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Doctoral Programme in Clinical Research – XXXVI Cycle

DIFFERENT TECHNIQUES FOR DENTAL IMPLANTS SITE PREPARATION: A CONTROLLED CLINICAL TRIAL

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A mia Zia Giulia,

Grazie per ispirarmi ogni giorno.

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INTRODUCTION

Implant treatment is nowadays an integral part of everyday dental practice, both for the rehabilitation of individual edentulous spaces and for more complex rehabilitations that may involve entire arches.

Moreover, with the help of modern techniques for bone augmentation volume and the constantly expanding range of fixture designs, prosthetic components, and surgical instruments, implant-prosthetic rehabilitation can meet the needs of almost all patients who require it.

Modern implantology emerged in the second half of the 1980s from two independent groups: the team led by Professor Branemark at the University of Gothenburg and the International Team for Implantology at the University of Bern.

It quickly established itself as a revolution in dentistry, thanks to the enthusiastic scientific and clinical interest it immediately garnered, leading to rapid and substantial progress.

The first 15 years are considered the years of significant development, during which the fundamentals of the implantology we still apply today were laid. From 2000 onwards, a second phase began, which can be described as a phase of consolidation and refinement of implant treatment.

We are currently in the midst of this phase, where the surgical fundamentals remain unchanged, but the surrounding elements evolve. This allows for increasing levels of function and aesthetics over time, reaching more and more patients, including those who were initially not considered suitable candidates for implantology.

Currently, there is a focus on minimizing invasiveness and reducing patient morbidity. This has led to the increasing popularity of implants with designs that can be placed even in limited horizontal space (narrow-diameter implants) or vertical space (short implants).

Several implant companies have started producing zirconia implants, which, besides being more aesthetically pleasing, can be used for patients who have metal allergies or titanium intolerance. The digital workflow, from digital impressions to computer-aided surgical planning and guided surgery, is surpassing its initial limitations and is becoming a valuable tool in clinical practice.

In recent years, the role of soft tissues has become central. It's now understood that the success of implant-prosthetic treatment doesn't solely depend on the available bone volume,

but also on the quality and quantity of the peri-implant soft tissues. Therefore, soft tissue analysis has been routinely introduced in diagnosis, and surgical techniques have been applied to enhance their thickness and/or level.

The subject of this study will be the evaluation of two types of drills for implant site preparation. Specifically, the study aims to assess whether the use of drills with apical steps, which could result in less bone overheating during osteotomy, leads to reduced marginal bone loss in the first year after implant placement compared to conventional straight drills.

The literature is in agreement that lower marginal bone loss is associated with a higher implant success rate. Numerous studies demonstrate how bone overheating during surgical site preparation can be one of the contributing factors to early marginal bone loss.

The study will follow a prospective comparative design and will be conducted at two centers (multicentric).

The design characteristics of the more advanced drill not only enhance user comfort but also improve cutting efficiency and minimize the overheating of the surrounding bone. These features will lead to more satisfactory outcomes for both the patient and the clinician in the short and long term.

CHAPTER 1
PERI-IMPLANT BONE: BIOLOGY AND PHYSIOLOGY

The mechanical strength and functional adaptation to implant load are determined by anatomical and structural conditions. Bone structure and density influence implant therapy and they are fundamental factors in treatment planning, choice of implant type, selection of surgical approach, timing, and progression of load application during prosthetic construction.

1.A Bone Structures

Bone tissue is a specialized connective tissue composed of two components, one organic and the

other inorganic, which together form the amorphous ground substance. The organic component is mainly represented by proteins such as type I collagen, osteocalcin, and osteonectin.

The inorganic component is represented by various calcium and phosphate ions, deposited in the matrix as hydroxyapatite. In adults, these mineral deposits account for 60-70% of the total bone mass.

The presence of mineral salts gives bone its distinctive hardness, making it the only rigid connective tissue.

This hardness enables bone to:

- Withstand mechanical loads;
- Protect sensitive organs from external forces (e.g., the central nervous system);
- Serve as a mineral reservoir that contributes to body homeostasis.

The macroscopic structure of the bone determines its mechanical strength and is crucial for implant treatment planning. Bone consists of both a soft and a hard component in varying proportions; the relative quantity of these two components allows distinguishing between cortical or compact bone and spongy or cancellous bone (fig. 1)

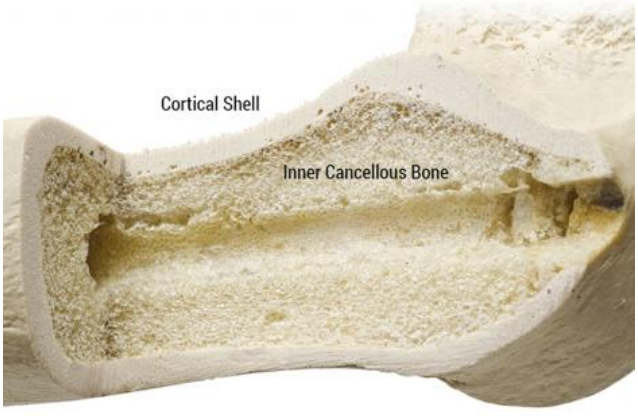

Figure 1 Femur cross-section. Compact bone surrounding trabecular bone.

At the microscopic level, cortical bone (fig. 2) is primarily composed of the dense, mineralized component of bone and is characterized by osteons.

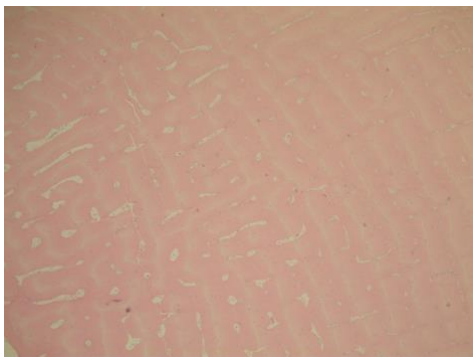

Figure 2 Optical microscope image of a cow's mandible, showing a detail of the cortical bone

The osteon or Haversian canal (fig. 3) is the functional unit present in cortical bone tissue. It is a cylindrical structure that is a few millimeters long and has a diameter of about 0.2 mm. The osteon is a concentric lamellar system, with a central canal called the Haversian canal, which contains one or more blood vessels responsible for its vascularization. The Haversian canals of different osteons are connected through transverse channels, known as Volkmann's canals or perforating canals (Rosati 2007).

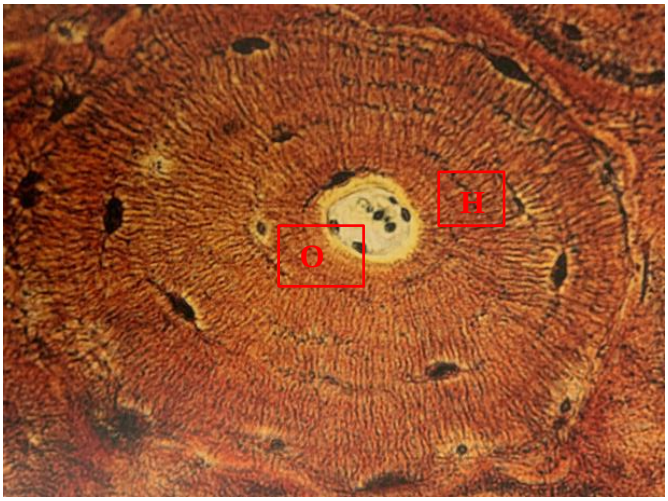

Figure 3 Cross-section of the diaphyseal shaft of a long bone. A single osteon, centrally traversed by the Haversian canal (H), is visible. Note the bone lacunae

Osteons are generally arranged parallel to one another; interspersed between the osteons are lamellae of the interstitial system. These lamellae are generally parallel within each interstitial space but have a different orientation in each interstitial space.

Spongy bone (fig. 4) is composed of a variable mixture of hard and soft, low-density components. It consists of layers of lamellae that are associated in trabeculae (hard component) of varying thickness, interconnected to form marrow cavities, which are intercommunicating spaces enclosed by bone marrow, blood vessels, and nerves (soft component).

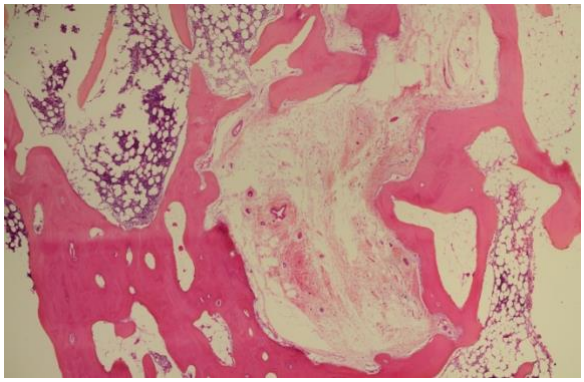

Figure 4 Optical microscope image of the human femoral head, showing a detail of trabecular bone.

The resistance of trabecular bone depends on the thickness of the trabeculae, their orientation, and their interconnectivity. The conditions of bone-implant contact differ significantly between the mandibular bone and the upper maxillary bone, influenced by bone density.

Resistance to tensile and bending forces is provided by the presence of collagen fibers, which determine the organization of the mineralized matrix into either woven bone (a less structured and less substantial phase) or lamellar bone (a mature and compact organized tissue composed of calcified lamellae).

Bone hardness, on the other hand, is determined by the presence of inorganic calcium phosphate crystals deposited along the collagen fibers.

The ultra-microscopic structure concerns the molecules of the bone, and within it are inherent the fundamental healing processes necessary for understanding the mechanisms of integration and healing of implants.

The ultra-microscopic component is represented by the chemical and molecular structure of the bone: bone is composed of an organic component (30%) and an inorganic mineral component (70%).

Among the organic components, in addition to collagen, there are proteoglycans, some non-collagenous proteins, cytokines, and growth factors like BMP (Bone Morphogenetic Proteins), which stimulate repair and regeneration processes whenever the bone undergoes trauma.

The most abundant element is type 1 collagen, which organizes into fibers that serve as a scaffold (matrix) for the deposition of calcium salts during the mineralization process. Other protein components (osteocalcin, osteonectin, osteopontin) function to modulate the formation, mineralization, and adhesion processes between cells and the bone matrix.
Collagen fibers are not arranged randomly; they align in an orderly manner, giving rise to the lamellar structure of the bone.
Among the inorganic components, minerals such as calcium, phosphorus, and magnesium are present, contributing to the bones' characteristic hardness. Calcium is found as calcium phosphate, deposited in the form of hydroxyapatite-like crystals anchored onto a collagen fibrous scaffold. These crystals align in an organized manner along the collagen fibers. Additionally, other salts are present, such as calcium carbonate and traces of magnesium phosphate and calcium fluoride (also significant in teeth).

1.B Bone tissue cells

The cells of bone tissue derived from a mesenchymal precursor and are of three types: osteoblasts, osteoclasts, and osteocytes.

Osteoblasts are responsible for synthesizing the intercellular substance of bone and its mineralization. They have a cuboidal shape and align on the surface of the matrix during deposition. Osteoblasts are more concentrated and voluminous in areas of intense bone deposition, while they are smaller and spaced out in regions with reduced activity.
They start by depositing organic osteoid, which consists of collagen and non-collagenous proteins within the first 10 days; minerals will form within the osteoid another 10 days later. Osteoblasts produce about 1 micron of osteoid tissue per day and require large amounts of oxygen. As a result, the vascularization of bone tissue plays a crucial role in the healing process.

Osteocytes are osteoblasts that have completed the mineralization phase and become trapped within the newly formed bone. They are responsible for maintaining and remodeling bone tissue by sensing the deformation of the bone structure in response to mechanical stimuli. Through their numerous cytoplasmic extensions, they can communicate with each

other to activate remodeling processes. Osteocytes are terminal cells; when they reach the end of their lifespan, they retract their extensions and degenerate.

Osteoclasts are cells derived from monocytes/macrophages and are responsible for bone resorption, playing an essential role in remodeling processes. They are relatively large cells and are typically multinucleated. They perform their specific activity when triggered by local and/or systemic stimuli, adhering to the bone surface.
Their morphology varies based on their functional state: when free and mobile, they have an undefined shape and exhibit lamellipodia; when active, they display clear polarity, with a brush border at the erosion front. In the portion of their cytoplasm facing the bone surface to be degraded, they concentrate lysosomes rich in lytic enzymes.

1.C Classification of maxillary bone density

Of clinical relevance in implant dentistry is the understanding of the bone type at the site where the implant will be placed. Indeed, bone structure and density determine the choice of implant type, site preparation, and the possibility of performing immediate loading versus delayed loading.
The Lekholm and Zarb classification (1985) categorizes bone into 4 types based on the amount of cortical vs. trabecular bone:

- Type 1: Entire bone is composed of very thick cortical bone;
- Type 2: Thick layer of cortical bone surrounds a core of dense trabecular bone;
- Type 3: Thin layer of cortical bone surrounds a core of trabecular bone of good strength;
- Type 4: Very thin layer of cortical bone with low density trabecular bone of poor strength. .

The challenge with this classification lies in the clinical difficulty of distinguishing between the four categories accurately.

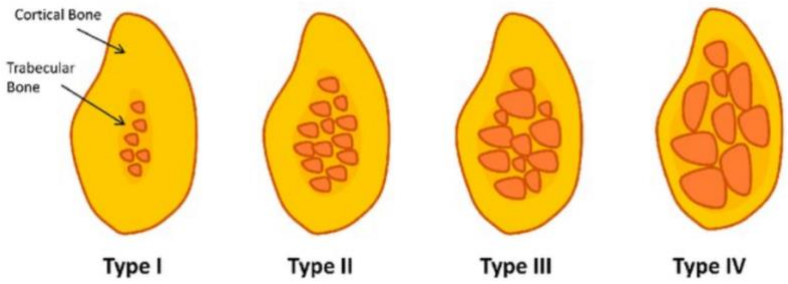

Figure 5 Lekholm and Zarb Classification

The subsequent Misch classification (Fig. 6) differentiates bone into four types based on hardness: D1, D2, D3, and D4, with D1 being the hardest and D4 being the softest (Misch 1990).

This is a radiographic classification based on the number of Hounsfield units from a CT scan image:

- D1 bone corresponds to values greater than 1250 Hounsfield units,
- D2 bone corresponds to values between 850 and 1250 Hounsfield units,
- D3 bone corresponds to values between 350 and 850 Hounsfield units,
- D4 bone corresponds to values lower than 350 Hounsfield units.

Each bone type is associated with a comparable material in terms of hardness:

- D1 bone is likened to oak wood,
- D2 bone to pine wood,
- D3 bone to balsa wood,
- D4 bone to polystyrene.

This classification helps guide decisions related to implant selection, site preparation, and loading protocols based on the bone's hardness.

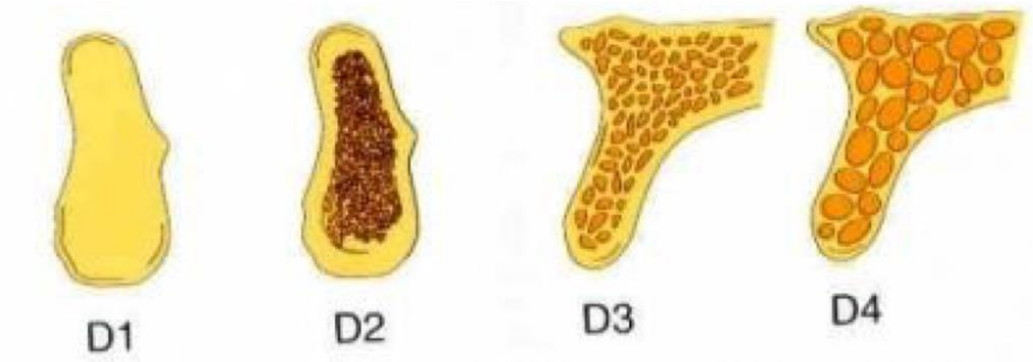

Figure 6 Misch Classification

Trisi and Rao (Trisi 1999) demonstrated that the clinician's hand is able to reliably and statistically significantly distinguish between D1 and D4 bone, but not between the intermediate classes D2 and D3 (Fig. 7). Therefore, they proposed a new classification scheme consisting of only 3 bone categories that can be differentiated through drilling with a bur (Table 1):

- Soft bone
- Hard bone
- Medium bone

Table 1 Comparison between Misch and Trisi and Rao classification

Misch classification	Trisi e Rao classification
D1	Hard bone
D2	Medium bone
D3	Medium bone
D4	Soft bone

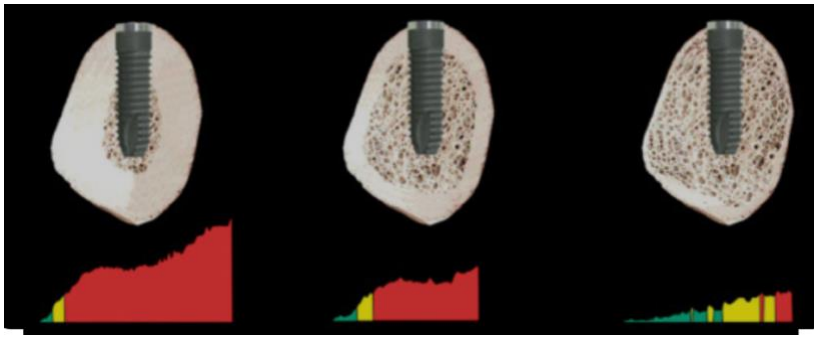

Figure 7 Trisi abd Rao classificazion

The literature shows that the density of the jaws varies continuously and significantly from one tooth position to another; however, it agrees in asserting that the anterior areas of the jaws are denser than the posterior areas. Numerous studies confirm that the highest density is found in the anterior mandible, followed by the anterior maxilla, posterior mandible, and finally the posterior maxilla.

The differing density between the upper and lower jaws could be explained by the role of the mandible in absorbing forces, which is different from the upper jaw. The upper jaw has the ability to distribute loads to the cranial structures it interacts with.

The fact that the anterior regions in both arches have higher density can be explained by the function of incisors and canines. Due to their role in tearing and cutting, they need to endure lateral forces, requiring a more resistant bone support compared to molars and premolars. The latter are mainly subjected to vertical masticatory forces (Fuh, 2010; Di Stefano, 2019).

1.D Classification of maxillary atrophies

The bone of the jaws consists of two distinct osseous components:

- The basal bone, which forms during fetal development and provides insertion points for muscular structures.
- The alveolar bone, which forms in response to tooth eruption and is a component of the periodontal apparatus.

Teeth transmit forces to the alveolar bone. Following the loss of dental elements, these forces decrease, leading to a gradual resorption of the alveolar process. This resorption typically occurs horizontally at first and later vertically. This progressive resorption results in the atrophy of the jaws. The basal bone, on the other hand, generally undergoes minimal changes in shape.

More specifically, changes in the shape of the alveolar bone follow a predictable pattern that varies depending on the site:

- Anterior mandible: Bone loss is both vertical and horizontal.
- Posterior mandible: Bone loss is primarily vertical.
- Anterior maxilla: Bone loss is both vertical and horizontal (from the buccal side).
- Posterior maxilla: Bone loss is both vertical and horizontal (from the vestibular side).

The stage of bone loss can vary between the upper maxilla and the mandible, as well as between posterior and anterior sites (Cawood, 1988).

Various classification systems have been proposed over the years to categorize the degree of atrophy, with the historically most widely used being the Cawood and Howell classification from 1988. This classification divides atrophy patterns into 6 classes (fig. 8):

- Class I: Dentition present.
- Class II: Immediate post-extraction alveolar ridge.
- Class III: Late post-extraction alveolar ridge with re-ossification of the post-extraction socket and a rounded but adequate alveolar process in height and thickness.
- Class IV: Adequate height but insufficient thickness, described as "knife-edge."
- Class V: Flat ridge, inadequate in both height and thickness.
- Class VI: Depressed ridge, with atrophy of the same basal bone.

This classification aids in assessing the extent of bone atrophy in various clinical situations.

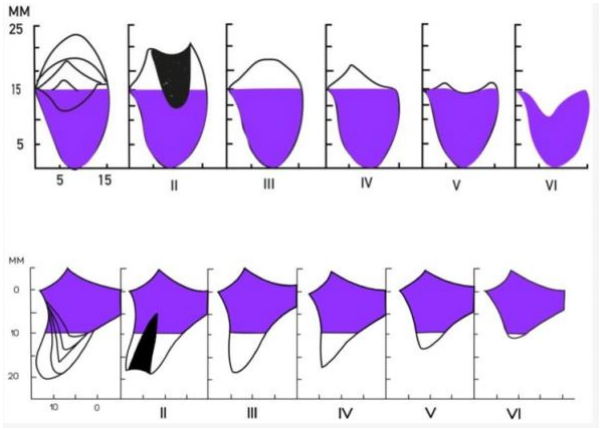

Figure 8 Cawood and Howell classification

In 2018, Chiapasco and Casentini introduced a new classification system for defects that not only considers the morphology of the defect but also correlates the degree of atrophy with the surgical solution (Chiapasco 2018). This classification includes 5 classes:

- Class 0: Immediate defects, where there is a lack of bone in the alveolus, not due to atrophy but because the tooth has just been extracted. For these defects, ridge preservation or immediate implant placement is considered.
- Class 1: Moderate atrophy. The implant is entirely surrounded by bone, but the crest exhibits a concave profile. Surgical techniques are applied to restore the proper convexity to the alveolar process, potentially achieved through soft tissue augmentation alone (fig. 9.a).
- Class 2: Moderate atrophy. There is enough bone for implant placement, but inserting the implant will result in either fenestration or dehiscence. Therefore, techniques involving soft tissue augmentation and/or simultaneous bone regeneration are necessary during implant placement (fig. 9.b).
- Class 3: More severe atrophy, with significant horizontal defects that make implant placement impossible. In this case, implants need to be placed at a later time following horizontal regenerative surgery (fig. 9.c).
- Class 4: Vertical resorption. The issue now extends beyond bone thickness to include its height. Implants cannot be placed concurrently with regeneration; vertical regenerative surgery is required prior to implant placement (fig. 9.d).

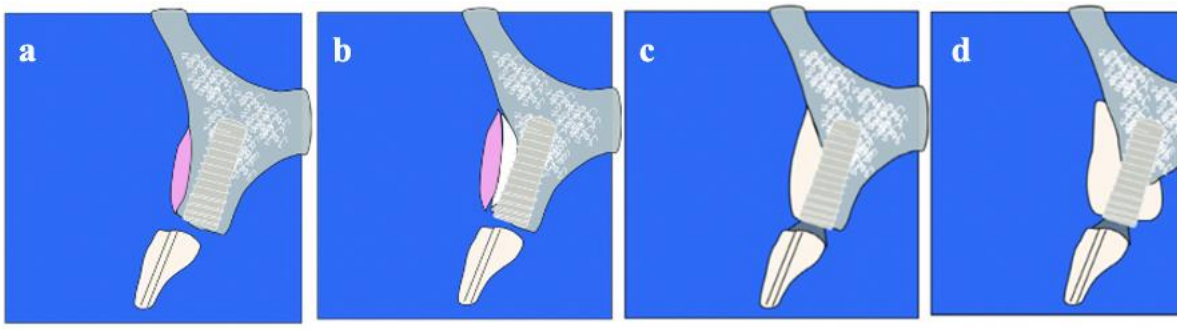

Figure 9 Classification of atrophie according to Chiapasco and Casentini. ***a****. Class 1;* ***b****. Class 2;* ***c****. Class 3;* ***d****. Class 4*

1.E Bone remodeling and bone modeling

Bone remodeling is the process that allows bone to maintain its structural integrity over time. It involves the strategic removal of a portion of the bone matrix by osteoclasts, which is then replaced according to prevailing lines of force exerted on the bone itself.

Remodelling processes persist throughout life, enabling a continuous reshaping of the bone matrix to adapt to the biomechanical demands of the skeleton. Approximately 5-10% of our skeleton is replaced with new bone every year.

In cortical bone, remodelling is concentrated within the remodelling of osteons, and the average formation speed of an osteon is about 4 months in humans. In the realm of trabecular bone, the remodelling involves the trabecular network.

The amount of bone formed must be equal to the amount of bone resorbed. If this balance is disrupted, a process called modelling occurs, which is distinct from remodelling. In modelling, the mass of resorbed bone differs from that of newly formed bone.

1.F Bone wound healing

The process underlying implant healing (osseointegration) is comparable to the healing of bone fractures. The healing of bone fractures and the healing of perimplant bone differ in the following ways:

- Number of active parts: In perimplant bone healing, there is the titanium surface (passive part) and the bone surface (active part). In the case of bone fracture healing, there are two active parts, represented by the two bone walls at the fracture site.
- Presence of mobility of superficial bone walls: In implantology, the implant is stabilized within the bone, while in the case of bone fractures, osteosynthesis techniques are typically used to immobilize the fracture.

The following table outlines the main phases of tissue healing after a bone fracture and after site preparation and implant insertion (Table 2).

Table 2 Healing process after bone osteotomy for implant bed preparation

Phases of the bone fracture healing process:	Phases of the bone healing process in implantology after osteotomy with a drill:
Hematoma Formation: After a fracture, blood vessels at the fracture site are damaged, leading to bleeding and the formation of a blood clot (hematoma). This hematoma provides a scaffold for the subsequent healing process.	**Blood Clot Formation:** Similar to the hematoma formation in bone fractures, the drilling process disrupts blood vessels, leading to bleeding and the formation of a blood clot around the osteotomy site.
Inflammatory Phase: Inflammation occurs as immune cells are attracted to the site. These cells remove debris and prepare the area for healing. This phase typically lasts a few days**.**	**Inflammatory Phase:** Immune cells are attracted to the site of the osteotomy, initiating an inflammatory response. This phase involves the removal of cellular debris and the preparation of the area for tissue regeneration.
Granulation Tissue Formation: New blood vessels and connective tissue, known as granulation tissue, start to form around the fracture site. This tissue provides nutrients and oxygen to support healing.	**Granulation Tissue Formation:** New blood vessels and connective tissue, known as granulation tissue, form around the osteotomy site. This tissue provides a supportive environment for healing and helps deliver nutrients and oxygen.
Callus Formation: Osteoblasts, bone-forming cells, begin to produce a soft callus of cartilage and collagen fibers around the fracture. This stabilizes the fractured ends and initiates the process of bone regeneration.	**Osteogenesis and Osseointegration:** Osteoblasts start to generate new bone tissue at the periphery of the osteotomy site. The implant surface, typically made of titanium, becomes integrated with the newly forming bone through a process called osseointegration. This phase can take several weeks to months.
Hard Callus Formation: The soft callus is gradually replaced by a hard callus made of woven bone. This process can take weeks to months, depending on the bone's location and the severity of the fracture.	

Remodeling Phase: Over time, the hard callus is reshaped and remodeled by osteoclasts (bone-resorbing cells) and osteoblasts. The bone gradually gains its original strength and structure through this continuous remodeling process.	**Maturation and Remodeling:** The newly formed bone continues to mature and remodel over time, adapting to the mechanical forces applied during function. Osteoclasts and osteoblasts work together to reshape and strengthen the bone around the implant.

When placing an implant in dense bone, a minimal bone-implant space remains (not even detectable under an optical microscope). In this space, the healing process is activated from the perimplant bone wall, which initially undergoes bone devitalization with the death of osteoclasts due to interrupted blood supply. About 1 mm of compact bone adjacent to the surgical wound dies immediately after the trauma, despite using optimal surgical techniques, due to the damage to the vascular support caused by the disruption of blood vessels within Haversian canals.

The only way for dense bone to heal relatively quickly is through a process known as RAP (regional acceleratory phenomenon), which enables rapid healing of cortical bone tissue. Thanks to this phenomenon, bone can increase the rate of osteon synthesis following an injury, transitioning from a remodelling rate of 3% to 50-60% within 3 weeks. This allows for effective healing of cortical bone within a few months.

The healing mechanism differs in trabecular bone: the fragments of fractured trabecular bone generated during drilling stimulate reparative processes. In the first month, this leads to the formation of micro-calluses, bridging the gap between trabeculae and the implant surface. Over the first two months, the remodelling process replaces immature bone and completes the restitutio ad integrum of the bone, forming new bone with similar characteristics to the original bone.

Critical factors in bone healing include:

1. **Mechanical Stability:** Adequate mechanical stability is crucial for proper bone healing. If the scar tissue is not stable, the cells responsible for forming new blood vessels (angiogenesis) that provide vascularization and oxygenation might not function properly. This can lead to the formation of cartilaginous or fibrotic tissue instead of bone.
2. **Vascularization:** Proper oxygen supply is essential for the differentiation of undifferentiated cells into osteoblasts. In a low-oxygen environment, these cells might

differentiate into chondroblasts, which can lead to the formation of cartilaginous tissue rather than bone.

3. **Solid Surface:** In conditions where mechanical stability and vascularization are achieved, osteoblasts start depositing new bone. This process often begins from an existing solid bone surface.
4. **Protection of the Blood Clot:** To encourage bone regeneration in a non-contained site, physical barriers are often used to create an osseous environment, separating it from surrounding soft tissues that could interfere with bone regeneration.

These critical factors underscore the complexity of the bone healing process and the importance of maintaining optimal conditions for successful bone regeneration.

1.G Dental implant osseointegration

The study conducted by Simion et al. in 2015, focusing on the canine mandible, examined the phases of the titanium implant osseointegration process by histologically analyzing the initial stages of healing up to 90 days (Simion 2015).

Immediately after implant insertion into the bone, the Bone-to-Implant Contact (BIC) surface area is limited, occurring exclusively at the apex of the implant threads. The spaces between the threads are filled with the formation of a blood clot, which serves as the foundation for new bone tissue production.

The blood clot contains platelets that release growth factors upon degranulation, facilitating the arrival of various cells responsible for the regeneration process. Initially, alongside the blood clot, there are bone chips found in the spaces between implant threads. These bone chips result from the preparation process using drills, thread tapping of the site, and the implant insertion itself. The self-tapping effect of implant insertion contributes to the production of bone chips, which remain within the blood clot (Fig. 10.a).

Around 7 days after implantation (Fig. 10.b), osteoclasts start to resorb the damaged bone present in the bone chips. This bone material consists of dead or dying bone, as it is a byproduct of the drilling process.

Osteoclasts have a coupling system with osteoblasts, which begin to deposit the matrix. As osteoclasts resorb these bone chips, they release cytokines and intrinsic growth factors specific to the bone particles. These substances act as stimulating agents for osteoblast activity. During this phase, bone formation activity is present only around the bone chips.

Around two weeks after implantation, the bone chips are almost entirely resorbed, revealing new bone in contact with the implant (Fig. 10.c).

Matrix proteins secreted by osteoblasts mineralize and form osteoid tissue. At this stage, immature non-lamellar bone can be observed, also known as woven bone.

Immature bone is abundant in cells, but lacks the organization of collagen fibers and the mineralization necessary for providing mechanical support.

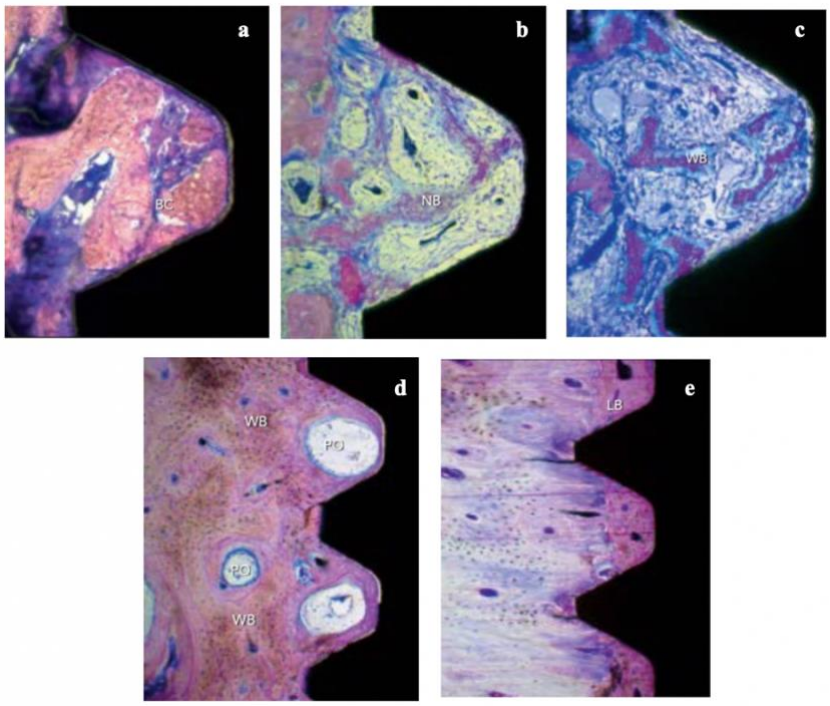

Figure 10 Fig: 8 Phases of Osteointegration in Dog Bone (Simion 2015)

a. *Bone chips between implant spirals. Photo at 0 days after implant placement. Magnification 20x. (Simion 2015).*
b. *Active resorption of bone fragments and consecutive formation of new bone (NB). Photo at 7 days after implant placement. Magnification 20x.*
c. *Bone chips are resorbed and replaced with woven bone (WB). Photo at 15 days after implant placement. Magnification 20x.*
d. *Woven bone (WB) and some immature primary osteons (PO). Photo at 30 days after implant placement. Magnification 10x.*
e. *Mature lamellar bone (LB) in contact with the implant surface. Photo at 90 days after implant placement. Magnification 10x.*

The body recognizes this inadequate bone and activates cutting cones, which are functional remodelling units (Fig. 11). Cutting cones consist of an advancing front of osteoclasts and a trailing tail of osteoblasts: osteoclasts excavate a tunnel in the bone tissue to be replaced, while simultaneously secreting or releasing substances from the degrading bone that activate osteoblasts. The structure of cutting cones leads to the formation of lamellar bone tissue with osteons.

At 30 days, intense osteoblastic activity with cutting cones is still present, indicating the process of maturation of bone tissue into lamellar tissue. Some osteons begin to appear (Fig. 10.d). In the empty spaces between the implant spirals, bone formation can be observed progressing from the native bone at a certain distance from the implant surface. Bone formation activity decreases significantly after 30 days from implant placement, and by 3 months, all immature bone is replaced by new bone with a lamellar structure directly in contact with the implant surface (Fig. 10.e).

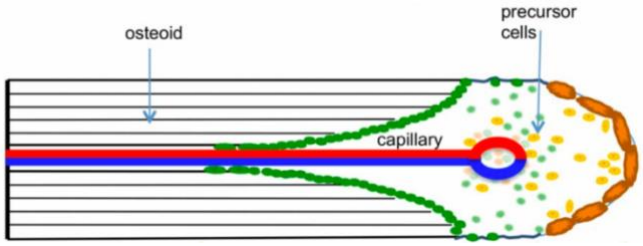

Figure 11 Representation of a cutting cone. The osteoclast in orange and the osteoblast in green (Smith 2012)

1.H Wolf's Law

The law of Wolff states that any change in the function of bone results in adaptation of the internal and external bone structure, meaning that form follows function.

Strain refers to the change in bone deformation in relation to the applied load; reduced bone deformations are measured in microstrain (με).

Studies conducted by Wolff demonstrate that strains between 50 and 1500 με stimulate an increase in cortical bone mass until the strains are reduced to a threshold limit. This process can initiate or cease bone remodelling.

Below 200 με, which indicates the absence of load, there is a process of bone resorption due to disuse atrophy or osteopenia. A clinical example is the loss of a tooth.

From 200 to 2500 με, there is equilibrium: the bone tends to maintain its mass since the tendency for resorption is comparable to the tendency for new bone formation. An example is a dental implant subjected to appropriate functional loading. From 2500 to 4000 με, bone undergoes hypertrophy, leading to an increase in bone density. For loads exceeding 4000 με, the bone experiences fatigue phenomena and multiple microfractures form, whose repair process is not sufficiently rapid. Consequently, new microfractures occur before the previous ones can be fully repaired. Initially, this leads to resorption, and if the stress is excessive, actual fractures can occur.

Progressive loading stimulates bone remodelling at the bone-implant interface, resulting in an increase in the density of lamellar bone and its load-bearing capacity. The principle of Wolff's law highlights the desirability and necessity of progressive loading to protect the new perimplant bone.

CHAPTER 2
FROM THE CONCEPT OF OSSEOINTEGRATION TO MODERN IMPLANTOLOGY

In the last fifty years, implantology has evolved from an experimental treatment to a routine and highly predictable technique for addressing cases of partial and total edentulism (Buser 2017, Patel 2023).

Modern implant therapy offers significant functional and biological advantages compared to conventional fixed or removable prosthetics. It eliminates the need to prepare healthy teeth, leading to greater patient comfort.

Furthermore, it provides excellent long-term results with success and survival rates exceeding 95%, as documented by numerous studies in the literature (Buser 2012, Degidi 2012, Fischer 2012, Gotfredsen 2012, Garcia-Sanches 2023).

2.A Origin of the concept of osseointegration and its initial application (from 1965 to 1985)

Professor Per-Ingvar Brånemark of the University of Gothenburg (Sweden) is widely regarded as the pioneer of modern implantology. He conducted the first preclinical and clinical studies in the 1960s and in 1985, he introduced the concept of osseointegration, which remains widely accepted to this day (Branemark 1969, Branemark 1977) (fig. 12).

Figure 12 Implant inserted in dog bone after 32 weeks from insertion and 16 weeks from loading. (Branemark 1969)

The Branemark group included highly esteemed members such as Albrektsson, Adell, Lekholm, and Jemt. In the late 1960s, the second pioneer, Professor Schroeder of the University of Bern (Switzerland), along with his group, the International Team for Implantology, began to investigate the tissue integration of implants made from various materials. He was the first to histologically document the direct contact between bone and titanium implants (Schroeder 1976). Several years later, he reported on the behavior of soft tissues around titanium implants.

Both Branemark and Schroeder led research teams that conducted significant preclinical and clinical studies during those years, laying the foundation for modern implant therapy. Initially, the Branemark team and the Schroeder team were not aware of each other's work and were operating independently, publishing the results of their initial studies in local journals.

Until the mid-1980s, several fundamental surgical concepts were established to achieve predictable osseointegration (Albrektsson 1981, Schroeder 1981):

- Use of a minimally traumatic surgical technique for implant site preparation to avoid overheating of the bone.
- Implant insertion with sufficient primary stability.
- A healing period of 3-6 months without functional loading.

These concepts laid the groundwork for successful implant integration and guided the early stages of implant dentistry, contributing to its development as a reliable and effective treatment option.

The Branemark team used screw-type titanium implants with a machined smooth surface, while the Schroeder team utilized titanium implants of various shapes with a plasma-sprayed surface, which was relatively rough and microporous.

Additionally, the Branemark protocol involved submerged healing of the implant, whereas the Schroeder-led International Team for Implantology preferred non-submerged transmucosal healing. This choice was influenced by the fact that the prototypes they tested were all designed as one-piece implants, with the abutment being an integral part of the implant itself.

In the initial phase of clinical testing, Branemark primarily used titanium implants in completely edentulous jaws to support fixed prostheses, aiming to improve masticatory comfort and patients' quality of life. The clinical results up to 15 years of follow-up were very promising, particularly in the mandible, where the 15-year survival rate reached 99% (Adell 1981, Branemark 1977).

The Schroeder team employed plasma-sprayed titanium implants not only in completely edentulous mandibles but also in patients with partial edentulism (Schroeder 1984).

During this developmental phase of implantology in the 1970s and 1980s, various materials and designs for implants were tested. Different types of implants were introduced, including aluminum oxide implants, titanium-aluminum-vanadium implants, and non-threaded titanium IMZ implants with plasma-sprayed surfaces (Schulte 1978, Babbush 1987, Niznick 1982).

Furthermore, the one-piece implants initially introduced by Schroeder's International Team for Implantology in the 1970s were further developed into two-piece implants. These two-piece implants offered greater prosthetic flexibility and allowed for the concept of non-submerged healing (Buser 1988).

By the late 1980s, the main implant systems primarily offered commercially pure titanium screw-type implants (Steinemann 1998), which were two-piece designs with either machined surfaces (Branemark) or plasma-sprayed titanium surfaces (Schroeder).

2.B The years of significant progress (from 1985 to 2000)

Starting from the second half of the 1980s, implantology became increasingly demanded by patients and began to find real application even in cases of partially edentulous patients who needed restorations of single teeth or groups of teeth. During this period, the concept of implant rehabilitation evolved to encompass not only function but also aesthetics. As a result, implant manufacturers started introducing a wide variety of prosthetic components onto the market, including angled abutments and aesthetic abutments.

In this phase of implantology, a preference emerged for cement-retained prostheses (Buser 2017, Sarafidou 2023), reflecting a shift towards considering both functional and aesthetic aspects of implant rehabilitation.

Furthermore, in order to rehabilitate patients with insufficient bone conditions, the concept of bone regeneration was introduced in the field of dentistry. The most documented techniques during this phase included guided bone regeneration (GBR) with barrier membranes and maxillary sinus lift procedures. The GBR technique had the potential for application in various sites within the maxilla, while the sinus lift procedure, due to anatomical constraints, was limited to the lateral-posterior areas of the upper jaw (Becker 1990, Dahlin 1991).

Throughout the 1990s, efforts were made to enhance the predictability of regenerative techniques and reduce the risk of complications. This was achieved through the refinement of surgical techniques, such as improved incision methods, the use of membrane fixation devices, and the application of bone grafts (Buser 1993). These advancements aimed to optimize the outcomes of bone regeneration procedures.

Initially, guided bone regeneration (GBR) was performed using non-resorbable membranes that required a second procedure for their removal at the end of the healing process.

Furthermore, exposure of these membranes could compromise the regeneration outcome. Subsequently, resorbable collagen membranes gained widespread use. These membranes did not require a second intervention for removal and could still be managed without compromising the regeneration outcome in case of exposure (Hämmerle 1998, Hockers 1999, Hürzeler 1998).

The maxillary sinus lift technique was introduced in the early 1980s using a lateral approach. This approach involved creating an antrostomy in the anterolateral bony wall of the maxillary sinus through an oral access (Boyne 1980, Tatum 1986). In the 1990s, a transcrestal approach was introduced as a less invasive technique, allowing access to the maxillary sinus through a transalveolar method (Summers 1994).

Both techniques, the lateral and transcrestal approaches, are still in use today. The former is also referred to as a major sinus lift, while the latter is called a minor sinus lift. These terms indicate the extent of bone regeneration achievable with each technique, helping guide the choice of approach based on the desired outcome.

In the 1990s, there was also a change in implant surface characteristics; as previously described, up to that point, the most commonly used surfaces were machined (smooth) or plasma-sprayed (rough) titanium surfaces. However, in 1991, the research group led by Professor Buser at the University of Bern initiated a preclinical study to examine the effect of different implant surfaces on bone apposition (Buser 1991).

Among the examined titanium surfaces, the one that was sandblasted with coarse particles and subsequently acid-etched proved to be the most effective in promoting bone apposition. This roughened surface provides a larger area for the adherence of bone cells and surrounding tissues, facilitating the osseointegration of the implant.

Furthermore, a surface coated with hydroxyapatite, a component similar to natural bone, was also studied. While this surface exhibited higher bone-implant contact values, it also led to significant bone resorption around the implant. Consequently, this surface has not been widely adopted in clinical practice.

Similar results have also been found in other studies that analyzed the behavior of microrough titanium surfaces achieved through sandblasting or double acid-etching treatments (Wennerberg 1995, Klokkevold 1997, Klokkevold 2001).

At this point, even the implants introduced by Branemark began to be manufactured with microrough surfaces, specifically produced through anodization, known as the TiUnite surface (Larsson 1994).

Today, moderately rough and microrough surfaces from various brands are accepted as the preferred surface choices (Wennerberg 2010). These surfaces promote enhanced bone cell attachment and osseointegration, contributing to the long-term success of dental implants.

In the same decade, the immediate loading protocol became well-documented, especially for fully edentulous patients. The protocol was initially tested for overdentures on mandibular implants (Babbush 1986) and was later introduced for fixed prostheses on implants (Schnitman 1997). The reduction in healing time was a significant development to enhance the attractiveness of implant therapy and was facilitated by the presence of the new and improved microrough implant surfaces, which allowed for faster osseointegration.

Currently, the clinical outcome for immediate loading in fully edentulous mandibles and maxillae is comparable to that of conventional delayed loading (De Bruyn 2014). Authors have reported failure rates ranging from 0% to 3.3% for edentulous mandibles and up to 7.2% for the upper maxilla. The success of immediate loading is a testament to the advancements in implant surface technology and the refinement of surgical protocols over the years.

In the early 1990s, a debate also emerged regarding submerged or transmucosal healing of implants to achieve highly predictable osseointegration. There is now consensus that both healing modalities can be applied in everyday practice based on the clinical situation (Buser 1997).

- When possible, a non-submerged healing modality is used, which benefits the patient by eliminating the need for a surgical procedure and reducing costs and morbidity.
- On the other hand, in cases involving bone or soft tissue regeneration procedures and in high-risk patients, there may be a benefit to a submerged healing period without functional loading.

Another theme addressed during this period was the possibility of immediate implant placement after tooth extraction, thereby reducing the time between extraction and implant placement to zero. The concept of immediate implant placement was first used in Germany and was subsequently adopted around 1990 (Lazzara 1989). This approach has enabled a more streamlined treatment process, minimizing the time gap between tooth extraction and implant placement.

2.C The years of refinement (from 2000 to present)

After the 15-year period of significant surgical technique development, a new phase began with the goal of refinement and achieving:

- Stable aesthetics and function over time;
- Reduction in complications during healing and follow-up;
- Decrease in the number of interventions and treatment times.

Numerous improvements have been introduced in implant and prosthetic components, as well as in surgical and prosthetic protocols. This includes a better understanding of the correct three-dimensional implant placement in relation to aesthetic outcomes (Buser 2004, Grunder 2005).

To reduce marginal bone loss, the concept of platform switching was introduced for implant design (Lazzara 2006). This approach shifts the microgap between the implant and abutment to a horizontally safe distance from the crestal bone (fig 13).

Figure 13 Non platform switching connection vs platform switching connection (Lazzara 2006)

Treatment protocols have also been enhanced in the realm of post-extractive implant placement. A classification of treatment options has been established, risk factors for mucosal recessions in immediate implants have been identified, and selection criteria for potential treatment options have been defined (Morton 2014, Toti 2017).

In the realm of bone regeneration techniques, in addition to the transition to resorbable collagen membranes, preclinical research began to focus on bone substitutes for GBR procedures. These bone fillers not only provide mechanical support to barrier membranes, reducing the risk of collapse during the healing process, but also possess biological properties

such as osteogenic potential (to activate new bone formation) and a replacement rate that influences the long-term stability of the bone (Jensen 1996, Jensen 2006).

Bovine-derived bone substitute has demonstrated a low replacement rate and is widely used both in GBR, often combined with autogenous bone, and as a socket filler in post-extractive sites (Buser, 2008, Chen 2007).

Regarding maxillary sinus lift procedures, successful use of solely heterologous (non-autogenous) material has been reported (Maiorana 2005).

Another significant improvement has been achieved with the introduction of cone-beam computed tomography (CBCT) as a preoperative examination (fig. 3). First described in the late 1990s (Mozzo 1998), exposing the patient to a considerably reduced dose of radiation compared to conventional tomography, it has enabled its application in routine clinical practice.

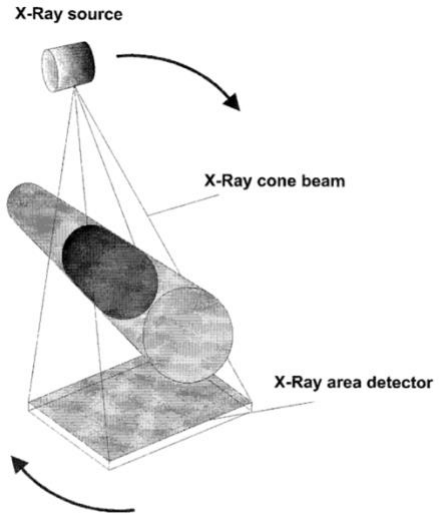

Figure 14 Representation of cone-beam technique (Mozzo 1998)

The advent of CBCT has also been a significant foundation for the advancement of digital implantology. In the surgical field, increasingly sophisticated surgical guides have been developed for computer-guided implant surgery, often associated with flapless techniques, which means without the need to open a flap of tissue (Brodala 2009). In the prosthetic field, initial steps have been taken towards digital design and manufacturing of prosthetic components.

2.D New trends in implantology

The impressive digital progress has simplified and improved the surgical-prosthetic workflow and is finding increasing adoption in everyday dental practice. Digital impressions taken with an intraoral scanner, besides being more comfortable for the patient, can help overcome errors that occur during conventional impression-taking and casting of plaster models (Gaikwad 2022, Albanchez-González 2022).

Furthermore, the fabrication of prosthetic components through computer-guided milling completes the digital workflow, also bringing about economic advantages (Papaspyridakos 2022). In recent years, milling machines have gained popularity in dental clinics, enabling the dentist to directly produce prosthetic components (such as inlays, crowns, bridges), with the possibility of cementing the restoration during the same appointment in which the digital impression is taken (fig. 15) (Kongkiatkamon S 2022).

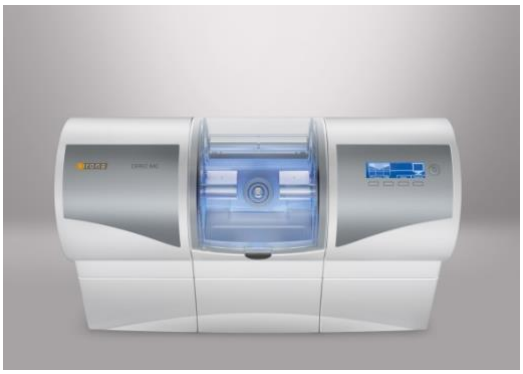

Figure 15 Dental milling machine (da www.dentsplysirona.com)

Another new trend in dentistry is the use of ceramic implants, based on implants made from zirconium dioxide or zirconia, and backed by successful preclinical tests (Gahlert 2007, Saulacic 2014). Current preclinical and clinical documentation of zirconia implants appears to be comparable to that of commercially pure titanium implants with modern microroughened surfaces. Zirconia implants may be the procedure of choice, particularly in the aesthetic zone, since they show a similar survival and success rate as titanium implants on a short-term follow-up (Padhye 2023). However, it's still unclear whether zirconia implants can become a valid alternative to commercially pure titanium, as this would require long-term study data that are not yet available (Cionca 2017).

Furthermore, zirconia implants are currently produced with a limited range of prosthetic components, often as one-piece fixture-abutment units. For widespread clinical application, manufacturing companies would need to develop various designs and components to accommodate diverse needs.

CHAPTER 3
CRESTAL BONE LOSS

Marginal bone loss is a parameter used to assess the variation in the bone level around dental implant. MBL is an important indicator of the health of implants and it is measured using dental x-ray. It is a multifactorial event happening around the cervical area of dental implants and can be considerate a key factor in the development of peri-implant diseases.

3.A Early crestal bone loss

The stability of the crestal bone around implants is crucial for the success and longevity of the treatment, and therefore cannot be underestimated (Linkevicius 2019). The only reliable means for assessing marginal bone stability over time is radiography (fig. 16) (Garcià-Garcià, 2016).

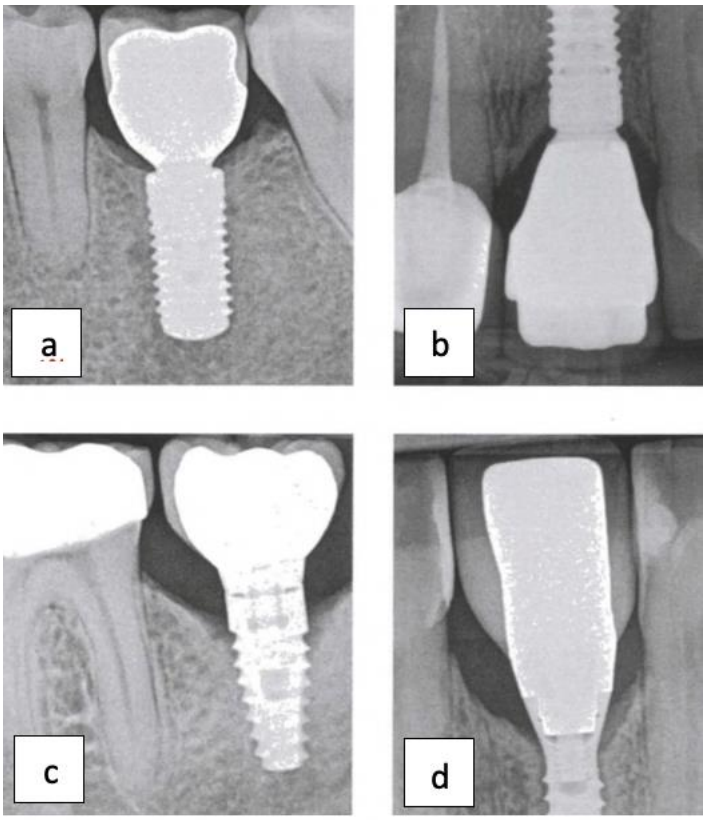

Figure 16 ***a, b*** *examples of bone stability;* ***c, d*** *examples of bone resurption (Linkevicius 2019)*

The scientific community has long agreed that bone remodeling around implants of no more than 0.2 mm per year is an indicator of the long-term success of implant treatment. However, this data must be accompanied by the presence of a physiological probing depth (not

exceeding 5-7 mm for implants) and the absence of bleeding on probing, which would indicate an active peri-implant disease (van Steenberghe 1999).

In 2018, Berglund (Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions) states that the diagnosis of peri-implant health can be made if the following criteria are met:

- Absence of clinical signs of inflammation
- Absence of bleeding and/or suppuration upon gentle probing
- No increase in probing depth compared to previous examinations
- Absence of bone loss beyond changes resulting from initial crestal bone remodeling.

If the bone crest is at least 3 millimeters more apical than the most coronal point of the intraosseous portion of the implant, in the absence of previous examinations for comparison, peri-implantitis is present, indicating failure (Berglund 2018).

The lack of crestal bone stability can lead to problems with peri-implant health, thereby making the long-term prognosis of the implant uncertain.

Early crestal bone loss is defined as the bone resorption around the neck of a dental implant from the time of placement to 1 year after loading. This definition is based on the implant success criteria suggested by Albrektsson in 1986, which consider bone loss of up to 1.5 mm within the first year and no more than 0.2 mm per year for all subsequent years as successful outcomes (Albrektsson 1986).

This concept was developed from observations on implants initially proposed by Branemark. However, implants currently used in dentistry have designs and surfaces with characteristics that lead to greater bone stability, hence greater success. Some more recent studies have questioned the accepted success criteria, suggesting that implants might exhibit lower amounts of bone loss after 1 year of function (Norton 1998, Norton 2006).

Indeed, it has been observed that using implants with micro-threading in the neck region and a conical interface between the implant and abutment, under physiological conditions, early bone loss in the first 12 months of loading would range from 0.33 mm to 0.56 mm.

In the literature, the typical radiographic pattern of early bone loss is described as "saucer-shaped," "ditch-like," or "crater-like." Historically, early bone loss has been considered a natural and inevitable outcome of biological remodeling (Schwarz, 2010).

Occlusal trauma has been suggested as a causal factor; however, if occlusal function caused a constant overload in the implant neck area, it wouldn't explain why bone loss stops after a certain period instead of continuing until complete implant failure.

To explain this phenomenon, it has been suggested that bone is less dense and more sensitive to stress at the beginning of prosthetic loading. Therefore, bone resorption occurs during this phase. However, after the first year of loading, the bone matures, becoming denser. As a result, the same occlusal forces that initially led to crestal bone loss are no longer intense enough to cause further bone resorption.

3.B Patterns of marginal bone resorption

In modern implantology, various patterns of peri-implant bone loss over time have been identified, leading to different prognoses and probabilities of success. Bone can exhibit different responses to the presence of the implant:

- *Crestal bone stability* (or zero bone loss, as introduced by Linkevicius).

  This refers to the ideal clinical condition in which marginal bone undergoes no form of resorption at any stage. Linkevicius introduced this term as a challenge for clinicians to aim for achieving no bone loss.

- *Stable remodeling*

  This term refers to the presence of initial bone loss that comes to a halt and does not progress over time. It can be caused by biological and/or mechanical factors. These implants are generally stable, and bone loss does not threaten the functionality of the implant. However, it would still be better to avoid initial bone loss since the bone around implants with stable remodeling, compared to bone with zero bone loss, is more prone to unforeseen future resorption due to factors like periodontal infection or decreased oral hygiene.

- *Progressive bone loss*

  After the initial remodeling, bone loss continues. This is a concerning condition for the success of the implant and affects the functional and aesthetic outcomes of the treatment. It's impossible to predict whether the remodeling will stop or continue, and if the bone loss isn't halted, it can lead to extensive issues, including peri-implantitis and implant failure.

- *Corticalization*

Corticalization is a process that occurs when the cortical plate of alveolar bone becomes denser and more mineralized over time. Radiographically, the cortical portion becomes more intensely white and increases in thickness over time after loading. One proposed explanation is Frost's law, which suggests that mild bone overload results in an increase in its mass (fig. 2).

- *Demineralization and Remineralization.*

  Crestal bone can behave differently at various stages of healing and development, and in some situations, bone remineralization or demineralization can occur based on increases or decreases in the mineralized component of the matrix. The exact reason for this phenomenon is not well understood, but it demonstrates that crestal bone loss is not always a true resorption of bone tissue; in fact, demineralized bone appears as an area of resorption on radiographs. This situation can be likened to the demineralization of bone around teeth with occlusal trauma. Generally, in dental contexts, when trauma, infection, or irritating substances are removed, the organic bone matrix undergoes remineralization (Rosling 1976). The same could apply around implants: clinical observations suggest that at the end of the prosthetic phase, the tissues are no longer disturbed, creating a favorable environment for bone remineralization (Qian 2012).

- *Bone Growth.*

  Currently, there are no clinical studies demonstrating a predictable process for achieving bone growth after implant placement and the completion of the prosthetic phase. However, it has been hypothesized that implant loading stimulates bone growth, as forces are transmitted from the implant to the bone. Vertical growth could also be explained by the ossification of the periosteum or connective tissue, which lies directly on the bone surface. The processes of bone remineralization and bone growth, not yet fully understood, are encouraging as they indicate that improvements can occur over time.

3.C The importance of bone stability

The stability of the crestal bone is primarily important because it ensures the implant's function; therefore, the goal should always be the prevention of bone loss. The literature shows that early crestal bone loss usually doesn't jeopardize implant osseointegration;

however, in specific cases, such as those with thin peri-implant cortical bone, short implants, or high aesthetic value, the presence or absence of crestal bone could significantly influence the survival and success of the implant (Aparna 2012).

Crestal bone plays an important role in both short-term and long-term implant stability. Primary stability, which refers to the mechanical stability present at the time of implant placement, is crucial for achieving osseointegration. Without primary stability, bone tissue formation adjacent to the implant surface cannot occur, and sufficient secondary stability, characterized by the biological integration between bone and implant surface, cannot be achieved (Fanuscu 2004).

While clinicians should aim for bone stability in all cases, there are two main situations that require greater attention:

- *Implants in the Aesthetic Zone.* In the aesthetic zone, the stability of the perimplant mucosal level is crucial (Lazzari, 2022). Following marginal bone loss, the soft tissue level also changes, significantly impacting the aesthetic outcome of the restoration. Peri-implant mucosal recession, which may follow crestal bone loss, results in the exposure of the crown margin, soft tissue recession, and loss of papilla (Lai 2008). When there is vertical crestal bone resorption, bone loss follows a circular pattern around the implant. If the bone is thick, a crater forms around the implant; if the bone is thin, the outer walls are also lost. Crestal bone loss can affect the position of the mesial and distal papillae and the level of soft tissues, all components of the pink esthetic score (fig. 17), an objective method for evaluating the aesthetic outcome of the treatment. If this score is low, as can be expected in cases of bone loss, the restorations cannot be considered aesthetic, and patient satisfaction will be lower (Belser 2004).

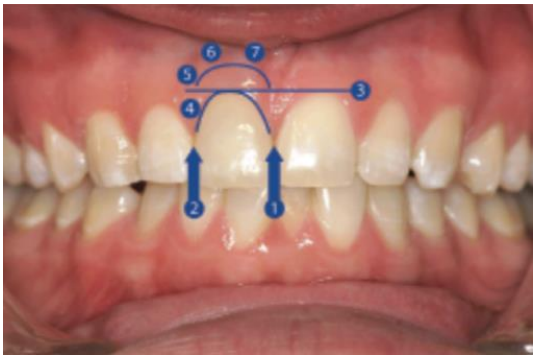

Figure 17 The PES score is based on seven variables: mesial papilla, distal papilla, soft tissue level, soft tissue contour, alveolar process deficiency, color, and soft tissue texture. Each variable was assessed with a score of 2-1-0, where 2 is the highest score, and 0 is the lowest score. (Fürhauser 2005)

It is important to emphasize that the correct three-dimensional (3D) positioning of the implant is as crucial as the stability of the crestal bone to achieve excellent aesthetic outcomes (Lai 2013, Stefanini 2023).

- *Use of Short Implants.* Short implants (meaning implants with a length ranging from 4.0 to 7.5 mm) provide survival rates of 98.3% after 5-10 years and can be reliably employed to simplify implant therapy in situations with reduced alveolar height (Srinivasan 2012, Vargas-Moreno 2023). These implants are designed with a wider diameter to compensate for the reduced implant surface area due to their shorter length. For this reason, while they do not tend to experience more vertical bone loss compared to standard-length implants, they tend to lose a higher percentage of bone-to-implant contact (BIC), which can influence long-term outcomes (Linkevicus 2015). For example, if a 4 mm implant lost 1.5 mm of bone, even if it meets the previously defined criteria of success, the implant would have lost almost 50% of the surface that should be in contact with the bone and might likely be considered a failure (fig. 18). Therefore, despite short implants being less susceptible to crestal bone loss, bone loss seems to be more critical for short implants because the bone resorption would result in a greater loss of BIC. Exactly, in a short implant, crestal bone loss can significantly alter the crown-to-implant ratio, leading to a higher risk of mechanical and biological complications compared to a longer implant. In a longer implant, the same amount of bone loss might not have as drastic an impact on the overall situation. The potential consequences of crestal bone loss are more pronounced in short implants due to the proportionally larger effect on the bone-implant interface, which underscores the importance of maintaining stability and bone support around short implants for successful outcomes.

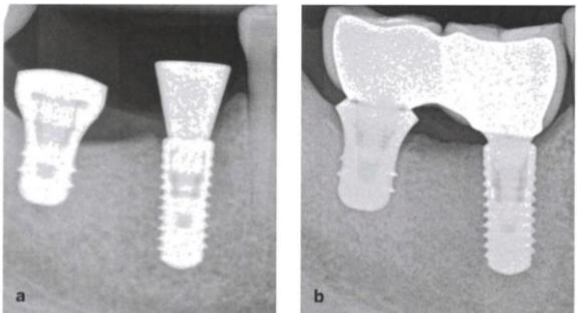

Figure 18 Example on how marginal bone loss id more dangerous for shorter implant. (Linkevicius 2019)

3.D Factors influencing bone loss

Understanding the underlying mechanisms of crestal bone loss is crucial. Several possible explanations for this phenomenon have been proposed, including overload, microgap presence, and polished implant collar (Qian 2012, Srinivasan 2012, Linkevicus 2015). The issue remains controversial, but it is certain that marginal bone loss is a multifactorial condition, not solely attributed to a single predominant factor.

All factors can be categorized as follows:

- Operator-dependent factors;
- Misdiagnosis factors;
- Patient-related factors;
- Implant design factors;
- Soft tissue-related factors;
- Infectious factors.

Operator factors or skills are crucial because if clinicians fail to perform procedures correctly (e.g., poor implant placement, surgical trauma, implant exposure, inadequate interimplant distance), it can lead to bone loss. Thus, various factors, including those related to the operator's abilities, play a significant role in preventing crestal bone loss (Romanos 2019).

Even in an ideal clinical situation, inadequate pre-surgical planning and poor surgical execution can lead to unfavorable outcomes. For individual surgeons, the operator-dependent component of bone loss typically decreases over time as their experience level increases.

During implant placement, especially in dense bone (type 1), substantial bone loss can occur due to heat generation. This type of bone loss should be distinguished from other forms of resorption since it occurs prior to the connection of the secondary healing component, and is therefore not related to loading.

For instance, if an implant is placed with excessive torque and high heat generation, resulting in bone compression, bone resorption can occur after implant placement, even if the implant is covered by soft tissues and not exposed.

The following table summarizes operator-related factors that can influence bone loss (Table 3).

Table 3 Operator-dependent factors

Operator-dependent factors	
Improper implant angulation	Erroneous loading protocol
Thin bone	Excessive torque
Surgical trauma (Excessive bone overheating)	Overloading
Reduced implant-to-implant or tooth-to-implant distance	Inadequate milling protocol
Infettive suture	Buccal position of the implant

Another group of factors influencing crestal bone stability are related to *misdiagnosis*. If patients have certain conditions that haven't been resolved or addressed, the end result will be bone resorption around the implants. The skills of the clinician can be excellent, but unresolved patient conditions will still lead to poor outcomes (Jemt 2017).

This group of factors includes the absence of periodontal health in the patient, insufficient bone thickness, and lack of supracrestal soft tissues. Active periodontal disease is an absolute contraindication for implant placement and must be resolved before initiating any implant therapy. If implants are placed in a patient with untreated periodontitis, there will be early and/or delayed non-physiological crestal bone loss due to infection (Dreyer 2018).

A third group of factors consists of *patient-related factors*: compromised patients with various genetic defects, bruxism, smoking, or very fragile bone are prone to greater marginal bone loss (Albrektsson 2000).

Factors related to implant design include the type of implant-abutment connection and the presence/absence of a polished implant neck. The microgap between the fixture and prosthetic components, if located at the bone level, is a factor predisposing to marginal bone loss because it provides space for bacterial proliferation and allows for micro-movements of

the abutment within the implant. The conical geometry of the connection (fig. 19) provides stability to the implant-abutment junction, but this stability alone does not guarantee the absence of bone loss (Sasada 2017).

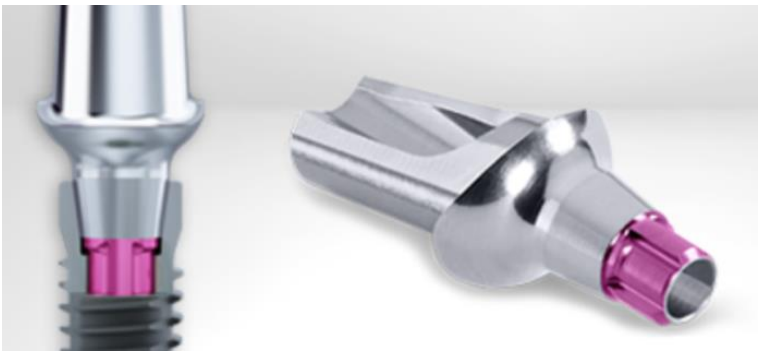

Figure 19 Conical connection implant-abutment
(da www.camlog.com/en/implant-systems/conelog/connection/)

Platform switching results in less marginal bone loss because it allows for shifting the implant-abutment connection inward, in a horizontal direction. Additionally, the characteristics of the implant neck surface must be taken into account; if it is polished, it will not osseointegrate and may cause bone loss if positioned below the bone level (Zukauskas, 2021).

Based on these considerations:

- Implants without platform switching should be positioned slightly supra-crestally to maintain the microgap, thus keeping bacteria away from the bone. In this position, even micromovements between the implant and abutment are not harmful, as there is a vertical safety distance from the bone tissue (fig. 20).
- Implants with platform switching, on the other hand, can be positioned at the bone level and even below it, because the connection with the abutment occurs at a certain horizontal distance from the bone.
- Implants must be positioned in a way that the polished implant neck is completely outside the bone.

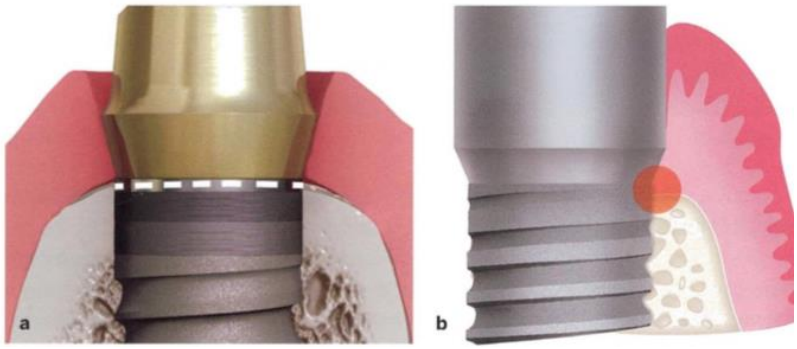

Figure 20 The incorrect positioning of an implant without platform switching. The microgap is in direct contact with the bone, which means bacteria and micro-movements will create inflammation that promotes bone loss (Linkevicius 2019)

Factors related to soft tissues include the thickness of soft tissues and the presence of attached gingiva. The vertical (crestal) thickness of soft tissue is a recently recognized biological factor that influences the stability of crestal bone and should be measured before implant placement. Current knowledge shows that at least 3 mm of vertical soft tissue thickness must be present to prevent any loss of crestal bone during the formation of the attachment apparatus around implants. Regarding attached gingiva, in implant sites, there should be at least 2 mm of attached gingiva vestibularly and lingually. Platform switching and a conical connection do not prevent crestal bone loss if implants are placed in thin vertical soft tissues (Schwarz, 2022).

A final group of factors that can cause not only short-term but also long-term bone loss are infectious factors, responsible for peri-implant disease, which will not be covered in this discussion.

3.E Bone overheating and its correlation with marginal bone loss

The use of drilling procedures for implant site preparation is associated with an increase in temperature at the osteotomy site (Eriksson 1984 Dec, Cordioli 1997, Abouzgia 1997). The elevated temperature during drilling can potentially harm hard tissues, causing irreversible damage to the bone and compromising new bone formation, thus affecting implant osseointegration. Specifically, excessive overheating can lead to necrosis of bone cells and protein degeneration (Albrektsson 1981).

Several studies have reported different values for the temperatures generated during osteotomy and the temperatures that would cause irreversible damage to bone tissue. According to various authors, temperatures ranging between 47°C and 56°C have been deemed responsible for irreversible bone injuries (Rouiller 1953, Green 1981, Matthews 1984,

Lundskog 1972, Eriksson 1982). Rouiller and Majno in 1953 demonstrated tissue damage at a temperature of 55°C for 3 minutes. In another study, Green and Matthews established the critical temperature level at 56°C, which corresponds to the denaturation point of alkaline phosphatase (Green 1981). Eriksson in 1982 showed that a bone temperature of 53°C for 1 minute led to changes in blood flow, resorption of adipose cells, and irreversible bone damage (Eriksson 1982).

Eriksson and Albrektsson subsequently demonstrated in vivo that heating bone up to 47°C/50°C for 1 minute would be sufficient to prevent bone growth; they considered this temperature as the threshold for bone damage (Eriksson 1984 Nov). However, their study did not clarify the effect of bone overheating on the osseointegration processes around dental implants, as it was conducted using growth chambers (titanium structure with a 1 mm wide transverse channel intended for bone tissue growth).

Yoshida et al. heated rat cranial bone to 48°C for 15 minutes and observed that this thermal treatment did not hinder bone formation after a healing period of 5 weeks (Yoshida 2009). The authors concluded that heating bone tissue caused a delay in the formation of hard tissue depending on the temperature, but new bone formation was not inhibited in any case. Trisi in 2014 demonstrated that implants placed in bone sites heated up to 50°C for 1 minute did not show any signs of bone resorption, indicating that this temperature cannot be considered a threshold level for heat-induced bone damage. Even heating up to 60°C for 1 minute does not significantly compromise the osseointegration of titanium implants; it only creates small infraosseous defects around the implants (Trisi 2014). In clinical practice, friction during osteotomy could lead to a much higher increase in bone temperature than what was tested in the studies mentioned. Elevated bone temperatures (above 100°C) during cortical bone drilling procedures have been reported in various in vitro studies; however, it has been observed that temperatures measured in vitro are not comparable to the clinical situation where much higher temperatures could develop, even when using sterile physiological solution for cooling.

Furthermore, the same drill with the same irrigation method causes a greater temperature increase after multiple uses: Chacon et al. demonstrated that the temperature generated during implant site preparation procedures increases after repeated drilling and sterilization cycles (Chacon 2006).

In conclusion, the heat generated due to friction during careless surgical preparation, without adequate irrigation, could be responsible for early perimplant bone resorption; it's not clear what the critical temperature might be that could compromise the osteointegration process. Certainly, the design of the drills, combined with an efficient cooling system and a proper milling protocol (both in terms of speed and drill sequence), can reduce temperature rise and, consequently, damage to the bone tissue (Strbac 2012).

CHAPTER 4
IMPLANT BUR DESIGN

In the design of implant drills, features should be sought to achieve optimal cutting efficiency while creating a minimal increase in temperature during the bone milling process. In fact, among the main causes of implant osseointegration failure is the increase in bone temperature beyond 47°C during drilling, resulting in irreversible osteonecrosis (Eriksson 1986, Eriksson 1984). Thermal damage in the drilling site inhibits the regenerative response in bone healing, impairing the osteointegration process and leading to a lack of secondary implant stability.

Therefore, the drill design plays a significant role in controlling the heat generated during drilling; a combination of surgical instruments with appropriate properties and an optimal technique for implant site preparation will result in better osseointegration, reducing the implant failure rate.

4.A Drills and bone overheating

Several parameters are considered significant for controlling heat generation during osteotomy, including spindle speed, feed rate, drill sequence, and drilling depth. Understanding the effect of each parameter will enable better control of the generated temperature, thus avoiding osteonecrosis (Lee 2012, Oh 2011).

Lee et al. studied the effect of drilling speed (rpm), feed rate, and drilling depth on temperature distribution during drilling of bovine femoral cortical bone. They found that the maximum temperature increases with higher spindle speed and decreases with higher feed rate. Additionally, it was observed that the highest temperatures were measured in the superficial portion (Lee 2012).

This could be related to the fact that cutting and friction forces are higher during drilling denser bone tissue, leading to greater overheating (Yacker 1996).

Cordioli and Majzoub, in their study on bovine femoral bone, observed that drilling at 1500 rpm with external irrigation resulted in higher temperatures at a depth of 8 mm compared to 4 mm (Cordioli 1997).

Sharawy et al. measured the heat generated at various drilling speeds (1225, 1667, 2500 rpm) and concluded that the average temperature increase decreases with higher drilling speed (Sharawy 2002).

Chacon et al. demonstrated that there is a decrease in the maximum temperature reached as the number of drills in the drilling sequence increases (Chacon 2006). Since a substantial volume of bone is already removed with smaller diameter drills, larger diameter drills remove less bone, leading to less overall overheating. Furthermore, it is recommended to pause the drilling procedure at least every 5 seconds for at least 10 seconds and apply physiological solution to the bone. This significantly reduces the time during which bone temperatures remain elevated.

4.B Bone overheating and cooling systems

The use of a cooling system is the factor that most effectively reduces bone heating during the drilling process (Augustin 2008).

Cooling can be achieved through two systems: internal or external. In an internal cooling system, the coolant passes through an internal channel and exits through the grooves of the drill bit. The coolant also acts as a lubricant, reducing friction during drilling, and provides irrigation, allowing for the removal of debris produced during the drilling process. In an external cooling system, the coolant is directed by a nozzle onto the outer surface of the drill bit and primarily reduces heat on the exposed part of the drill bit and the more superficial bone. When examining the various effects of these two methods, the literature acknowledges that both cooling systems significantly reduce bone temperature during drilling, but external cooling proves to be more effective on the bone surface, while internal cooling becomes more effective as depth increases. Augustin et al. (Augustin 2012) analyzed the performance of internal cooling systems during the drilling of pig femurs and found that this cooling system maintains bone temperature significantly below the threshold of thermal osteonecrosis (47°C).

Sener et al. studied bone overheating in bovine mandibles and observed that a large portion of heat is generated in the superficial area of the cavity being drilled, rather than at depth (Sener 2009). For this reason, they believe that external irrigation is a sufficient cooling system during osteotomy.

Additionally, field experience has shown that the lumen of internal irrigation can become blocked when using internal cooling systems.

Computer-guided surgery, which is gaining increasing popularity in dentistry, involves the use of a surgical guide based on the planned implant position in the 3D scan. The guide facilitates site preparation and potentially implant placement, but it acts as a physical barrier to external cooling. As a result, sterile physiological solution has a more difficult time reaching the site where osteotomy is being performed.

4.C Mechanical characteristics

In the design of a drill bit, numerous parameters must be considered to achieve the following goals:

- Maximum cutting efficiency
- Minimum heat generation

The grooves (Fig. 1) on the surface of the drill bit serve two main functions: creating the cutting edge and allowing the removal of bone chips and debris that form during osteotomy.

In various studies, Bertollo et al. (Bertollo 2008, Bertollo 2010) tested surgical drills with two and three grooves and concluded that the latter showed greater bending rigidity and cutting efficiency. A higher number of grooves could potentially restrict the channels required for the removal of bone chips, leading to a reduction in cutting efficiency and an increase in friction. However, at this point, there has not been a statistically significant difference observed in the maximum temperature generated between the two types of drills.

Further studies are necessary to determine the optimal number of grooves and their effect on stability, cutting efficiency, and heat generation due to friction.

The helix angle refers to the angle formed between the edge of the groove and the line parallel to the central axis of the drill bit (Fig. 21). Depending on the measurement of the helix angle, the drill bit will have a design with a spiral of different width (Natali 1996). Increasing the helix angle reduces cutting efficiency but achieves a higher feed rate of the drill, reducing the time required for drilling. To achieve a good compromise between these two characteristics, the helix angle for dental implant drills should be between 12° and 28° (Narasimha 1987, Saha 1982, Davidson 2000, Wiggins 1976).

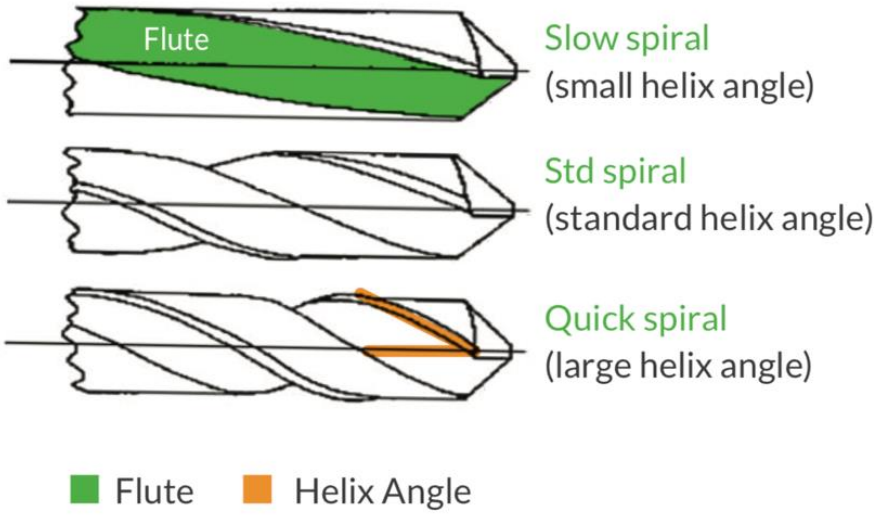

Figure 21 Flute and helix angle
(da https://alphabioendpoint.azureedge.net/media/2503/clinical_book_final.pdf)

The relief angle (Fig. 22) is defined as the surface adjacent to and below the cutting edge when the tool is in a horizontal position. The body clearance (Fig. 22) is defined as the surface that follows behind the cutting edge and through the drill bit's groove.

Both the relief angle and the body clearance reduce bone overheating because they minimize the contact between bone and the drill bit during site preparation (Chacon 2006, Oh 2011).

A larger relief angle generally tends to produce a better finish as a smaller surface of the drill bit's side rubs against the bone (Oberg 2012).

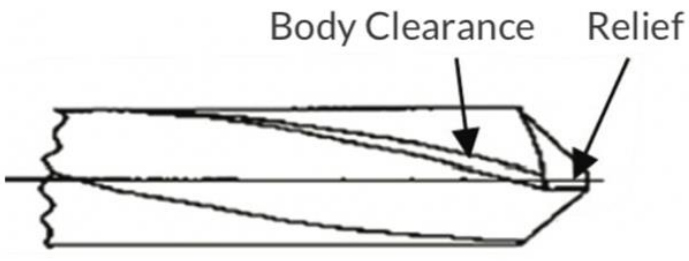

Figure 22 Relief angle e body clearance
(da https://alphabioendpoint.azureedge.net/media/2503/clinical_book_final.pdf)

Most dental drills have a relief angle; however, many of them lack body clearance (Fig. 23).

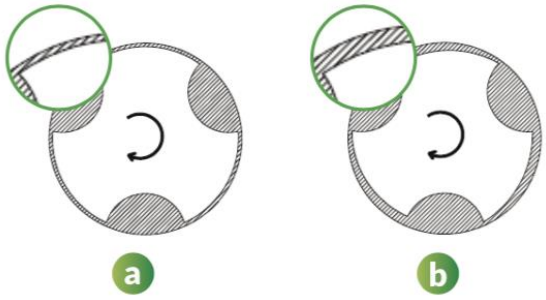

Figure 23 Drill section without body clearance and drill section with body clearance (da https://alphabioendpoint.azureedge.net/media/2503/clinical_book_final.pdf)

The point angle is located at the apex of the drill and is defined as the angle formed at the tip of the drill between the two primary cutting edges (Fig. 24).

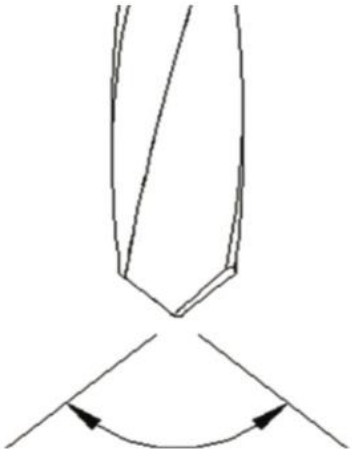

Figure 24 Point angle (da https://alphabioendpoint.azureedge.net/media/2503/clinical_book_final.pdf)

A smaller point angle determines an easier way to center the drill in the material and avoid drill slippage. A lower point angle is associated with longer cutting edges, while a higher point angle is associated with shorter cutting edges. When using a sharper drill with a smaller point angle, higher temperatures develop in the initial moments of drilling because only a reduced percentage of the cutting edge surface is engaged in the cutting action. Conversely, using a more chamfered drill with a larger point angle results in greater contact between the bone and the entire cutting edge surface earlier in the drilling process (Augustin 2012) (Fig. 25).

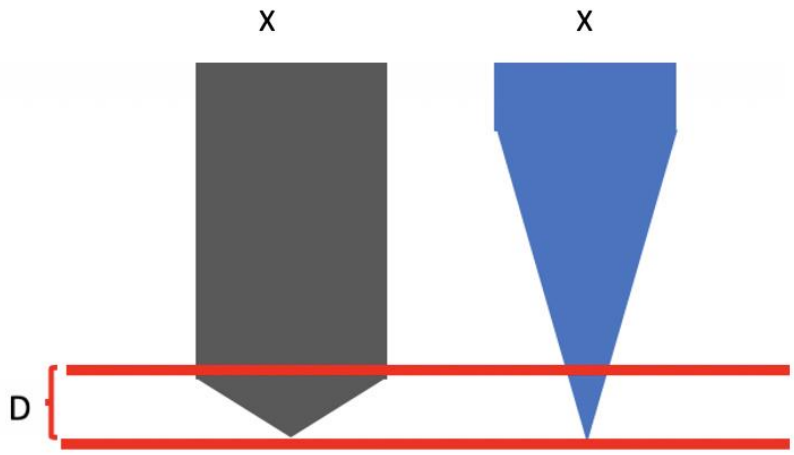

Figure 25 Same diameter (X) and depth of perforation (D) but two different point angle.

Considering the advantages and disadvantages associated with small/large point angles for surgical drills, the literature recommends a point angle of 90° for initial drills, which create the first hole, and angles of 100°-130° for all subsequent diameter drills (Jacobs 1974, Natali 1996, Wiggins 1976, Saha 1982, Karmami 2004).

Another characteristic element of implant drill design is the presence or absence of *steps*, which refers to an apical portion with a smaller diameter (Fig. 26). The presence of steps significantly helps maintain the drilling centered, making it easier for the operator to maintain the same inclination established by the previous drill passage. The presence of the smaller-diameter apical portion guides the drill through the previously drilled hole.

Udiljak et al. observed that drills with steps have an effective design in minimizing temperature increase due to gradual material removal from the drilling site.

Therefore, comparing the heat development between conventional drills and drills with steps, the maximum temperature reached by the bone during drilling is lower when using the drill with steps (Udiljak, 2007).

Figure 26 Example of step drill (step coronal diameter 3.65 mm; step apical diameter 3,2 mm) (from https://alphabioendpoint.azureedge.net/media/2503/clinical_book_final.pdf)

The following table summarizes the characteristics of the optimal drill based on what has been analyzed in the studies present in the literature (Table 4).

Table 4 Optimal drill characteristic

	***Design* suggested**	**Description**
Cooling system	External irrigation	External irrigation is more efficient than internal irrigation on the surface and in the upper portion of the osteotomy. Field experience, on the other hand, shows a blockage in the internal irrigation lumen.
Flute	3 flutes	Three flutes exhibit higher flexural rigidity and generate less heat on the bone due to increased cutting efficiency.
Helix angle	10°-30°	For surgical drills, a helix angle range of 10°-30° is recommended to achieve the best cutting efficiency."
Relief e *body clearance*	Both present	Both the relief angle and the body clearance reduce heat generation due to reduced contact between the bone and the drill bit during osteotomy.
Point angle	90° for the first drill, 100°-130° for the subsequent ones	*Point angle* of 90° for the initial drills. *Point angle range* of 100°-130° for the subsequent diameter drills.
Step drill or straight drill	*Step drill*	A step drill bit features a highly effective design in minimizing temperature rise due to the gradual removal of material from the drilling site. The step drill bit helps maintain the centering of the preparation site, thanks to the step that guides through the site prepared by the previous drill bit.

The following table summarizes the variation of drill properties with changes in helix angle, relief angle, and point angle (Table 5).

Table 5 Changes in drill properties as the helix angle, relief angle and point angle

Angle	If angle increase	If angle decrease
Helix angle	Lower cutting efficiency Higher feed rate	Higher cutting efficiency Lower feed rate
Relief angle	Finer finish	coarser finish
Point angle	Less sharp drill	Sharper drill

CHAPTER 5
STUDY PROTOCOL

5.A Background

Dental implants should be considered a highly predictable long-term and evidence-based treatment option for single, partial, and complete edentulism of the jaws, as indicated by numerous scientific articles (Esposito et al., 2014, Jimbo & Albrektsson, 2015, Moraschini et al., 2015, Messias 2020, Del Fabbro 2022). Moreover, patients demonstrated a high appreciation for implant treatment, having the possibility to overcome aesthetic and functional deficits that follows tooth loss. (Filius et al., 2018, Yao 2018, Oh et al., 2016).

Apart from biological complications that follows the bacterial invasion and persistence at the level of the peri-implant soft and hard tissues (peri-implant mucositis and peri-implantitis) (Lang and Berglundh, 2011; Lindhe and Meyle, 2008), as discussed in Chapter 3, bone resorption after implant placement could follow physiological bone remodeling (Lang & Berglundh, 2011, Lindhe & Meyle, 2008, Albrektsson et al., 1986).

Furthermore, marginal bone resorption may result from an inadequately traumatic implant site preparation technique (Albrektsson et al., 1986, Esposito et al., 1998). In order to reduce trauma to the surrounding bone tissue, mainly due to overheating generated by the use of the drill, the implant site preparation procedure should be carefully chosen and executed (Kerawala et al., 1999, Lundskog, 1972). As discussed in Chapter 4, the design of the drill should be considered an important factor influencing thermal injuries to bone (Kerawala et al., 1999). Moreover, patient-reported outcomes (PROs), defined as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” (Food and Drug Administration [FDA]) might be influenced by the greater traumatic nature (if present) of one of the two treatements.

5.B Aims

The main objective of the present study was to determine whether the application of one implant site preparation protocol (“Step drilling sequence”) could lead to a statistically significant difference in marginal bone resorption as compared to another protocol (“Straight drilling sequence”), at 1-year follow-up (Appendix 1).

The secondary aims of the study were to evaluate if the tested protocol (Step drilling sequence) could modify the clinical and/or patient-centered variables. Specifically, the clinical outcomes had been investigated as a possible change in peri-implant probing depth (PD), bleeding index (BI), and plaque index (PI) over time; the patient-centered outcomes have been assessed as pain perception, limitation in daily activity, taste alteration and taste sensation for seven days after the surgical procedure. Resonance Frequency Analysis (RFA) was taken as an optional variable.

5.C Authorization

The research protocol was approved by the Ethical Committee of the Università degli Studi di Milano, Milan, Italy. All patients were informed about the study protocol and signed an informed consent form before enrolment.

5.D Study duration

Enrolment phase: 12 months

Treatment phase: 36 months

Total duration: 48 months

5.E Study design

This was a multicentric, non-randomized, comparative prospective clinical study.

5.F Selection criteria

Inclusion criteria:

1. Men and women over the age of 18 years who need implantation of 1-4 implants;
2. Patients who were able to understand the requirements of the study and were willing and able to comply with its instructions and schedules;
3. Patients who had provided written informed consent to participate in the study prior to any study procedure;
4. Patients in general good health in the opinion of the principal investigator as determined by medical history and oral examination.

Exclusion criteria:

1. Immediate loaded implants;

2. Cases involving immediate implant placement after extraction;
3. Treatment with anticoagulant drugs (INR above 2);
4. Treatment with intravenous bisphosphonates;
5. Treatment with anticonvulsants drugs;
6. Untreated Periodontal disease and inability of the patient to maintain reasonable oral hygiene according to study requirements;
7. Patients with history of alcohol, narcotics or drug abuse;
8. Patients under steroid therapy;
9. Patients receiving radiotherapy, chemotherapy or any other immunosuppressive treatment or who have been administered radiotherapy in the last 5 years;
10. Patients through at any time received radiotherapy to the head and neck region will be excluded anyway;
11. Metabolic bone disorders and/or bone augmentation; (XII) Uncontrolled bleeding disorders such as: hemophilia, thrombocytopenia, granulocytopenia;
12. Degenerative diseases;
13. Osteoradionecrosis;
14. Renal failure;
15. Organ transplant recipients;
16. HIV positive;
17. Malignant diseases;
18. Diseases that compromise the immune system;
19. Unbalanced diabetes mellitus. (HbA1c above 7.2);
20. Psychotic diseases;
21. Hypersensitivity to one of the components of the implant in general and titanium in particular;
22. Women who are pregnant or lactating at the time of recruitment and of surgery;
23. Lack of patient cooperation;
24. Uncontrolled endocrine diseases;
25. Any systemic condition that is unbalanced and therefore precludes surgical procedures;
26. Parafunctional habits- e.g Severe to moderate Bruxism;
27. Temporomandibular joint disease;

28. Various pathologies of the oral mucosa for example: Benign mucous pemphigoid, desquamative ginigivitis, erosive lichen planus, malignancy of oral cavity, bolus erosive diseases of the oral mucosa;
29. Flapless procedures;
30. *Bone density 5;*
31. Site where a history of failed implant exists;
32. Heavy Smokers (10 cigarettes and more per day).

5.G Outcomes measures

Primary Outcome

The primary outcome was the difference in marginal bone level (MBL) (Marginal bone resorption=MBR) calculated as the difference between in MBL at 1-year measurements and baseline measurements (at the time of implant placement), made on periapical radiographs taken with individualized holder. MBL was calculated as the distance in mm between implant neck and the bone level. A negative value of MBL represent a resorption. All measurements were made using a software called ImageJ (Rasband, W.S., ImageJ, U.S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997-2016) and taken by two independent examiners that were previously calibrated on five patients not included in the study. The agreement tolerance was posed to be 0,2mm.

Secondary Outcomes

Clinical outcomes

- BI and PI measured as described by Corbella et al. 2011 (Corbella et al, 2011)
- BI:

  0) no bleeding;

  1) bleeding on probing without redness and swelling;

  2) bleeding on probing, redness and swelling;

  3) spontaneous bleeding;
- PI:

  0) no plaque accumulation;

  1) plaque accumulation only detectable using a probe;

2) moderate accumulation of visible plaque/ calculus;

3) high accumulation of visible plaque/calculus.);

- PD measured as the distance between the MM and the most apical extent of the peri-implant pocket, measured using a force of no more than 0.25N;
- Soft Tissue Level: measured as the distance between the MM and the most apical part of the crown;
- RFA if available, measured at the time of implant placement with Osstell™ (Integration Diagnostics Ltd., Goteborgsvagen, Sweden).

The two examiners were previously calibrated examining five patients not included in the study.

Patient-centered outcomes

The following evaluations were made immediately after the intervention and in each of the seven days after the intervention:

- pain perception measured with a 10-mm long VAS scale being 0 equal to no pain;
- limitation in daily activity measured with a 10-mm long VAS scale being 0 equal to no limitation;
- taste alteration measured with a 10-mm long VAS scale being 0 equal to no alteration;
- taste sensation measured with a 10-mm long VAS scale being 0 equal to good taste.

5.H Treatment procedures

All patients were recruited from two different private dental clinics. All surgeries were performed by two oral surgeons (S.C. and S.T.) that had more than 10 years' experience in implant dentistry. The allocation of the treatment was balanced and decided through computer table.

Visit 0

Full-mouth POH manoeuvres (supragingival scaling and polishing) and clinical evaluation. Individual OHI were given. After evaluation of the radiographic images (CT or periapical radiographs) patients were allocated to Group A or to Group B.

Visit 1 (Treatment)

→ Both groups

After local anesthesia with Articaine 4% + epinephrine 1:200.000 or Articaine 4% + epinephrine 1:100.000 a full thickness flap was elevated in the site of implant placement.

→ Group A (fig. 27)

The implant site was prepared following the instructions of the manufacturer (Alpha-Bio Tec, Kiryat Arye, Petach Tikva, Israel) for the so-called Step Drilling Technique (see Appendix 2), using a handpiece at 2000 rpm under abundant irrigation with sterile saline solution.

→ Group B (fig.28)

The implant site was prepared following the instructions of the manufacturer (Alpha-Bio Tec, Kiryat Arye, Petach Tikva, Israel) for the so-called Straight Drilling Technique (see Appendix 2), using a handpiece at 2000 rpm under abundant irrigation with sterile saline solution.

→ Both groups

Both groups were implanted with NEO CS implants. (Alpha-BioTec., Israel).

RFA measurement, if available, were made immediately after implant positioning. Then, the flap was repositioned and sutured. Clinical photos and periapical radiographs were taken as part of the standard routine.

Postoperatively, written instructions and drug prescription were provided to the patients

Visit 2 (7 days after intervention)

The suture has been removed and the questionnaires have been collected. Clinical evaluations have been collected.

Visit 3 (4 months after intervention - Second stage surgery)

Placement of the healing screw.

Visit 4 (Placement of the prosthesis)

All the prosthesis were single crowns, screw-retained crowns made of ceramic / composite.

a)

Periapical radiograph and clinical photo were taken as part of the standard routine.

Visit 5, 6, 7, 8, 9 (Respectively 3 months, 6 months, 12 months, 18 months and 24 months from prosthesis)

Periapical radiographs and clinical photos were taken as part of the standard routine. BI, PI and PD were measured and recorded for each implant. Professional oral hygiene was performed 6, 12, 18, and 24 months after positioning of the prosthesis. (fig. 29; 30).

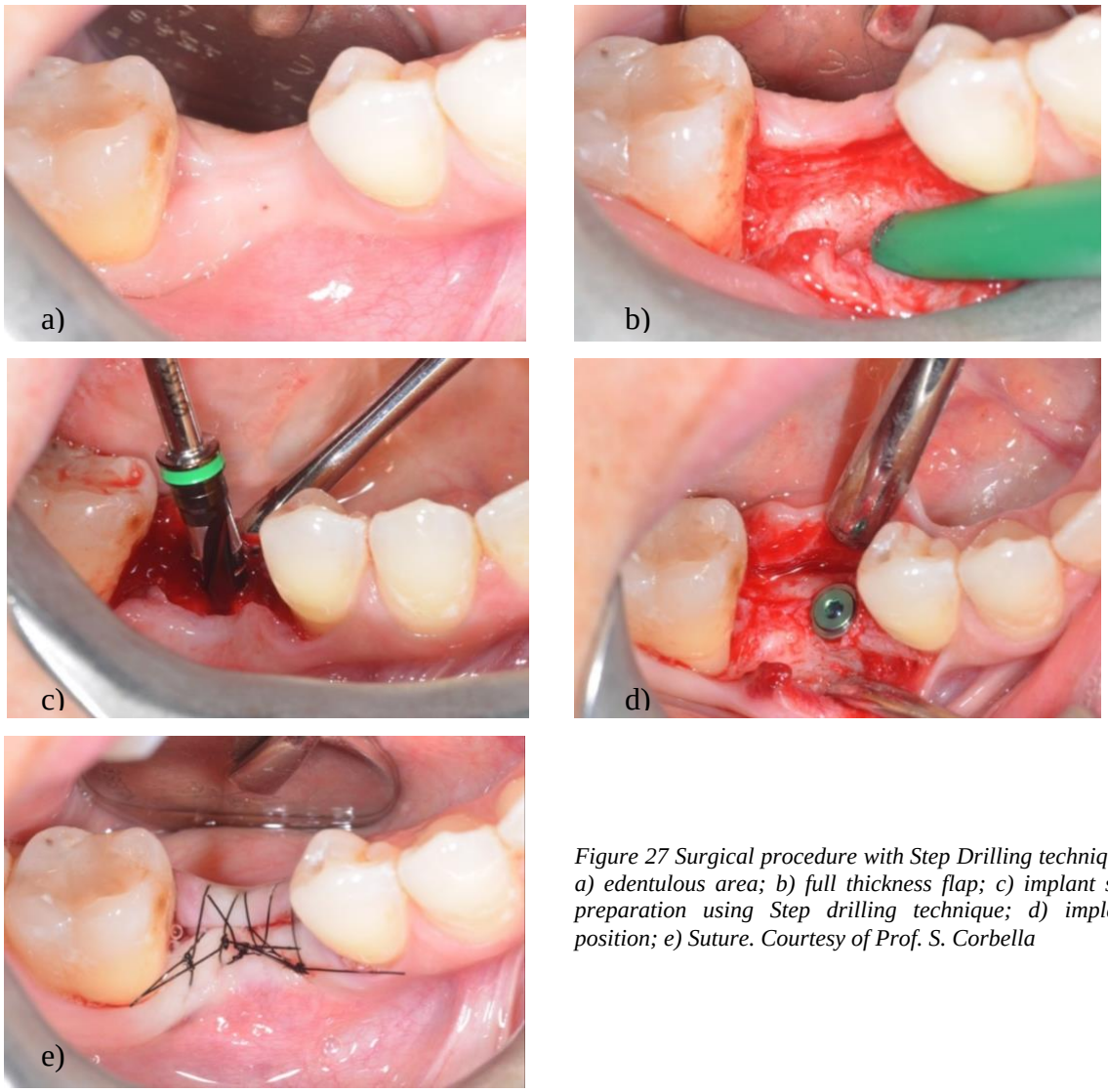

Figure 27 Surgical procedure with Step Drilling technique: a) edentulous area; b) full thickness flap; c) implant site preparation using Step drilling technique; d) implant position; e) Suture. Courtesy of Prof. S. Corbella

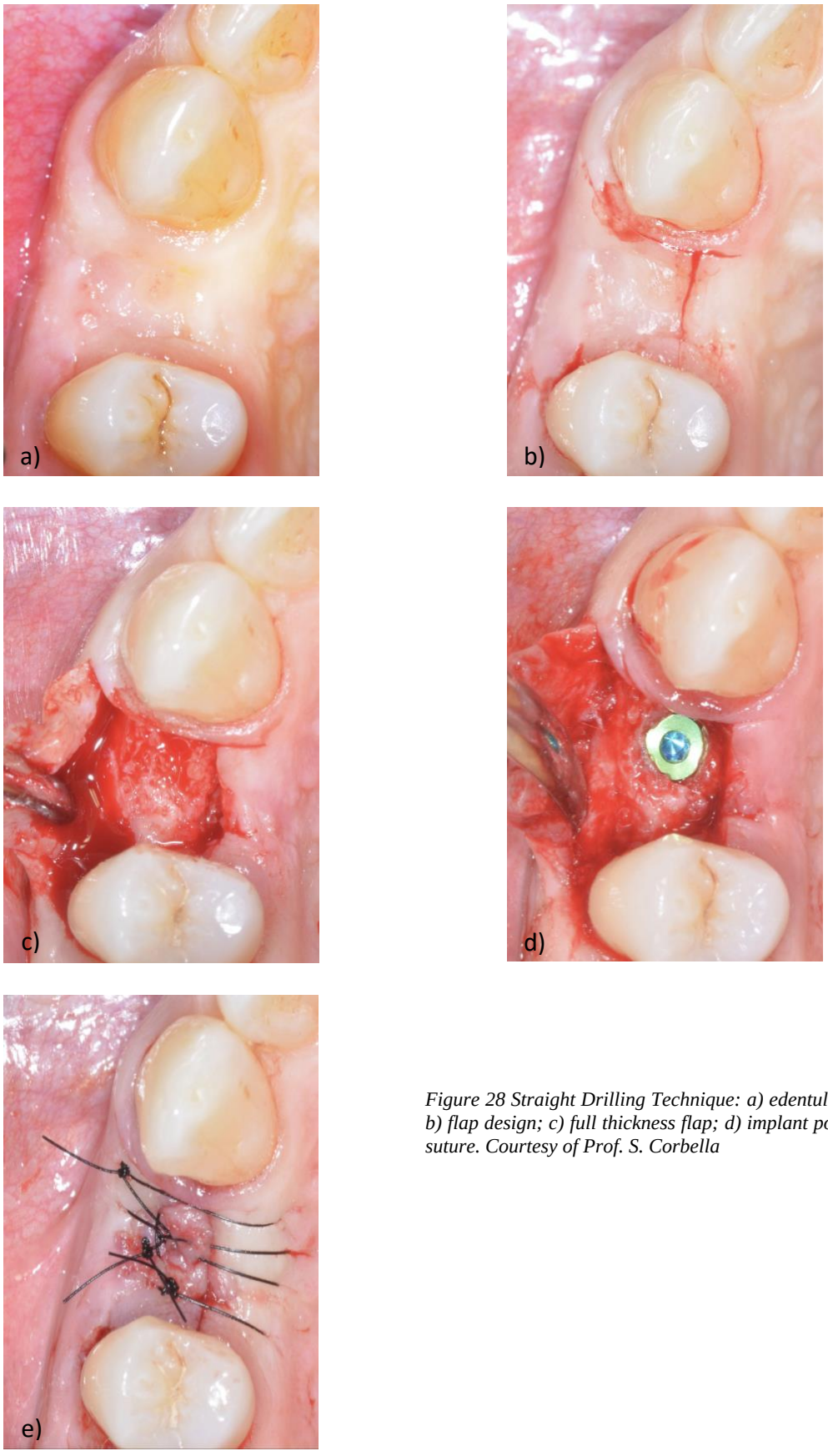

Figure 28 Straight Drilling Technique: a) edentulous area; b) flap design; c) full thickness flap; d) implant position; e) suture. Courtesy of Prof. S. Corbella

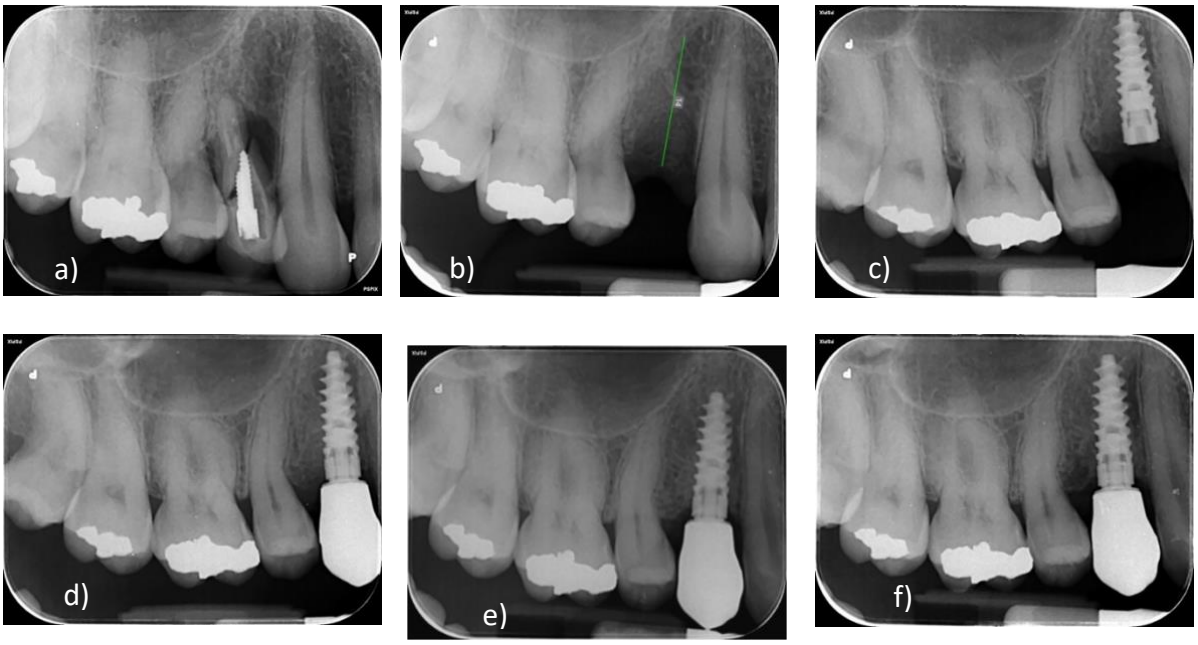

*Figure 29 Periapical radiographs taken **a)** before tooth extraction; **b)** after tooth extraction; **c)** at the end of the surgery, after implant placement; **d)** at the placement of the crown; **e)** at 12 months after prosthesis; **f)** at 24 months after prosthesis. Courtesy of Prof. S. Corbella*

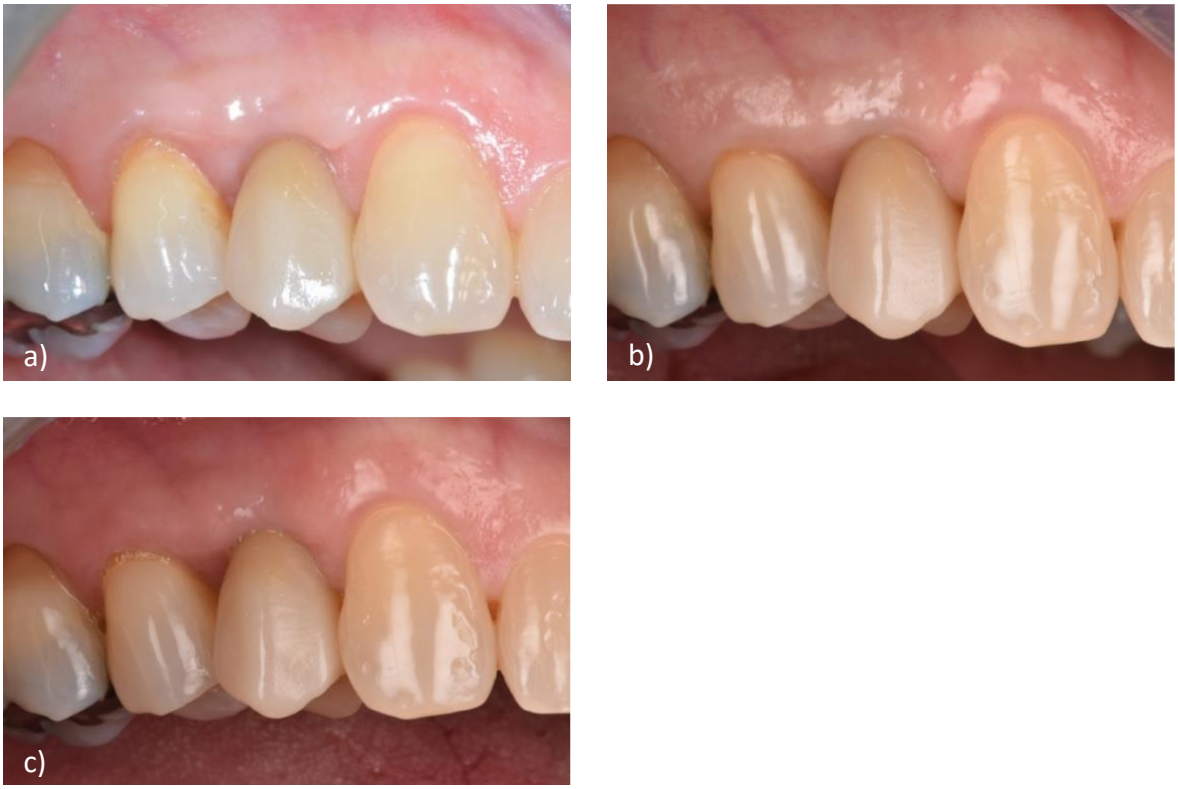

*Figure 30 Prosthesis delivery. **a)** baseline; **b)** 1 year follow-up; **c)** 2 years follow-up. Courtesy of Prof. S. Corbella.*

5.I Hypothesis and number of patients

The null hypothesis was that no difference existed between the two groups in term of marginal bone resorption at 1-year. The study was planned to detect a difference of at least 0.25 mm

between the two groups. The minimum number of subjects for each group was calculated to be 27. This number was augmented of 10% for drop-outs. A total of 60 patients were included. The sample size was based on a non-inferiority study and the unit of analysis was the implant. The allocation ratio was 1:1.

5.L Statistical analysis and methodology

Descriptive statistics provided mean and standard deviations for continuous variables.

The Shapiro-Wilk test was applied to test normality of distributions of primary and secondary outcome variables. Differences between group for normally-distributed variables were tested by means of Student's t test. Wilcoxon-Mann-Whitney test tested differences between group for non-normally distributed continuous variables. The significance was posed to $P<0.05$. Regression analysis was performed to explore the effects of independent variables on the amount of bone resorption rate.

5.M Potential risk and benefits of the study

Benefits

The potential benefits for the subjects involved was related to the possibility to obtain an implant-supported prosthesis to treat single or partial edentulism. In this way, it can be hypothesized a complete restoration of function (e.g. masticatory function) and of aesthetics. Implant placement have been provided to the patients for free.

Risks

Since the tested techniques were both in accordance to the characteristics of a normal procedure, we cannot hypothesize the presence of risks strictly related to the research protocol. With regard to the implant placement intervention in general, the risks were the same that were described in literature; they were enlisted in the informed consent form and explained to the subjects. Such risks included: (I) direct or indirect damage to neurological or vascular structures; (II) postoperative infection; (III) early loss of osseointegration; (IV) maxillary sinusitis following a damage to maxillary sinus membrane; (IV) postoperative pain, swelling, hematoma.

All adverse reactions will be recorded.

5.N Ethical considerations

The protocol was compliant with current Declaration of Helsinki, with EN ISO 14155: 1 and EN ISO 14155: 2 and the Good Clinical Practice (GCP) and all the staff involved in the study is committed to acting in accordance with the principles contained therein.

FLOWCHART VISIT	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
PHASE	Baseline/ Enrolment	Treatment	Suture removal	II Stage surgery	Prosthesis placement	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5
TIME			7 days +- 1 from V1	120 days +- 7 day from V1	180 days +- 7 days from V1	90 days +- 7 days from V4	180 days +- 7 days from V4	360 days +- 15 days from V4	540 days +- 15 days from V4	720 days +- 15 days from V4
ELIGIBILITY CRITERIA VERIFICATION	X									
INFORMED CONSENT	X									
ALLOCATION	X									
ORAL HYGIENE INSTRUCTIONS[(2)]	X	X	X[(1)]	X[(1)]	X[(1)]	X[(1)]	X[(1)]	X[(1)]	X[(1)]	X[(1)]
MEDICAL HISTORY[(2)]	X		X	X	X	X	X	X	X	X
PPD, TL, BI, PI[(2)]	X					X	X	X	X	X
VISUAL ASSESSMENT[(2)]	X	X	X	X	X	X	X	X	X	X
FULL-MOUTH EXAMINATION[(2)]	X	X	X	X	X	X	X	X	X	X
PERIAPICAL RADIOGRAPH[(2)]	X	X			X	X	X	X	X	X
CLINICAL PHOTO[(2)]	X	X		X	X	X	X	X	X	X
PATIENT-CENTERED OUTCOMES		Questionnaire will be given to the patient at visit 1, filled in the following 7 days and collected by the operator at visit 2								
RECORDING OF AEs[(2)]		X	X	X	X	X	X	X	X	X

CHAPTER 6
RESULTS

In the study we included and treated 60 subjects, 34 female and 26 males, for a total of 86 implants. The demographic characteristics of the sample are presented in Table 6.

At one-year follow-up we lost 6 patients and 12 implants: 1 subject passed away, 2 subjects moved away, 1 implant failed and 2 patients have been lost at follow-up. At two-year follow-up we screened 50 subjects for 69 implants: 4 patients didn't attend the 2-year visit. The diagram representing the patients' flow is presented in Figure 31.

Parameter	Control group (n=30)	Test group (n=30)	All (n=60)	Difference
Age	57.2 +- 7,4	50.5 +- 8.1	52.5 +- 7.9	NS
Sex	18 Female; 12 Male	16 Female; 14 Male	34 Female; 26 Female	NS
Smokers	4 / 30 (13.3%)	6 / 30 (20.0%)	10 / 60 (16.7%)	NS

Table 6 Demographic characteristics of the sample

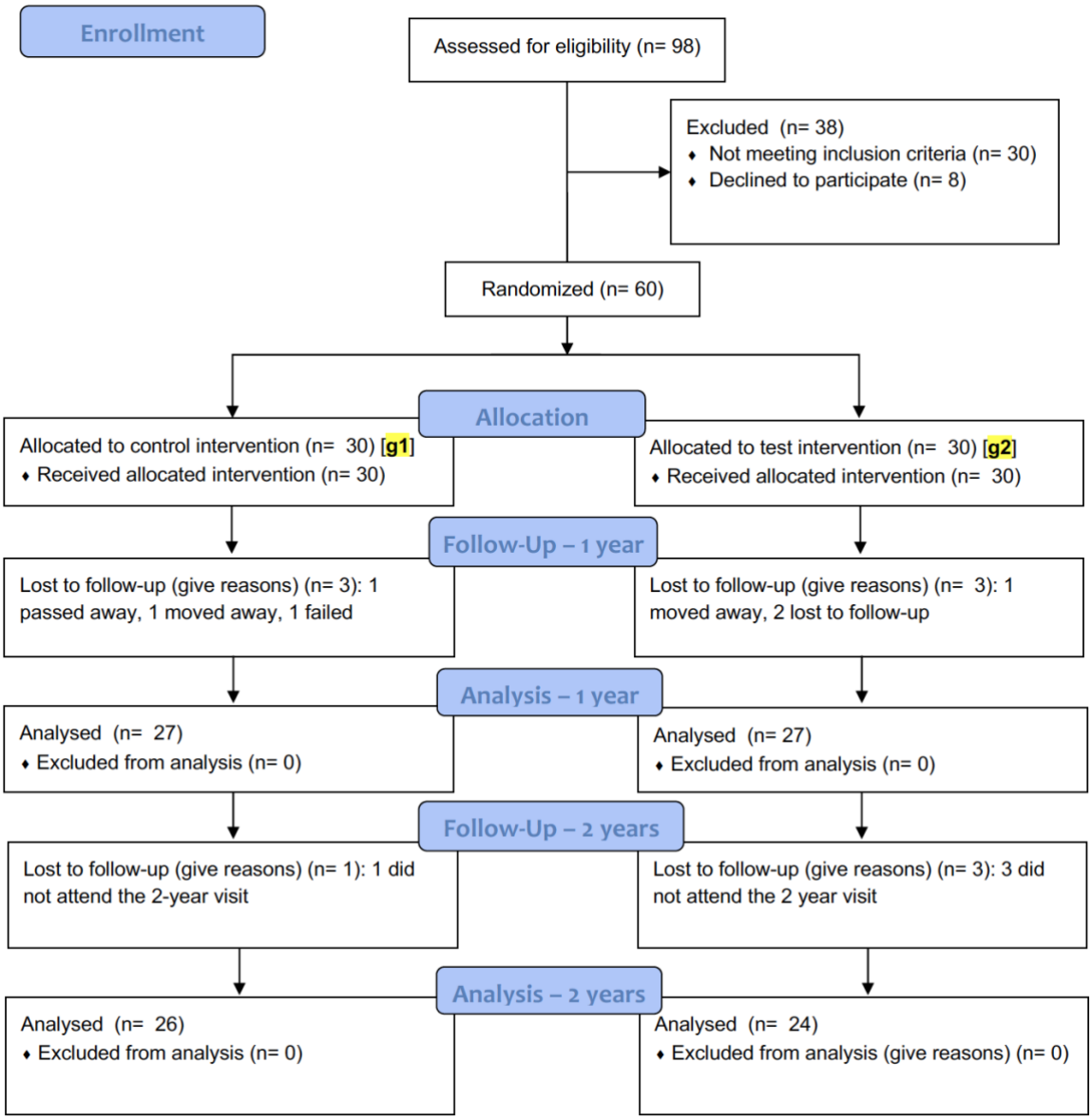

Figure 31 Diagram of patients' flow

Implants have been placed in both the mandible and the upper maxilla, either in the posterior and anterior regions. The distribution of the sites in which the implants have been placed for the study is shown in the histogram (Figure 32).

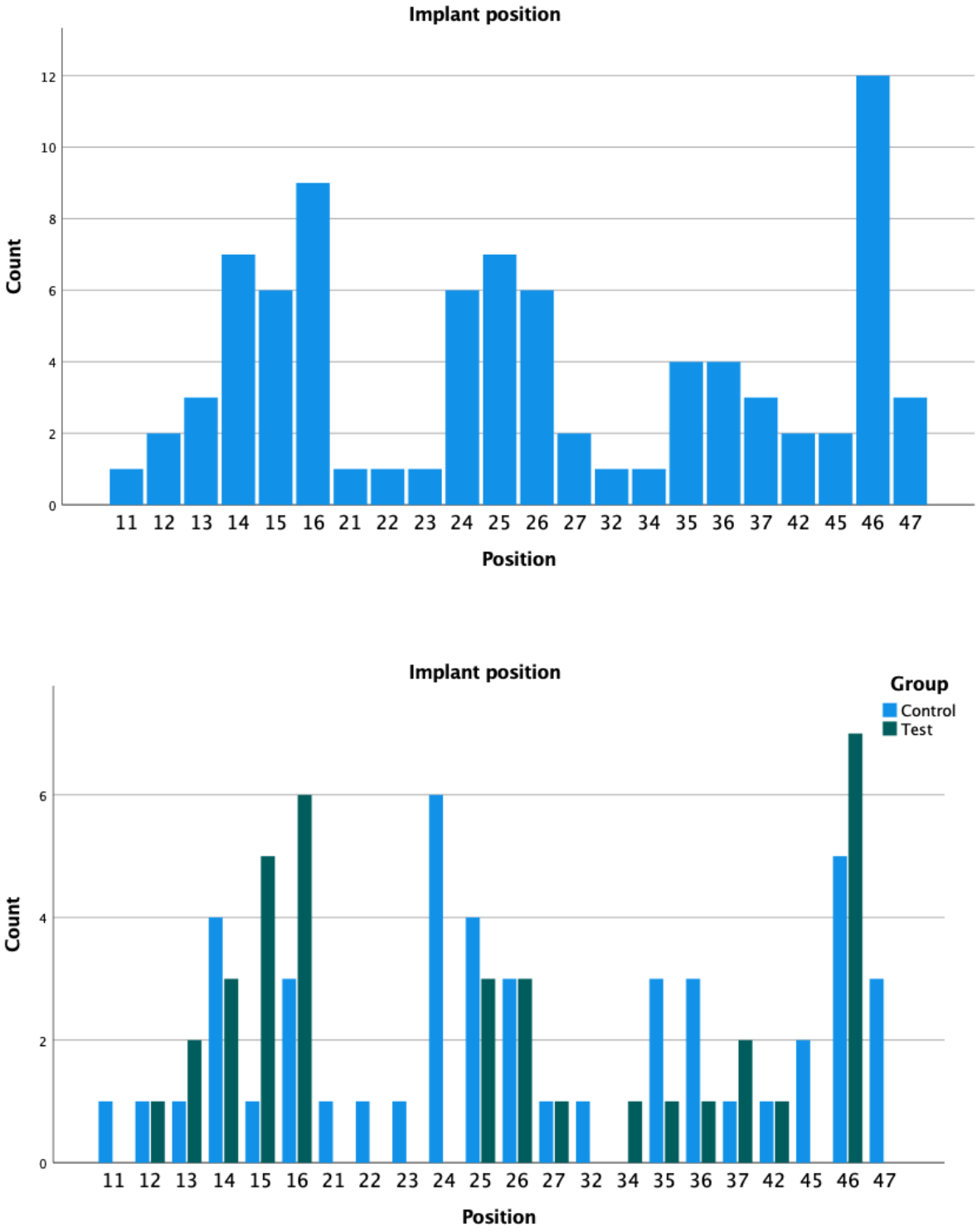

Figure 32 ***a)*** *Implants distribution.* ***b)*** *Implants distribution considering the allocation group*

The most commonly used implants had a diameter 4,2 mm and a length of 10 mm. According to Misch s' classification based on radiographic analysis, the predominant bone density in which the implants included in the study were placed was D2.

The characteristics of the implant placed such as diameter, length, insertion, torque and bone density are shown in table 7.

Parameter	Control group (n=48)	Test group (n=38)	All (n=86)	Difference
Implant diameter	3,75 mm: 43.5% 4.20 mm: 45.7% 5.00 mm: 10.9%	3,75 mm: 41.7% 4.20 mm: 50.0% 5.00 mm: 8.3%	3,75 mm: 42.7% 4.20 mm: 47.6% 5.00 mm: 9.8%	NS
Implant length	8.00 mm: 21.7% 10.0 mm: 39.1% 11.5 mm: 26.1% 13.0 mm: 8.7% 16.0 mm: 4.3%	8.00 mm: 16.7% 10.0 mm: 44.4% 11.5 mm: 22.6% 13.0 mm: 16.7%	8.00 mm: 19.5% 10.0 mm: 41.5% 11.5 mm: 24.4% 13.0 mm: 12.2% 16.0 mm: 2.4%	NS
Insertion torque	36.6 +- 11.1 Ncm	40.7 +- 10.3 Ncm	38.5 +- 10.8 Ncm	NS
Bone density	D1: 18.2% D2: 54.5% D3: 11.4% D4: 15.9%	D1: 5.7% D2: 62.9% D3: 25.7% D4: 5.7%	D1: 12.7% D2: 58.2% D3: 17.7% D4: 11.4%	NS (P=0.067)

Table 7 Implants characteristics

Of a total of 86 implants one implant failed in a smoker patient of the control group during the healing period, before the placement of the prosthesis. Thus, the cumulative implant survival rate was 98.8% after two years from the placement of definitive prosthesis. We found no occurrence of peri-implantitis during the investigation period.

Primary outcome

With regard to the primary outcome (radiographic bone loss at 1 year) we found no evidence of a difference in bone resorption, which increased significantly over time, between the two groups (table 8).

Group	Prosthesis placement - Baseline	1 year follow-up	2-year follow-up	Difference
Control group	0.00 +- 0.00 mm	0.67 +- 0.67 mm	0.91 +- 0.74 mm	Baseline vs 1y: P=0.042 Baseline vs 2y: P=0.010 1y vs 2y: P<0.001
Test group	0.13 +- 0.40 mm	0.76 +- 0.64 mm	0.93 +- 0.74 mm	Baseline vs 1y: P=0.001 Baseline vs 2y: P=0.002 1y vs 2y: P=0.006
Difference	NS	NS	NS	

Table 8 Bone resorption

Secondary clinical outcomes: were recorded in each follow-up visit and are presented in Table 9.

- Probing depth: no statistically significant difference was found between the test group and the control group regarding the depth of probing around the implants;
- Tissue Level: no statistically significant difference was found between the test group and the control group regarding the level of the tissue around the implants;
- Plaque index: we found evidence of difference between the test group and the control group regarding plaque accumulation but the effect size was not relevant from the clinical point of view;
- Bleeding index: no statistically significant difference was found between the test group and the control group regarding the bleeding around the implants.

Parameter	3 months		1 year		2 years	
	Control group	*Test group*	*Control group*	*Test group*	*Control group*	*Test group*
Probing depth (mm)	2.19 +- 0.77	2.39 +- 0.80	3.15 +- 0.87	2.98 +- 0.76	3.12 +- 0.81	3.23 +- 0.66
Tissue Level (mm)	0.12 +- 0.28	0.04 +- 0.20	0.08 +- 0.21	0.02 +- 0.07	0.20 +- 0.78	0.00 +- 0.00
Plaque index	0.18 +- 0.29 *	0.03 +- 0.08 *	0.25 +- 0.40 *	0.06 +- 0.15 *	0.45 +- 0.68 *	0.13 +- 0.28 *
Bleeding index	0.16 +- 0.28	0.07 +- 0.14	0.17 +- 0.29	0.10 +- 0.18	0.34 +- 0.67	0.20 +- 0.25

*Table 9 Clinical outcomes * means a statistically significant difference between the two groups (P<0.05)*

Patient-centered outcomes: the results of postoperative questionnaire about quality of life are presented. No evidence of a difference could be found, for such outcomes, between the two groups (Table 10).

Parameter	Group	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day7*
Pain	*Control*	11.3 +- 13.2	6.3 +- 11.5	0.8 +- 2.9	0.8 +- 2.9	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0
	Test	24.0 +- 23.9	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0
Limitations in daily activities	*Control*	7.1 +- 12.9	0.4 +- 1.4	0.4 +- 1.4	0.8 +- 2.9	1.3 +- 4.3	1.3 +- 4.3	5.0 +- 17.3
	Test	11.0 +- 22.8	5.0 +- 15.8	5.0 +- 15.8	2.0 +- 6.3	1.0 +- 3.2	0.0 +- 0.0	0.0 +- 0.0
Taste alteration	*Control*	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0
	Test	3.0 +- 9.5	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0
Taste sensation	*Control*	1.3 +- 4.3	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0
	Test	3.0 +- 9.5	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0	0.0 +- 0.0

Table 10 Results of postoperative questionnaire about quality of life

We performed a regression analysis to explore the effects of independent variables on the amount of bone resorption rate. None of the baseline parameters resulted correlated to bone resorption rate 1 or 2 years after the placement of the prosthesis. We found no differences related to the clinic where the implants were placed. In Figure 29 we can see a graphic showing one-year bone resorption rate in correlation with bone density. We found statistical evidence of a difference between D1 and D3 (P=0.038).

As an ancillary analysis, we performed a multi-level analysis in order to reveal if an effect due to multiple implants on one patient was present, finding no evidence of this. Finally, no adverse events were recorded.

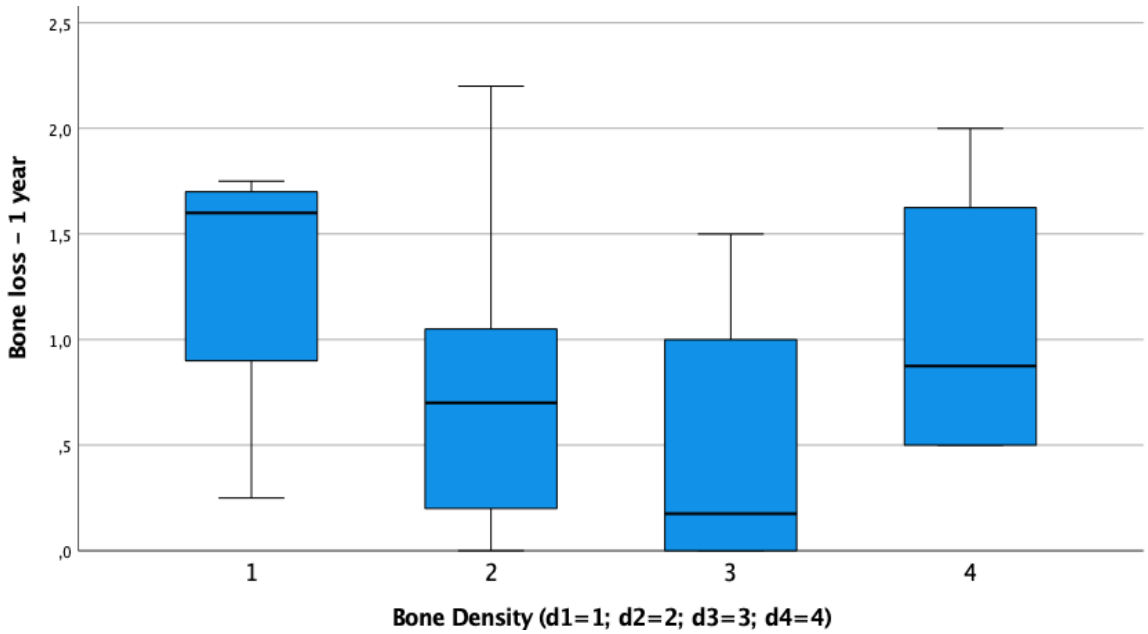

Figure 33. 1-year bone resorption rate with different bone density.

CHAPTER 7
DISCUSSION

This Multicentric non-randomized controlled clinical trial didn't find any statistically significant differences in marginal bone level changes between "Step drilling" implant site preparation and "Straight drilling" implant site preparation either at one or at two years follow-up. Both techniques were clinically successful with no major complications occurring and the cumulative implant survival rate was 98.8% after two years from the placement of definitive prosthesis.

As we found in our results, the literature also agrees that after implant placement, bone undergoes a physiological remodelling (Terheyden et al., 2012). Over the years, different causes have been taken in consideration, such as trauma from surgery for surgical protocol or overheating (Esposito et al., 1998), micromovement of the abutment (Liu and Wang, 2017), inflammation in the microgap area (Ericsson et al., 1995), formation of biological width (Cochran et al., 1997), plaque accumulation (Lang et al., 1993) and occlusal trauma in conjunction with inflammation (Naert et al., 2012, di fiore 2022). The most commonly cited definition of implant success allows for 1 mm marginal bone loss (MBL) during the first year and a subsequent annual rate of 0.2 mm in the following years (Albrektsson et al., 1986, Roos et al. 1997). As demonstrated by many different studies, marginal bone loss can be affected by numerous factors such as timing of implant placement (Kinaia et al., 2014), bone grafting (Yang et al., 2016), implant's macrodesign / surface topography/ neck design (Vandeweghe et al., 2012; De Bruyn et al., 2017; Penarrocha-Diago et al., 2013), configuration and shape of the implant-abutment connection (Lemos et al., 2017), prosthetic design (Derks et al., 2016), soft tissue thickness (Vervaeke et al., 2014), patient's oral hygiene and history of periodontitis (Ramanauskaite and Tervonen, 2016; Sgolastra et al., 2015), etc.

In our study we took in consideration the surgical procedure. The literature shows that the increase in bone temperature during drilling may damage hard tissues, causing irreversible damage to the bone and compromising implant osseointegration (Albrektsson 1981, Eriksson 1982). Udiljak et al. observed that step drills have an effective design in minimizing temperature rise due to the gradual removal of material from the drilling site. Therefore, when comparing heat development between conventional drills and step drills, the maximum temperature reached in bone during drilling would be lower when using step drills (Udiljak,

2007). However, we didn't have a greater marginal bone loss using Straight drilling procedure but, since this is not a thermal study, we cannot have an evidence of bone overheating. Therefore, our findings are not in contrast with Udiljak since it does not imply that step drills do not result in lower bone overheating compared to conventional drills.

What has been obtained from the analysis of the data in this study is not either contradictory to what was stated by Albrektsson and Eriksson, as it does not exclude the possibility that excessive overheating of the bone may lead to irreversible damage to the bone tissue.

An interesting fact is that we found statistical evidence of a difference in marginal bone resorption rate in correlation with bone density D1 and D3. Specifically, D1 bone underwent a greater remodelling compared to D3. This data is in accordance with what is reported in literature: hard bone may be associated with higher insertion torque that can excessively compress the cortical bone, leading to early marginal bone loss (Marconcini et al, 2018, Barone et al., 2016).

Regarding the clinical secondary outcomes, no statistically significant difference was observed between the test group and the control group, neither for RFA at the time of implant placement (when it has been possible to measured it), nor for peri-implant probing depth (PD), bleeding index (BI), and plaque index (PI) over time. Moreover, RFA at the time of implant placement is a method used for evaluating primary stability (O'Sullivan 2000) and is commonly associated with the surface and macroscopic design of the implant, surgical techniques such as sequence of drills used, and bone quality around the implant site (Elias 2012, Chatvaratthana 2017). We were unable to measure the RFA values of all the patients, but the partial data collected showed that the presence or absence of an apical step does not affect the primary stability of the implant and, consequently, RFA.

Similarly, the presence or absence of an apical step in the drills used in implant site preparation does not influence PD, BI, and PI over time, which are more likely to be related to the patient's hygiene status, their inflammatory condition and prosthesis characteristic (Renvert 2018, Heitz-Mayfield2018) .

For patient-centered outcomes, no statistically significant difference was observed in the 7 days following the procedure. Pain, taste alteration, taste sensation, and post-surgical functional limitations do not vary based on the presence or absence of an apical step in the drills used in implant site preparation. In addition, post-operative pain in dental implant surgery is the result of a surgical insult to the tissue and the subsequent inflammatory process

(Bryce 2014) and it primarily depends on the duration of the surgery and whether the analgesic drug is taken postoperative (Mai 2021).

The major limitations of this study were the short follow-up, the inability to measure bone overheating and the lack of control over confounding factors that could determinate marginal bone loss such as, for example, soft tissue thickness and phenotype (Galarraga-Vinueza 2023), implant position, history of periodontitis and a presence of a prosthetic emergence profile with an angle ≥ 45° (Corbella 2023).

CHAPTER 8
CONCLUSION

Whitin the limitations of this study, it cannot be claimed that the use of step drills leads to a lower marginal bone resorption at two years follow-up after prosthetic loading. Both the literature and the present study do not provide strong evidence in favour of using this type of drill, but they certainly do not document any biological disadvantages.

From a clinical perspective, however, these drills are advantageous as they allow for maintaining the centering of the implant site preparation. The presence of the reduced-diameter apical portion compared to the body of the drill facilitates inserting the drill into the tunnel created by the previous drill, making it easier to maintain the preparation axis.

In conclusion, from a purely biological perspective, there is currently no evidence in favour of using a step drill over a traditional straight drill. However, from a clinical standpoint, the use of step drills is advantageous for operator convenience compared to traditional drills. Since they do not result in any biological, prosthetic, or patient quality of life disadvantages, it can reasonably be considered to incorporate this type of drill into routine implant clinical practice. The literature on the clinical use of step drills is still lacking, so further studies on the subject are needed.

APPENDIX 1
DRILLING SEQUENCES

Step Drilling Sequence

Ø Diameter	Soft bone Type IV	Medium bone Type II&III	Hard bone Type I
Ø 3.75	2.0 2.4/2.8	2.0 2.4/2.8 2.8/3.2	2.0 2.4/2.8 2.8/3.2 3.2/3.65 Cortical*
Ø 4.2	2.0 2.4/2.8 2.8/3.2	2.0 2.4/2.8 3.2/3.65	2.0 2.4/2.8 3.2/3.65 3.65/4.1 Cortical*
Ø 5.0	2.0 2.4/2.8 3.2/ 3.65	2.0 2.4/2.8 3.2/3.65 3.65/4.1	2.0 2.4/2.8 3.2/3.65 3.65/4.1 4.1/4.5 4.5/4.8 Cortical*

* Cortical – Drill through cortical plate with the larger diameter

Straight Drilling Sequence

Ø Diameter	Soft bone Type IV	Medium bone Type II&III	Hard bone Type I
Ø 3.75	2.0 2.4 2.8**	2.0 2.8 3.2**	2.0 2.8 3.2** 3.65 Cortical*
Ø 4.2	2.0 2.8 3.2**	2.0 2.8 3.2 3.65**	2.0 2.8 3.2 3.65** 4.1 Cortical*
Ø 5.0	2.0 2.8 3.2 3.65**	2.0 2.8 3.2 3.65 4.1**	2.0 2.8 3.2 3.65 4.1 4.5** 4.8 Cortical*

* Cortical - Drill through cortical plate
** 3mm shorter than implant's length. Note that drill can be replaced by a corresponding step drill, throughout entire implant's length, see step protocol

APPENDIX 2
POST-SURGICAL QUESTIONNAIRE

Giorno 1

Dolore
Limitazione attività
Alterazione gusto
Sensazione gusto

Giorno 2

Dolore
Limitazione attività
Alterazione gusto
Sensazione gusto

Giorno 3

Dolore
Limitazione attività
Alterazione gusto
Sensazione gusto

Giorno 4

Dolore
Limitazione attività
Alterazione gusto
Sensazione gusto

Giorno 5

Dolore
Limitazione attività
Alterazione gusto
Sensazione gusto

Giorno 6

Dolore
Limitazione attività
Alterazione gusto
Sensazione gusto

Giorno 7

Dolore
Limitazione attività
Alterazione gusto
Sensazione gusto

APPENDIX 3
USED ACRONYMS

MBL: Marginal bone level

MBR: Marginal bone resorption

RFA: Resonance frequency analysis

BI: Bleeding index

PI: plaque index

PB: probing depth

POH: Professional oral hygiene

OHI: Oral hygiene instructions

AE: Adverse event

SAE: Serious adverse event

CHAPTER 9
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CHAPTER 3: CRESTAL BONE LOSS

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CHAPTER 4: IMPLANT BUR DESIGN

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