendations no longer systematically advocate a period of discontinuation in order to reduce the risk of BONJ; they stipulate that, in all cases, no cessation of treatment can be envisaged without prior consultation with the prescribing physician, depending on the urgency of the act and the patient's medical conditions. [156]

- **What are the surgical precautions and follow-up procedures?**

When an invasive treatment is scheduled, the prescription of chlorhexidine mouthwash, before the procedure and during the following days, is recommended. Antibiotic prescription is suggested when bone extraction or surgery is scheduled to reduce the risk of developing BONJ [157]. The prescription of prophylactic antibiotic therapy for oral surgery involving bone tissue should be motivated, in patients treated with oral BPs, by the risk of infection and not by treatment with oral BPs.

Professional recommendations agree that any invasive oral or maxillofacial action involving bone should be as minimally traumatic as possible, avoiding lifting one or more flaps of total thickness and taking care to regulate the alveolar ridge and to ensure a primary closure of wounds when possible. [158]

In order to assess the risk and to avoid exposing the patient to an extensive ONJ, experts recommend, when several implants are needed, a segmented approach can be used. Thus, by extrapolating, the localized installation of an implant will allow us to know the tissue responses before considering an extensive installation on other sectors.

As with any surgical procedure, the implant in patients on BPs should be performed by observing certain precautions:

-antibiotic prophylaxis (amoxicillin or clindamycin) the day before the procedure and then until complete healing (several days after surgery if necessary)

-Atraumatic surgical technique (minimal periosteal removal)

-Primary healing of soft and bony tissue wounds

-Regulation of sharp bony edges.

-Prolonged scarring monitoring and regular maintenance follow-up are necessary to detect and treat any signs of peri-implant inflammation early on. If a change in treatment by BPs and therefore a change in the associated risk occurs, the controls should be adapted. [159]

3-3 Therapeutic measures for patients with dental implants:

- **3-3-1 Peri-implantitis:**

Like periodontal disease, is likely to increase the risk of ONj and should therefore be treated as soon as possible [160]

Non-surgical measurements based on a mechanical (least traumatic) and pharmacological approach should be preferred, with follow-up every 4-6 weeks. If these conservative measures fail, then surgical revision of the tissue around the implant is recommended. As for periodontal surgery, primary closure of wounds will be preferred, avoiding as much as possible the exposure of the periosteum.

- **3-3-2 Implant failure:**

Recommendations for tooth extraction can be extrapolated to implant removal. Although the risk of ONJ is minimal, the patient should be informed of the potential risk associated with dental avulsion or dento-bone surgery. If removal of the implant is necessary, the technique must be as less traumatic as possible; primary closure of the wound without tension should be preferred if possible, taking care to regularize the alveolar crest.

Prescribing chlorhexidine mouthwash (2 times daily for 4 to 8 weeks) and antibiotic is recommended and should be motivated by the risk of infection that may occur.

- **3-3-3 Peri-implant ONJ:**

Based on recommended protocols for stage 2 of BRONJ (apparent bone necrosis associated with infection with pain and erythema in the exposed area with or without purulent discharge) or recommended in the presence of a localized BRONJ (for alveolar bone and not the basal bone of the mandible or maxilla) as well as on protocols used in series of cases with implants, measures may be recommended to treat a periimplantary BRONJ. These measurements are performed in a hospital setting to treat pain, infection of the soft and bone tissues and to minimize the progression of necrosis. These measures are:

- Antiseptic oral rinse (for example, 3 times/day with 0.12% chlorhexidine).

-Analgesic treatment.

-Antibiotics: Oral amoxicillin is recommended at a rate of 2g per day, in two doses, for 7 days, for adults. In case of lactam allergy, clindamycin is recommended, at a rate of 1200 mg per day, in two doses, for 7 days in adult.

Antibiotic treatment is continued until symptoms improve. Superficial debridement to remove soft tissue irritations. In the absence of favourable evolution, the removal of the implant will be considered, without fear of exacerbating the ONJ lesion and in order to eliminate any future source of inflammation and infection.

Any mobile bone sequestery and irritating bone spines will be eliminated without further exposing healthy bone. Close follow-ups are essential and further treatment with BPs will be discussed with the prescriber.

When therapeutic measures based on a minimal and localized approach have failed, extensive debridement of necrotic bone will be performed. For a small number of patients, when other approaches have failed or in the presence of a pathological fracture, radical resection of the bone and reconstruction will be considered.

In the literature, a series of cases (27 peri-implantary ONJs) reported the results obtained after several months of antibiotic treatment. The response to treatment was better in patients with oral BPs: in this group, complete healing was estimated at 63% while it was estimated at 31% in the BPs IV group.

For 16 patients, the implants had to be removed due to the failure of the antibiotic treatment prescribed for several months (Doxycycline 100 -200 mg/day) and the antibiotic treatment was continued. It was usually prolonged a few weeks after the first signs of improvement. Of these patients, 7 had total healing, 7 had partial healing (reduced bone exposure, significant loss of pain and cessation of purulent exudate) and 2 had no healing.

For the remaining 11 patients, implant removal was not necessary due to improved symptoms with antibiotic therapy; 45% of patients had total healing and 55% partial healing. [161]

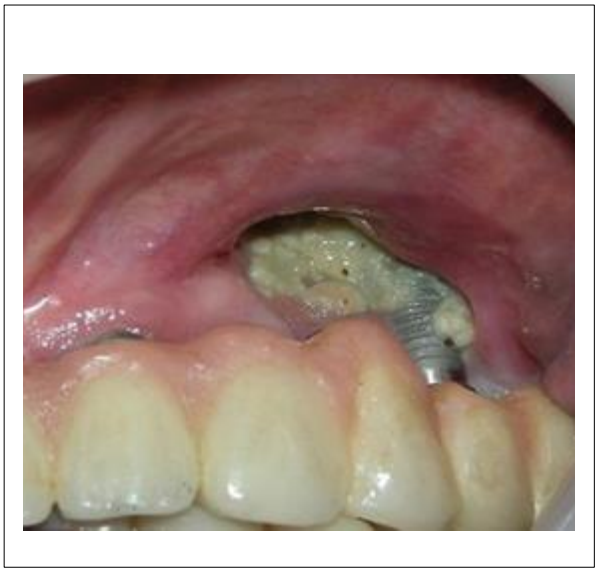


Fig 24: Clinical photograph at presentation; exposed necrotic bone with purulent drainage and debris around the left posterior maxillary implant.

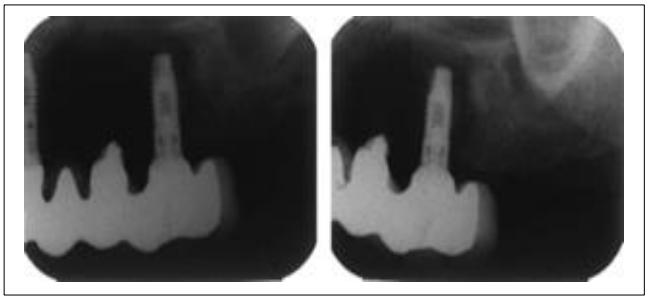


Fig 25: Periapical radiographs at presentation. Area of necrotic bone is evident around the left posterior implant, extending to the floor of the maxillary sinus.

- **3-3-4 BRONJ preventive protocol:**

The followed protocol used for the surgical procedures is based on the expert panels referred to in literature as there are no definitive protocols concerning the prevention and treatment of BRONJ.

- Pre-operative phase:

- Professional oral hygiene must be performed at least 2 weeks before the intervention.

- Oral rinses with chlorhexidine mouthwashes 0.2% every 12 hours for 2 weeks before the intervention.

- Antibiotic therapy with amoxicillin, 2 gr per day, 1 week before the intervention.

- Intra-operative phase:

-The intervention must be performed minimizing the soft tissues and bone trauma.

- Post-operative phase:

- Oral rinses with chlorhexidine mouthwashes 0.2% every 12 hours for 2 weeks after the intervention.

- Antibiotic therapy with amoxicillin, 2 gr per day, at least for 2 weeks after the intervention.

3-4 Follow-up and success criteria:

Clinical monitoring should be carried out one, three, six, nine and twelve months after surgery and then annually, with clinical examinations. Three to four months after implant placement, abutments should be connected and prosthetic rehabilitation must initiate. Panoramic radiographs must be obtained prior to, immediately after, and 6 months following implant placement surgery.

Success criteria should include effective placement and primary stability of the planned implant, implant stability at each control (absence of mobility), absence of pain or any subjective sensation at each control, absence of peri-implant infection with suppuration, and absence of continuous radiolucency around the implant. [162]

4-CLINICAL CASE REPORT:

Prosthodontic treatment of a patient taking nitrogen-containing Bisphosphonates to preserve the integrity of the epithelial attachment: A clinical report

In September 2008, a 68-year-old woman presented to a private practice with the mandibular right second premolar, an endodontically treated tooth, fractured off at the gingival margin.

A review of the patient's medical history revealed that she had no history of head and neck radiation exposure but had been taking Fosamax, 10 mg, once a day since April 2000. Although the patient had not presented with any clinical signs Of BP induced ONJ, the patient's history was of significance in selecting an appropriate treatment plan.

All treatment options, risks, benefits, and alternatives were discussed with the

Patient which included:

-No treatment,

-Extract and replace with implant, removable prosthesis or nothing, and perform a coronectomy of the mandibular right second premolar and restore with a cantilever partial fixed dental prosthesis from the existing gold implant abutments mesial to the fractured premolar.

To minimize risks, traditional prosthodontic procedures were followed. The tooth was decoronated subgingivally without disrupting the epithelial attachment.

The existing implant-supported partial fixed dental prosthesis was removed, and new

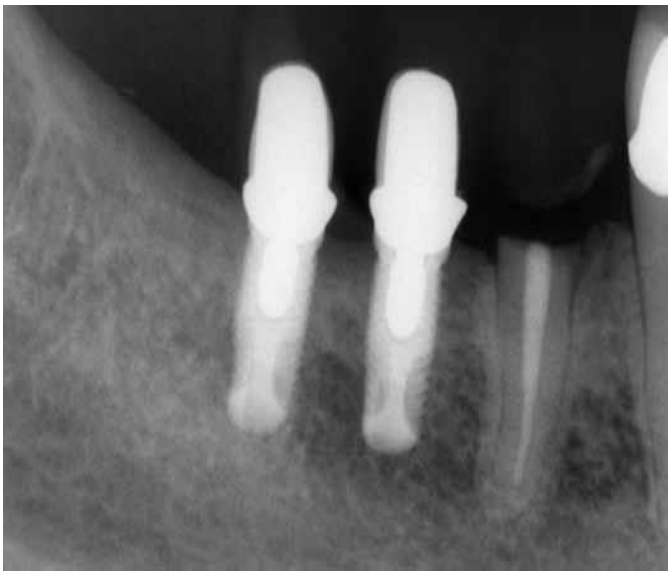
Impressions (Identic Alginate; Dux Dental, Oxnard, Calif) were made for a provisional partial fixed dental prosthesis cantilevering the mandibular right second premolar from the existing distal implant abutments.

The patient was placed on a chlorhexidine rinse (Peridex; 3M ESPE, St Paul, Minn) twice a day for 6 weeks, at which time healing was reassessed.

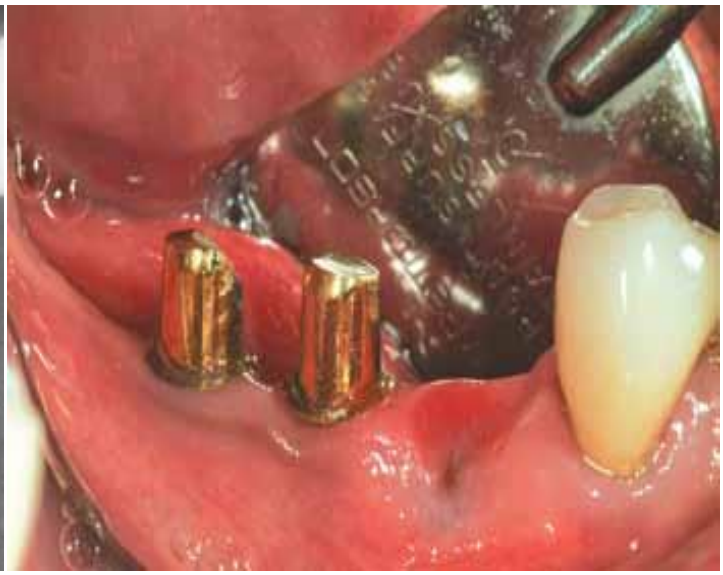
At the 6 week re-evaluation, the tissue had almost completely covered the remaining root structure and was without any signs of inflammation or infection.

Definitive impressions (Flexitime; Heraeus Kulzer, South Bend, Ind) were made, and shortly thereafter, a definitive implant cantilever partial fixed dental prosthesis was cemented with provisional cement (Temp Bond; Kerr Dental, Orange, Calif) for retrievability .

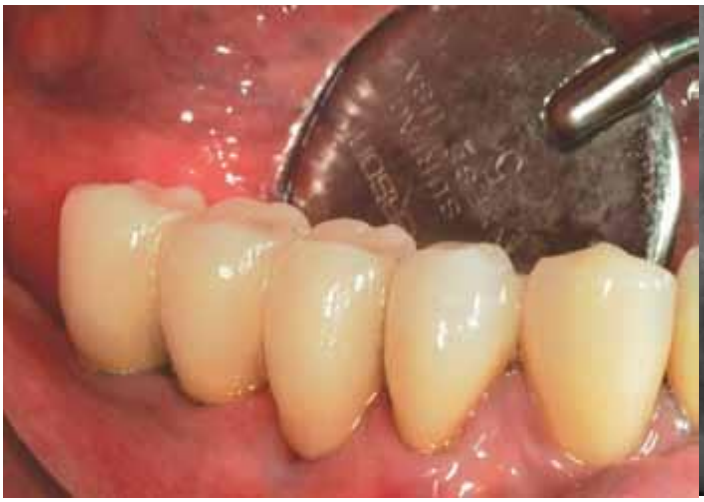
The patient has maintained excellent tissue health for 42 months.[163]

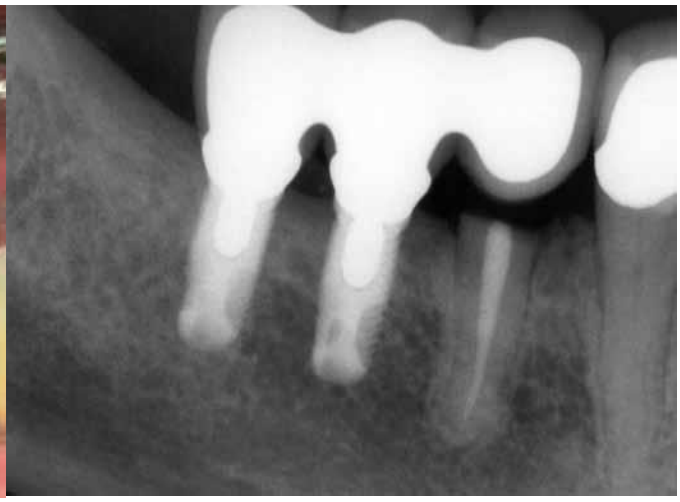


Radiographic presentation of mandibular right second premolar after decoronation procedure.



Clinical presentation after 6 weeks of healing. Note healthy soft tissue covering remaining root structure.





A, Definitive metal ceramic partial fixed dental prosthesis. B, Radiographic presentation of definitive prosthesis in place

Fig 26: Pictures illustrating the prosthodontic treatment of a patient taking nitrogen-containing Bisphosphonates to preserve the integrity of the epithelial attachment.

❖ Conclusion:

Bisphosphonates are now on the front of the medical scene thanks to their anti-osteoclast virtues. This feature now makes them indispensable in the treatment of benign pathologies such as osteoporosis and Paget's disease and in osteolytic malignant pathologies such as multiple myeloma and bone metastases.

Their activity is not limited to the inhibition of bone remodeling, bisphosphonate molecules have other properties, such as their anti-angiogenic action. All these effects are also the cause of more or less restrictive side effects, the most feared is the osteonecrosis of the jaws.

The occurrence factors of this complication are not yet clear, and are based on several hypotheses. The therapeutic possibilities recommend the conservative approach, even if it is not always effective, and must sometimes give way to other more or less invasive techniques.

Prevention remains the best initiative, it involves informing the patients about the risks of treatment and education to good oral hygiene.

Studies have shown that this osteonecrosis is generally found in patients treated with bisphosphonates administered intravenously, compared to patients treated with bisphosphonates administered orally whose frequency, the severity and delay of this side effect are reduced. This variation is due to high bioavailability and cumulative dose over time in intravenous bisphosphonates used for malignant conditions.

The initial question was whether it was possible to consider prosthetic therapy for patients treated with bisphosphonates. The answer, unfortunately, cannot be simple; it varies according to several parameters, such as the administration route of the molecule, the duration of the treatment and the cumulative dose.

There are many opinions regarding removable and irremovable prostheses , some authors contraindicate them because of their negative effect on the ONJ and others remind us that the absence of wearing the prosthesis in edentulous patients leads to an imbalance in the diet which in turn becomes unfavourable to a remission of the ONJ, which leads us to conclude that the solution of a treatment by removable or irremovable prosthesis should not be abandoned provided that all precautions are respected.

As for implant prosthesis, there are divergent opinions and a general consensus on the formal contraindication of implants in patients treated with bisphosphonates intravenously.

In the case of patients treated with oral bisphosphonates, there are no absolute contraindications to the placement of implants but precautions to be taken as the recoil is low on bisphosphonates and their action in the development of ostechemonecrosis.

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Abstract:

Healthy jawbones ensure a better tooth anchorage and the ability to masticate and maintain metabolism. This is achieved by a delicate balance between bone formation and resorption in response to functional demands. Bisphosphonates are antiresorptive drugs, a class of agents used to treat various systemic conditions affecting this balance and other metabolic bone diseases. Despite their benefits, Bisphosphonate-Related Osteonecrosis of the Jaw is an important complication in the subset of patients undergoing this treatment. The prosthodontic management of this category of patient isn't very common nowadays and many dental practicians seem to ignore the appropriate approach to take with these patients. This work aims to bring increased understanding on the prosthodontic therapy with all the types of dental prostheses for patients undergoing this antiresorptive drugs treatment, and the preventive protocols and the right approaches in order to avoid and prevent the BRONJ.

Keywords: bisphosphonates, jawbones, remodeling, BRONJ, dental prostheses, prosthodontics.

Résumé :

Les maxillaires saines assurent un meilleur ancrage des dents et une capacité de mastiquer et de maintenir le métabolisme. Ceci est obtenu par un équilibre délicat entre la formation osseuse et la résorption en réponse aux exigences fonctionnelles. Les bisphosphonates sont des médicaments antirésorptifs, une classe d'agents utilisés pour traiter diverses affections systémiques touchant cet équilibre et d'autres maladies osseuses métaboliques. Malgré leurs bienfaits, l'ostéonécrose des maxillaires induite par les bisphosphonates est une complication importante chez l'ensemble de patients qui suivent ce traitement. La prise en charge prosthodontique de cette catégorie de patients n'est pas très courante de nos jours et de nombreux dentistes semblent ignorer l'approche appropriée à adopter avec ces patients. Ce travail vise à mieux faire comprendre la thérapie prosthodontique avec tous les types de prothèses dentaires pour les patients subissant ce traitement antirésorptif, et les protocoles de prévention et les bonnes approches pour éviter l'ONMB.

Mots-clés : bisphosphonates, maxillaires, remodelage, ONMB, prothèses dentaires, prosthodontie.

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