TILTED IMPLANTS

IMPLANT-PROSTHETIC REHABILITATION OF THE ATROPHIC PATIENT

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Tilted Implants is a book that arises from the desire to share with the highest number of colleagues over 15 years of experience on implant-prosthetic rehabilitations with tilted implants. These types of restorative solutions were initially considered as innovative methods, while today they are commonly used by many clinicians around the world. Years of commitment and enthusiasm for the revolution that tilted implants brought into implant dentistry, but also frustration for the initial ostracism we have seen, have allowed us to develop a profound surgical and prosthetic knowledge that we wanted to share in its entirety, without concealing anything from the reader. The main objective from our side was to provide clinicians not only with a practical guide for the available treatment options, but also to analyze the individual procedures, with a detailed description of each step.

The World Health Organization reports a progressive aging of the population and a growing number of patients who are completely edentulous in advanced age. Added to these are the patients with a previous implant rehabilitation that has failed, those with terminal periodontitis, and those who have severely compromised fixed or removable prostheses where it will not be possible to preserve any teeth for the new rehabilitation. Very often dentists must face situations of limited bone quantity, systemic conditions that are not ideal, and the need to reduce both biologic and financial costs.

To meet this growing need, treatment protocols have been used in the last decade that incorporate tilted implants, supported by an extensive scientific literature and with high success rates in the long term. The first of these protocols is undoubtedly the All-on-4. Its winning feature, which allowed its diffusion on a global scale, was the apparent simplicity of application, even in the most complicated clinical scenarios. In reality, the excellent survival rate, reported by the most accredited scientific publications, occurs only if precise surgical techniques, a proper prosthetic protocol, and biomechanics principles are adopted, leaving limited space for improvisation. As with all surgical techniques, a good basic predisposition is therefore necessary, as well as a learning curve and a continuous critical review of what has been done.

This manuscript therefore includes a detailed description of treatment protocols that include the use of tilted implants, such as All-on-4, V-II-V, transsinus implants, and zygomatic implants.

Starting from a review of the scientific basis of immediate loading and the advantages deriving from implant inclination, we have addressed all the necessary diagnostic aspects for a correct treatment plan. We focus on presurgical planning, a fundamental starting point for the correct management of the immediate provisional prosthesis. The part dedicated to the surgical protocols—the true heart of the book—allows the reader to learn the ideal rehabilitative path, both for contained bone deficits and for extreme atrophy, guiding the operator in use of the patient's residual bone as a function of immediate loading. The work concludes with a step-by-step description of the provisional and definitive prosthetic protocols that have been developed over 15 years of clinical and research experience.

Tilted Implants is not just an implant surgery book but represents a practical guide and a daily resource for anyone who wants to approach these techniques and is looking for a point of reference to perform cutting-edge rehabilitative treatments in the interest of their patients. For those who already apply these techniques successfully, the wish is that they can find confirmation in what they do and maybe new ideas for further professional growth.

Finally, we would like to thank all our contributors for their excellent cooperation. Special thanks to the main contributor, Dr Matteo Clericò. Without his fundamental work, this book would still be a splendid project for the future. Thank you to Dr Parveen Virdee and Dr Kristen Frantz for their help with the linguistics.

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To all my teachers. There are too many to remember them all, considering I have learned from all the people I have been lucky enough to meet. One exception—a special thanks to Paulo Maló, who gave me the honor of his friendship, his explosive desire to innovate, and his intellectual liveliness, to which I owe much of everything I managed to do in the field of rehabilitation of compromised patients.

Last but not least, a big thank you to my dental technicians Matteo Consonni, Stefano Rota, and Marco Ghisleni, who gave me the honor of working with them. Thanks again to the other contributors who helped us with their valuable scientific contributions: Raffaele Vinci, Riccardo Benzi, Alessandra Carrera, Federico Mandelli, Stefano Panigatti, Michele Manacorda, Vittoria Terraneo, Marco Vigoni, and the young doctors Daria Saporiti and Federica Grangia.

—EA

The biggest thanks goes to my parents, Elio and Lina, model of life and source of inspiration, for having guided and sustained my steps with their smile and for transmitting to me the values of honesty, perseverance, and sacrifice.

To my wife Michelle, for the infinite love and joy that fill my days, and for the patience and the strength with which, as a colleague, she supports my every professional choice. To my friend and teacher, Dr Enrico Agliardi, who has believed in me since I was a young student of dentistry and who gave me the honor of participating in his clinical and professional activities. Without envy or self-interest, he opened the doors of his practice, showing me the art of oral surgery. The teachings he has transmitted to me are innumerable, while he infected me with the passion he has for this profession. Being at his side is a privilege that few have had, and it is an honor that I find difficult to repay. My eternal gratitude goes to him for wanting to combine his name with mine in this book, which I hope will represent a starting point for many future projects. To the many colleagues, technicians, and assistants who also wanted to share with the undersigned just a moment of their life's work.

—DR

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The All-on-4 concept is an immediate function rehabilitation protocol developed at the Maló Clinic in Lisbon, Portugal. The concept is based on the optimal number of four implants placed as cornerstones for supporting an edentulous arch with a complete-arch prosthesis and immediate loading. Tilted implants are key for this rehabilitation. Using implants in this way allows for the implant support to be moved posteriorly and for the implants to be longer. In the maxilla, the implant passes through a dense bone structure—the anterior wall of the maxillary sinus—and reaches high density in the anterior maxilla, enhancing the primary stability. Thus, an immediate provisional prosthesis can be delivered to provide function and esthetics.

The All-on-4 concept was proposed for the first time in 2003 with a clinical study in the mandible and in 2005 for the maxilla. Those pioneering publications were initially received with considerable skepticism and criticism from the dental community, although they were the result of years of preliminary analysis and experimental investigations conducted in the Maló Clinic. Nowadays, the protocol is accepted worldwide, and for many clinicians, it represents the first choice in some categories of patients for whom bone grafts are not possible or in which outcomes are questionable.

When I first met Enrico in 2004, I immediately understood that he has a clear mind regarding the advantages and benefits of this revolutionary approach, and he started to adopt it in his private practice and at the University of Milan. At the beginning, he faced the same difficulties I had, but his perseverance and belief in what he was doing allowed him to succeed. I can say that he is now one of my best references for these rehabilitations. We share the same passion for what we do.

The All-on-4 concept has undergone continuous development, from standard to extramaxillary approaches with the insertion of four zygomatic implants. Bone grafts can now be avoided even in severely atrophic maxillary arches. Each protocol is supported by clinical studies that report the outcomes and provide feedback for future improvements.

Enrico has always supported the same philosophy we have at the Maló Clinic. He didn't just limit his practice to performing surgeries—he has run prospective and experimental studies with the same critical eyes and has shared his experience in international venues. Our close collaboration in delivering zygomatic implants has overcome many complex clinical situations, providing benefits for a subset of patients who lost hope in implant therapies.

Enrico has taken the esthetics of the provisional and definitive rehabilitations into great consideration. The chapters dedicated to prosthetics are enriched by excellent photographs that guide the reader through each phase of the treatment. Enrico has extensive experience with All-on-4, as well as tilted implants.

This book contains 15 years of activity of Enrico and his team in this type of solution and defines the state of the art of rehabilitations supported by tilted implants with immediate function, from situations of recent edentulism to the most severely atrophic alveolar ridges. For all the aforementioned reasons, it is a great pleasure and honor for me to present this landmark text, which I'm sure will receive great acclaim not only in private practice, but in academic settings as well.

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The Biology of Osseointegration

Definition of Osseointegration

Implant dentistry is based on the fundamental principle of osseointegration, defined by Prof P-I Brånemark as "a direct structural and functional connection between ordered, living bone and the surface of a load-bearing implant."[1] Prof Brånemark is without a doubt the founding father of modern implant dentistry. The concept of osseointegration began with a study published in 1959 when Prof Brånemark was observing rabbit bone marrow using a titanium chamber with a transilluminating optic system. At the end of the experiment, he realized that it was very difficult to remove the chamber from the rabbit's fibula and that the mineralized tissue perfectly fitted the microirregularities of the titanium surface, showing no sign of inflammation.[2]

In light of these observations, Prof Brånemark began to further experiment with animals (specifically rats, rabbits, and dogs), and a study on dogs allowed him and his colleagues to analyze the factors influencing the stability of titanium screws supporting dental prosthetic components.[3,4] The next step was human clinical trials, as is shown in the seminal 1977 publication that contained the results of 10 years of experience with full-arch implant-supported prostheses.[1]

However, because it was technically impossible to prove this osseous integration with objective data, the scientific world was skeptical of this idea at the time. The first researcher who managed to scientifically prove the integration of endosseous implants was Dr André Schroeder. His team revealed the phenomenon of osseointegration histologically using innovative techniques that allowed simultaneous sectioning of the decalcified bone and the implant without losing anchorage.[5]

The first definitions of osseointegration (from the Greek word *ostéon*, meaning *bone*, and the Latin word *integratio*, meaning *growth/rearrangement*) were of a histologic nature: direct connection between bone (as a mineralized bone matrix) and implant with no interposition of the soft tissue.

Prof Brånemark's definition is true at the optic microscopic level. Nowadays, it is known that the titanium implant surface undergoes oxidative processes when in contact with air, and that this oxide layer (TiO_2) interacts with certain noncollagenous osseous proteins (mainly osteopontin and bone sialoprotein) that are present in the hematologic fluid of the osteotomy, developing chemical and physical connections.[6]

Meffert et al[7] divided the concept of osseointegration into *adaptable osseointegration* if the osseous tissue was adjacent to the implant surface and *biointegration* if it was possible to find a direct biochemical bone-to-implant connection. According to Boyne and Scheer,[8] it is accurate to use the term *osseointegration* when the implant is entirely integrated in mature bone tissue with of all its components (ie, vascular lacunae, hematopoietic tissue, adipose tissue, connective tissue, and calcified matrix). However, there will never be 100% anchorage between the bone matrix and the implant surface. After this study, a series of discussions occurred relating to the minimum bone-to-implant contact needed to consider an implant osseointegrated.

The problem of defining the exact degree of bone-to-implant attachment led to a definition of osseointegration based on implant stability, which is a clinical criterion rather than a histologic criterion. Osseointegration thereby becomes a process that allows an alloplastic material under functional load to be rigidly fixated without any clinical symptoms.[9] Osseointegration is not a characteristic of a material, but a condition in which there is no movement at the bone/implant interface.

In one publication,[10] osseointegration was considered from the following different points of view:

1. Patient's point of view: An implant is osseointegrated if there is lack of mobility, stability of the prostheses under functional load, and absence of pain and inflammation.
2. Biologic point of view: Osseointegration is the apposition of newly formed bone along the implant surface without the interposition of fibrous tissue. There is a direct and functional connection that is able to sustain loads without deformation or rejection.
3. Biomechanical point of view: An implant is osseointegrated if there is no relative movement between the implant and the surrounding bone, and the deformation under loading is equal between the implant and the surrounding bone.
4. Microscopic/biophysical point of view: Osseointegration implies that under an electron microscope, the components of tissue around an implant are identified as normal bone and marrow components.

Some researchers consider osseointegration as a foreign body response to the implanted device, stating that only a biomechanical factor was responsible for the development of soft tissue integration or for an osseous covering.[11] Indeed, the authors behind these statements have demonstrated that even amalgam compounds can be embedded into bone.[11] However, there is documented evidence that the bone response is quantitatively different depending on the type of biomaterial and its surface roughness, which opposes the view of osseointegration as simply a foreign body reaction.[12–16]

Osseointegration has clearly evolved as a concept and can be considered from different viewpoints, including anatomical, histologic, and ultrastructural.[17–19] The concept of osseointegration in the scientific community has grown from the passive and blind acceptance of bone-to-implant contact to indisputable evidence supported by histologic data. Osseointegration and the stability of the implant are now used as definitive measures of clinical consequences in both the short and long term.

Today, where immediate loading of implants is a predictable reality in many clinical situations (from single implants to full-arch rehabilitation), both in native bone and in postextraction sites, implant survival in the short term is often expected. The focus has now shifted to the long-term stability of peri-implant tissues (ie, bone and gingiva) due to the increasing esthetic need in the anterior zone for single and partial rehabilitations and for hygienic maintenance in complete fixed solutions.

Experimental Studies on the Intraosseous Anchorage of Dental Prostheses

Since the early 20th century, many authors have published techniques to substitute missing teeth in partially or completely edentulous patients. Those techniques required implants of different shapes and different materials: Maggiolo's gold implants (1809), Greenfield's platinum–iridium lattice cage (1909), Casto's (1914) and Kauffer's (1915) spiral platinum–iridium implants, Abel's porcelain screw (1934), Dahl's subperiosteal button (1942), Formiggini's steel and tantalum hollow spiral shape screw (1947), and more recently, Linkow's[20,21] and Pasqualini's (1972) blades, Scialom's tantalum needle implant,[22] and Tramonte's, Garbaccio's, Marini's, and Pierazzini's screw (**Fig 1-1**).

At those times, early failures were frequent due to the lack of sterility of the surgical field. Therefore, many authors assumed that the implant had to be surrounded by a layer of fibrous tissue (ie, fibroosseous integration) that ensured stability with some grade of mobility, mimicking the periodontal ligament. After 10 years of loading, the implant survival rate ranged from 40% to 70%.[23] A few implants showed no complications and worked well, but the majority of them required removal because of severe peri-implant infections[24] (**Figs 1-2** and **1-3**).

In 1969, Prof Brånemark performed an experimental study on dogs to analyze which factors may influence the stability of endosseous implants and the clinical success of dental prostheses.[4] The endosseous implants consisted of a cylindrical titanium screw with perforations at the inferior end to allow for bone growth and to ensure solid anchorage in the mandible. A slot in the middle of the screw head connected the implant to the prosthetic structure.

The aim of the study was to analyze the biologic response of the bone around the implant at different time intervals without considering the long-term prognosis of the implants. The implant head was exposed after a healing period of 6 to 8 weeks to

Fig 1-1 Implant-supported prosthesis with various morphologies of fixtures. Note the infectious processes around the mandibular implants.
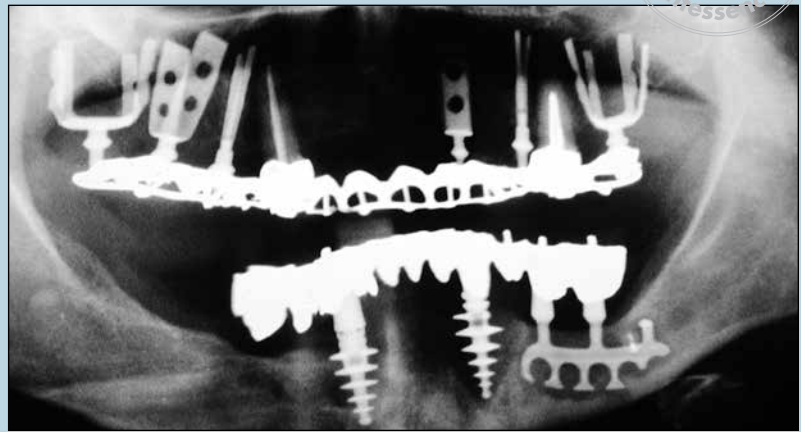

Fig 1-2 This complete mandibular fixed prosthesis failed 10 years after loading. *(a to d)* Note how the bone loss involved the entire length of both the teeth and the implants. *(e to g)* Panoramic radiographs taken during the treatment phases and at the 5-year follow-up. (Clinical case in collaboration with Dr Alessandra Carrera, Galbiate, Italy.)

allow a healing abutment to be placed. During the next 2 weeks, the prostheses were delivered and loaded. After the animals were sacrificed, the surgical sites were investigated clinically as well as with a stereomicroscope, radiograph, and optical microscope both before and after removal of the implants. The results showed how the hard and soft tissues accepted the implants without any sign of inflammation. In nearly all cases, the bone grew around the threads without fibrous tissue interposition, and the prosthesis was well anchored to the implants. These encouraging results led Prof Brånemark to begin a clinical study in humans.
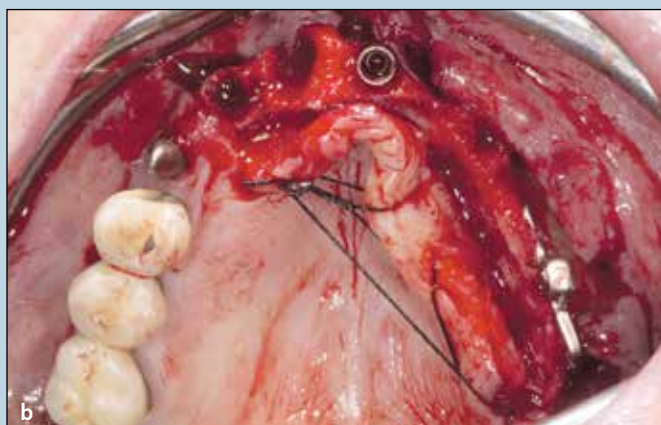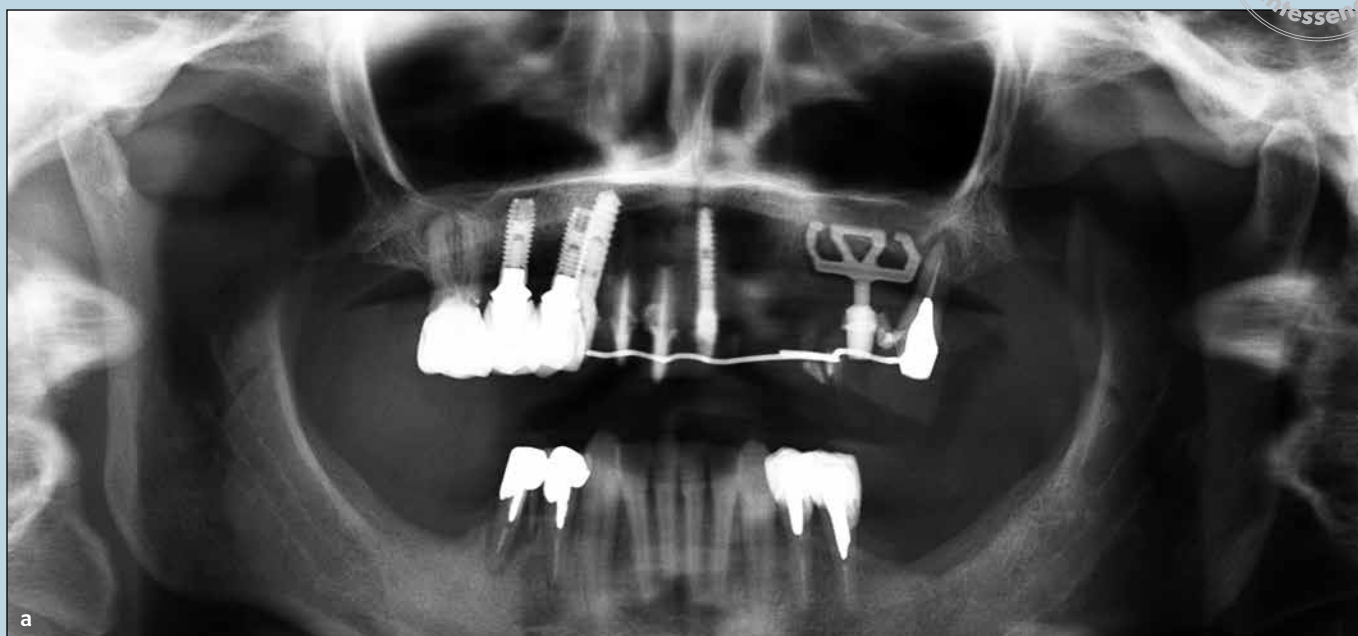
Fig 1-3 *(a to e)* After implants were removed from infected areas, extensive bone defects can be seen throughout the alveolar process. This complicates immediate implant placement. Thanks to the inclination of the implants, however, it is possible to achieve functional primary stability for immediate loading without the need for bone grafts.

Fig 1-3 cont. *(f and g)* The failing implants were carefully removed. *(h)* The panoramic radiograph after delivery of the immediate prosthesis showing the two axial implants and single tilted implant. *(i)* The follow-up radiograph after 1 year of loading demonstrates peri-implant bone stability. *(j)* Bone stability is still evident after 7 years. *(k and l)* A functional balance is maintained, and esthetics are not compromised.

Prof Brånemark's 10-Year Clinical Study

In 1977, Prof Brånemark published an article that can be considered one of the milestones of implant surgery.[1] From 1965 to 1975, together with his team, he treated a total of 128 maxillae and 107 mandibles in 211 patients, for a total of 1,618 implants supporting full-arch fixed prostheses. Of the 211 patients, 24 received treatment in both arches. The experimental time of 10 years was divided into three phases: the initial stage, the development stage, and the routine stage, with a few differences in surgical technique, prosthetic protocol, and healing time according to the acquired experience.

In the mandible, a full-thickness flap half the height of the alveolar process was raised on the labial aspect. The flap continued along the crest of the ridge distally to locate the mental foramen and the neurovascular bundle. In the maxilla, the incision was made along the crest to expose the incisive foramen and to isolate the nasopalatine nerve.[1]

During the initial and development project periods, Prof Brånemark and his team raised fairly extensive flaps to clearly identify the noble neurovascular structures. Consequently, extensive hematomas often developed beneath the flaps, and postoperative bone loss was higher because the cortical bone was deprived of part of its periosteal blood supply. In the third project period (ie, the routine phase), better preoperative planning (especially more accurate radiographic protocols) and an improved clinical experience led to smaller and more conservative flaps, resulting in fewer postoperative problems, less bone resorption, and increased patient comfort.

Implant positioning was conditioned by bone quantity and the need to completely submerge the implants without leaving any threads exposed. In most cases, due to advanced mandibular atrophy, four to six implants were placed only in the interforaminal region because bone height in distal areas was insufficient to place implants with a minimum length of 10 mm. In cases of extreme atrophy, the lower mandibular cortex became part of the implant site. In severe atrophies of the maxilla, the floor of the nose and the sinus cavities posteriorly represented the biggest challenges.

The implants were placed fully submerged in bone and covered by the mucoperiosteal flap for a variable healing time, depending on the clinical experience of the practitioners as well as relevant studies on the healing processes of bone.[3,25–30] When osseointegration was considered complete, the cover screw was replaced with a healing abutment of adequate height. The impression was taken, and the vertical dimension of occlusion was assessed to build a chrome-cobalt framework with acrylic teeth and pink gingiva. During the healing and remodeling period, no radiographs were taken because of the belief that radiation could impair newly forming bone at the bone/implant interface (**Figs 1-4** and **1-5**).
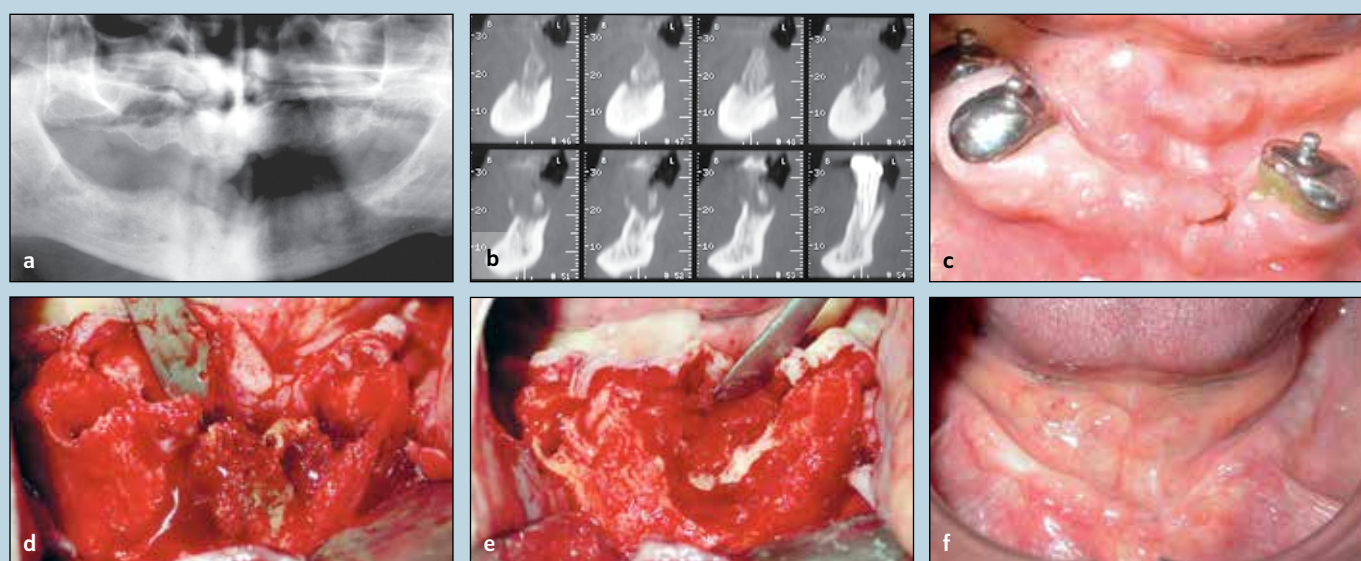
Fig 1-4 Mandibular rehabilitation with delayed loading according to the original Brånemark protocol. *(a to c)* The radiograph, CBCT scan, and clinical examination demonstrate osteonecrosis in the region of the mandibular left incisors. *(d to f)* The area is debrided and left to completely heal for 4 months.
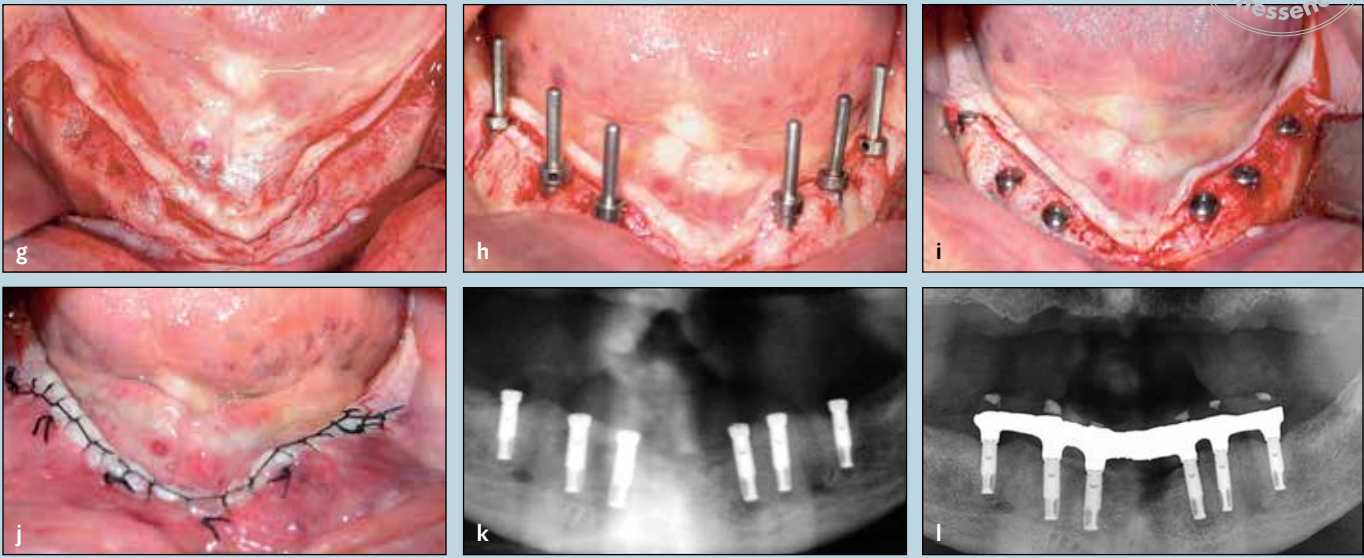
Fig 1-4 cont. *(g to k)* Once the site had healed, implants were placed. Loading with a definitive prosthesis occurred 6 months later. *(l and m)* Radiograph and clinical view after 15 years. The original definitive prosthesis had been replaced with a new definitive prosthesis 12 years after the implants were placed.
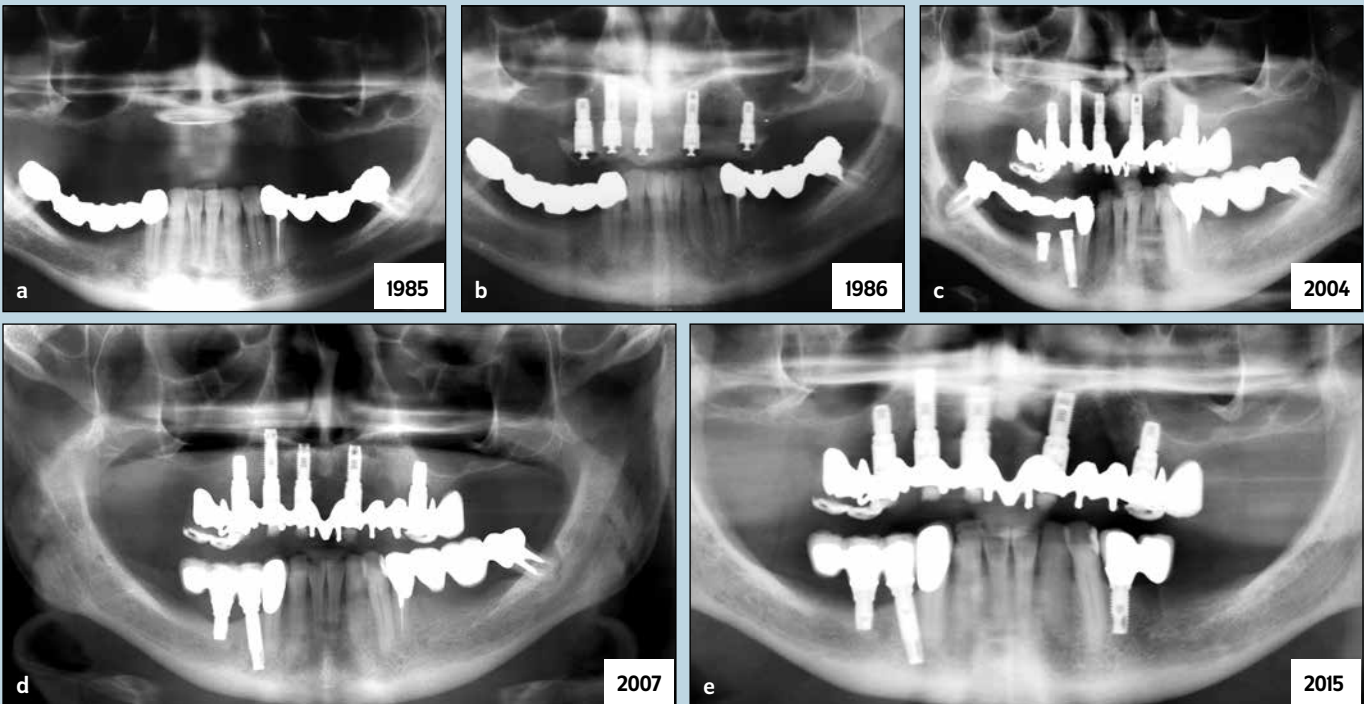
Fig 1-5 *(a to e)* Panoramic radiographs show 30 years of follow-up of a patient treated with a Toronto-Brånemark maxillary prosthesis. Over the years, the mandible has undergone various interventions, such as the replacement of dental-supported fixed prostheses with implant-supported fixed partial dentures. (Courtesy of Dr Federico Gualini, Bergamo, Italy.)

Reevaluation of the Brånemark Protocol

In their long-term prospective study, Brånemark et al[1] proved that it was possible to achieve predictable results and stable bone-to-implant integration following a scrupulous surgical and prosthetic protocol that can be summarized in nine points:

1. The use of a biocompatible material, such as titanium
2. Two-stage surgical protocol
3. Stress-free healing time of at least 3 months for the mandible and 5 to 6 months for the maxilla
4. Minimally invasive surgical technique, paying particular attention not to overheat the bone when drilling
5. Performing either a vestibular or mucobuccal incision
6. Surgery under sterile conditions
7. Using titanium instruments where needed
8. Avoiding radiographs during the integration phase
9. Placement of prostheses with acrylic occlusal surfaces

Before the introduction of this protocol, implants were regularly loaded at the time of placement because it was commonly thought that immediate stimulation could prevent crestal bone resorption and promote bone growth around the implants.[20,21] The interposition of fibrous connective tissue, evidenced in many situations, was regarded as an ideal response to the implant because it resembled the natural periodontal ligament.[20,21] However, the idea of immediate loading was abandoned when it became evident that a fibrous layer between the implant and the bone threatened the long-term stability of the implant. A stable situation could have been obtained only with direct contact between implant and bone.[1,4]

The Brånemark school rejected the idea of connective anchorage in that the direct contact between the bone and the implant was the fundamental requirement for long-term success. The surgical protocol adopted by Prof Brånemark was made up of a two-stage approach. In the first stage, an implant made of inert and carefully cleaned material was inserted with minimal trauma into a suitable surgical site and left to heal for at least 3 months without any external communication. Postinsertion immobility, total absence of loading during the healing period, and elimination of occlusal interferences and masticatory overloads were essential requirements.[31]

One of the most controversial points of the protocol is undoubtedly the waiting time before prosthetic loading. In fact, different loading times were tested during the experimentation, ranging from 84 days in 1968 to 45 days in 1970, with some borderline cases of 2 to 4 weeks. It was noted that insufficient healing time increased the risk of early or late mobility of the implant. Therefore, the healing time was altered to 174 days in 1974, and a slight reduction to 89 days was introduced in (**Table 1-1**).[1] After 10 years of experience, the period of time without loading was reduced to 3 months in the mandible and 5 to 6 months in the maxilla, based on the different bone densities.[1,9,27]

The stages of Prof Brånemark's study and the decision to have a long waiting period before the routine stage were made as a result of careful observation of some key parameters. The first parameter was about patient selection: 80% of patients presented with advanced mandibular atrophy, with a thin layer of cortical bone containing low-density trabecular bone marrow that could not guarantee good mechanical retention for the implants. The second parameter was about the implant design in terms of dimensions and microstructure, with a total of 22 different implant morphologies that were tested and discarded before the final period. The third parameter was the surgical protocol that underwent many changes: in the routine stage, more conservative flaps were raised that not only avoided exposing the bone too much, but also did not interrupt the blood supply, decreasing the healing period and postoperative complications. In the first phase, shorter implants were placed associated with site tapping, while in the third phase, implants were longer and were placed deeper. The fourth parameter regarded the prosthetic components. Very often, because of the patients' bone resorption, prostheses had unfavorable loading conditions due to long abutments and nonaxial loading directions.

In conclusion, it was impossible for Prof Brånemark's team to set scientifically accurate data about the correct healing period because of the heterogeneous composition of the sample and the continuous changes in the protocol.[1] Furthermore, data about the relationship between the different parameters with the healing times were missing. As a result, these parameters were established empirically. Brånemark et al considered the proposed time as completely empirical and not based on scientific evidence. They were not a fundamental requirement for the final success, but a therapeutic precaution for the clinician.[32]

Histodynamics of Endosseous Wound Healing

As a means of structural and functional connection between implant and bone, osseointegration is an essential prerequisite for the long-term stability of implants and implant-supported restorations. The biology of this process can be influenced by many variables, such as characteristics of the bone site, the drilling protocol and extent of surgical trauma, and macroscopic and microscopic features of the implant.[33] Many of these parameters have been extensively analyzed in animal models to understand how they influence osseointegration.[34–38]

TABLE 1-1 | Mean healing periods of Prof Brånemark's study[1]

Year	Mean healing time (days)	Phase of the study	Evolution of the protocol
1965	No loading	Initial stage	Implant design modifications, surgical protocol changes, negative selection of patients
1966	No loading		
1967	NA		
1968	84	Development stage	
1969	68		
1970	45		
1971	77		
1972	116	Routine stage	Definitive implant design, improved surgical and prosthetic protocols, negative selection of patients
1973	124		
1974	174		
1975	89		

NA, not applicable.

In 1980, the terms *contact osteogenesis* and *distance osteogenesis* were introduced by Osborn and Newesley[39] to distinguish the phenomenon of osseointegration based on different implant surfaces rather than in relation to biologic processes. Later on, Davies et al[6,40–47] conducted in vitro studies to explain the sequence of events that occur at the bone/implant interface.

In distance osteogenesis, the bone formation starts from the walls of the osteotomy: the cells with osteogenic potential lay a new bone matrix that surrounds the implant[47] (**Fig 1-6a**). In contact osteogenesis, the surface is colonized by osteogenic cells that deposit a bone matrix that extends from the implant to the walls of the surgical site[47] (**Fig 1-6b**).

Even if both processes lead to the deposition of new bone around the implants, the biologic process is different, and the role of implant morphology and implant surface is crucial in this regard. In fact, distance osteogenesis is more common with smooth surfaces, while both types of osteogenesis are present with rough surfaces.

According to Davies,[45] contact osteogenesis can be divided into the following three stages:

• Osteoconduction
• Formation of new bone
• Arrangement of the newly formed bone
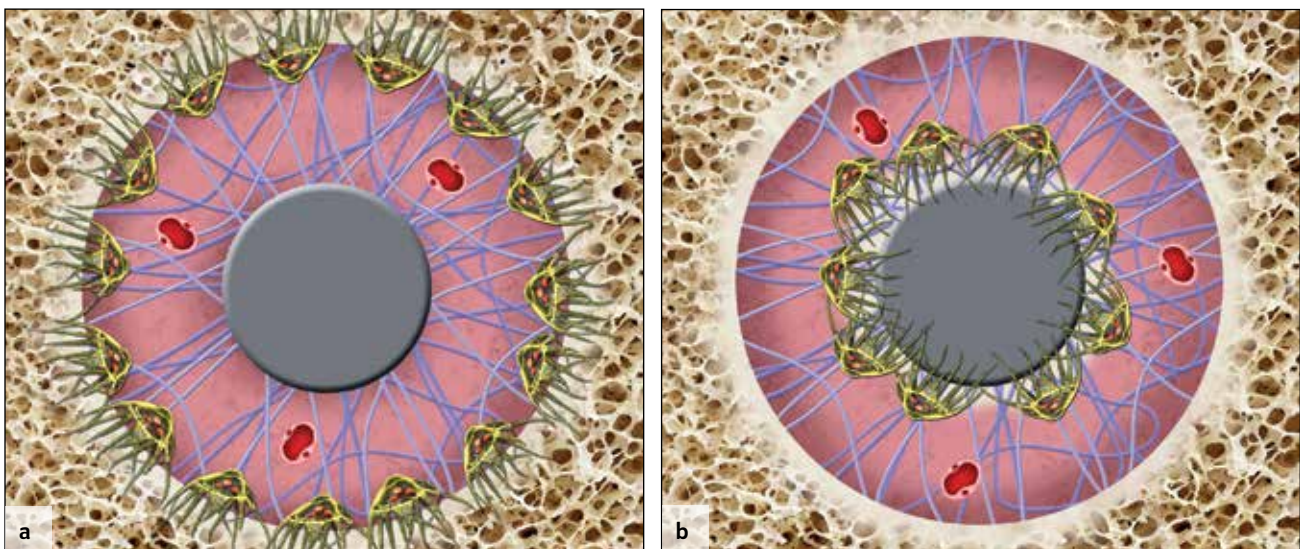
Fig 1-6 *(a)* Illustration of distance osteogenesis. *(b)* Illustration of contact osteogenesis.

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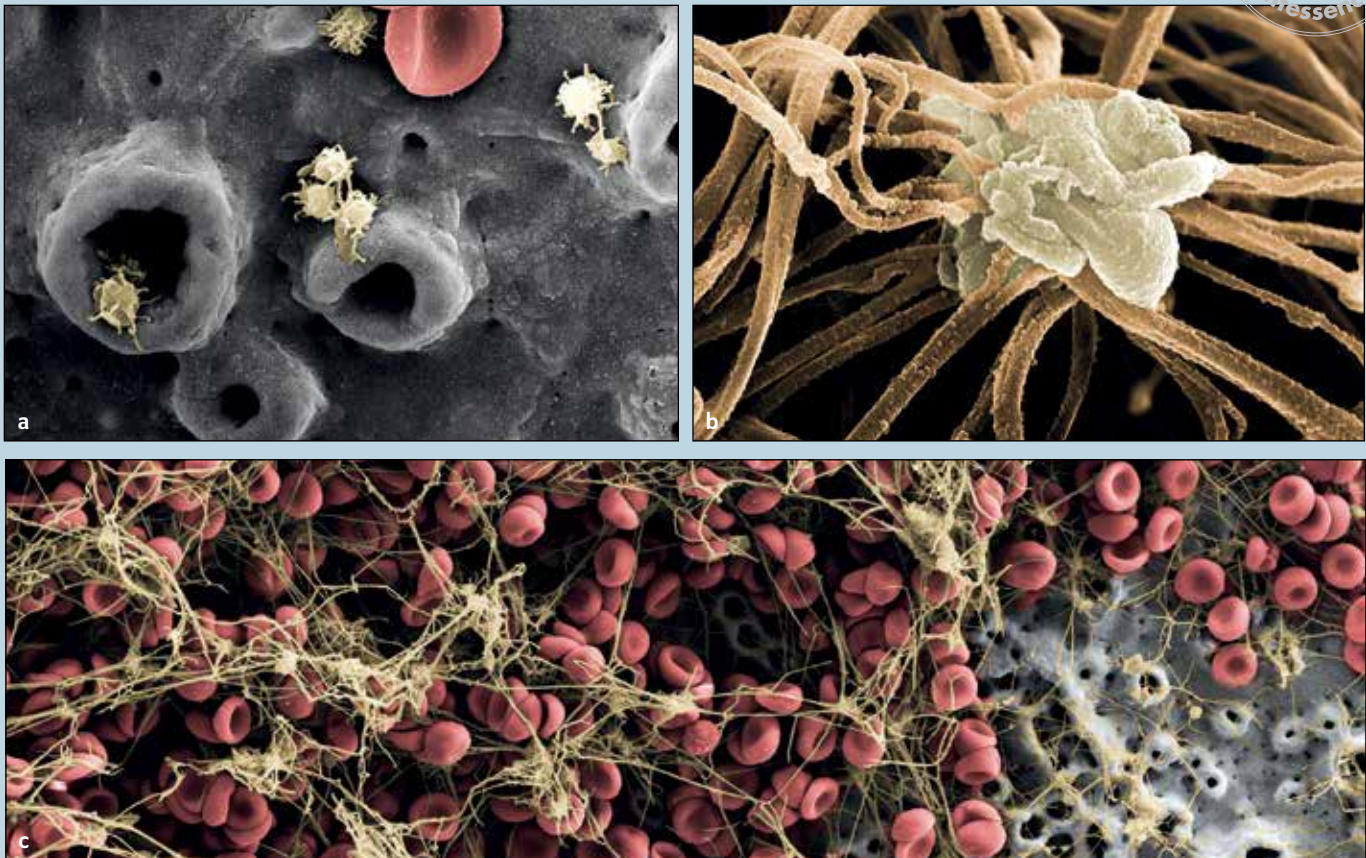
Fig 1-7 *(a to c)* Scanning electron microscope (SEM) images show the interaction between the TiUnite surface (Nobel Biocare), the red blood cells, and the activated platelets trapped in the fibrin network.
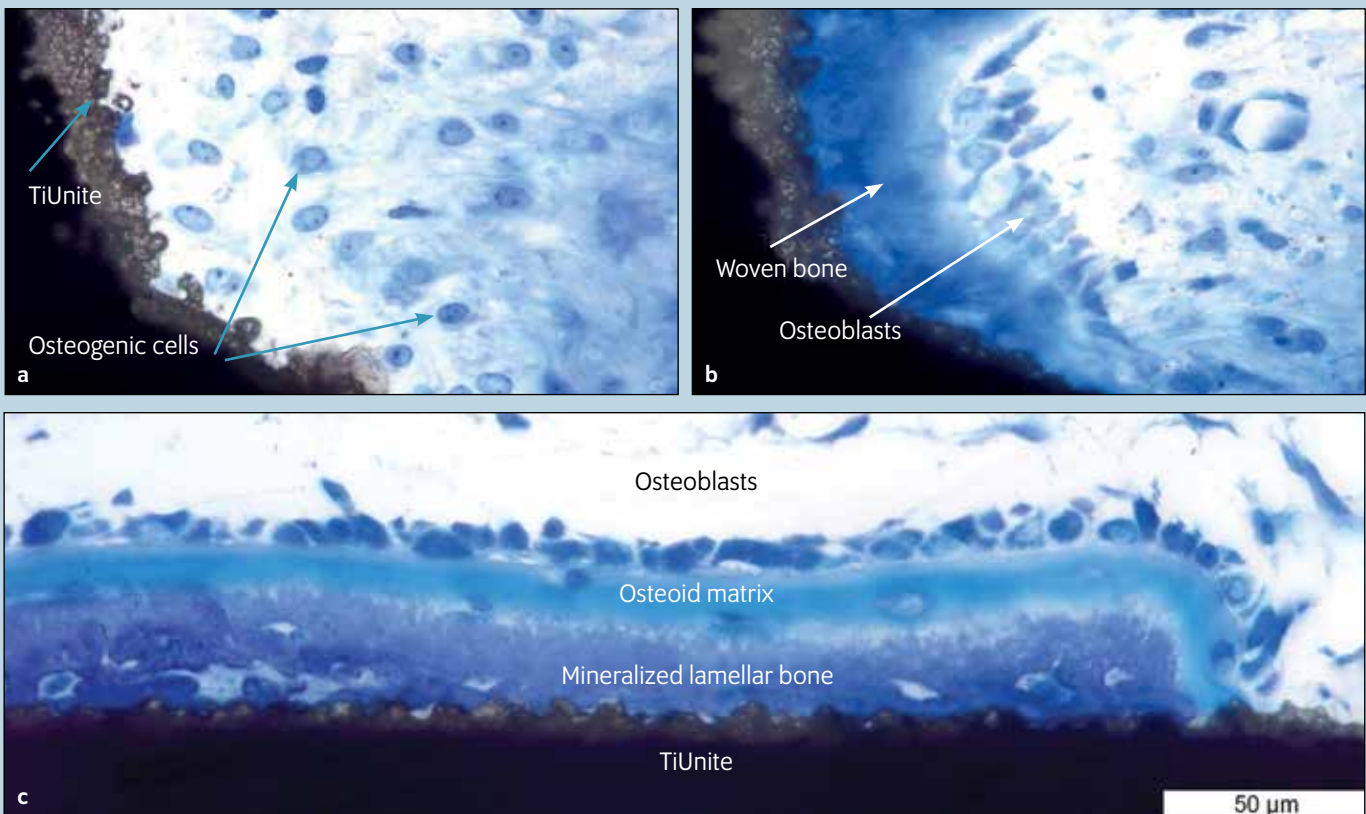
Fig 1-8 *(a to c)* The osteogenic cells make contact with the TiUnite surface and then migrate, producing an osteoid matrix. The newly formed bone is distributed on the osteoconductive surface, forming a thin band of trabecular bone. This thin layer will grow and through subsequent adaptations become lamellar bone. (Courtesy of Dr Peter Schüpbach, Langenthal, Switzerland.)
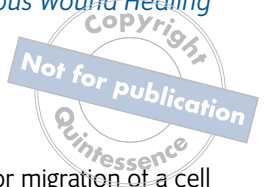
Osteoconduction

Osteoconduction is based on the migration of mesenchymal stem cells (MSCs) toward the surface of the implant. These cells are in the process of differentiation as they approach the osteogenic line, and they move through the fibrin clot formed in the surgical site between implant and bone.[45]

During the drilling phase, a small hemorrhage is produced in the microcirculation, and this initiates the coagulation process and the formation of a fibrin clot.[45] Furthermore, as a consequence of hemostasis, local ischemia will occur with necrosis of the bone component located no more than 0.1 mm from a capillary.[48] In the clot, leukocytes converge, attracted by chemotactic factors (eg, platelet-derived growth factor [PDGF] and transforming growth factor β [TGF-β]), thrombin, and products of tissue degradation.[49–52] Initially, a large number of neutrophils are present in the healing site, but macrophages soon become numerically predominant.[53] Cytokines play an important role not only in the resolution of inflammation, but also in wound repair[54]; PDGF can accelerate the mitosis of fibroblasts and bone cells, while TGF-β acts on the formation of collagen type I.[55–57] The first components that interact with the implant surface are proteins and other macromolecules present in the blood fluid, whereas the cellular component operates after this.[45,58] An implant with a rough surface promotes osteoconduction, first favoring the absorption and retention of macromolecules (especially thrombin and fibrinogen) and subsequently increasing the surface area available for the fibrin matrix to anchor.[59,60] Furthermore, the surface roughness affects the number and the activation degree of platelets as well as the level of adhesion of red blood cells[61] (**Fig 1-7**).

Cells with osteogenic potential and mature fibroblasts migrate to the implant, generating contraction forces and causing a reorganization and deformation of the fibrin matrix as well as wound contraction.[6] Macrophages and polymorphonuclear leukocytes have a negligible traction compared with platelets and fibroblasts.[6] If the contraction forces of the fibrin clot exceed the adhesive forces of the fibrin clot, this process may cause the clot to detach from the implant surface, resulting in a discontinuity that can slow the osseointegration process. Therefore, the retention of the clot by the implant is an essential prerequisite for the migration of osteogenic cells, and the microstructure of the implant surface has a very important role in the retention of the fibrin clot and preventing its detachment.[6,62] An in vitro study showed that there are no statistically significant differences in fibrin retention values passing from one surface treatment with mild airborne-particle abrasion up to a very aggressive etching, while there is a difference between a titanium plasma-sprayed surface and a machined surface.[47]

Formation of new bone

Bone formation requires the recruitment or migration of a cell population with osteogenic potential, and this population must also differentiate into mature cells that are able to secrete osteoid[47] (**Fig 1-8**).

Osteoblasts are the cells responsible for bone formation, and they have the following characteristics[63]:

- Osteoblasts are derived from osteoprogenitor cells of mesenchymal origin. They end their differentiation cycle as osteocytes.
- These cells have a high secretory capacity; they synthesize a matrix composed mainly of collagen type I and bone proteins, adjusting the mineralization of the matrix in a highly specialized tissue.
- Osteoblasts demonstrate autocrine regulation. They synthesize and deposit growth factors in the bone matrix and respond to these factors during repair and remodeling phases.
- Osteoblasts mediate systemic and local signals for the recruitment and activity of osteoclasts, which are involved in the processes of peri-implant bone repair and remodeling.

Before bone formation can begin, these cells have to face various stages[64]: recruitment, adhesion, proliferation, and differentiation.

Recruitment

It is essential that a sufficient number of osteoblasts reach the implant surface. These cells originate from the pool of mesenchymal cells of bone marrow and from cellular layers between the periosteum and the endosteum.[65] They are recruited through the direct action of cytokines on progenitor cells, particularly bone morphogenetic proteins (BMPs).[66–68]

Adhesion

The characteristics of each biomaterial (eg, the microscopic appearance of its surface, chemical composition, and surface energy) play a fundamental role in osteoblast adhesion, affecting the proliferation process and cell differentiation in proximity with the implant surface.[67]

The adhesion to a biomaterial consists of two stages: *(1)* a stage of aggregation that occurs rapidly and includes short-term events such as physiochemical bonds between cells and material (ie, ionic bonds and van der Waals forces); and *(2)* a stage of adhesion, which takes place over a longer period of time and
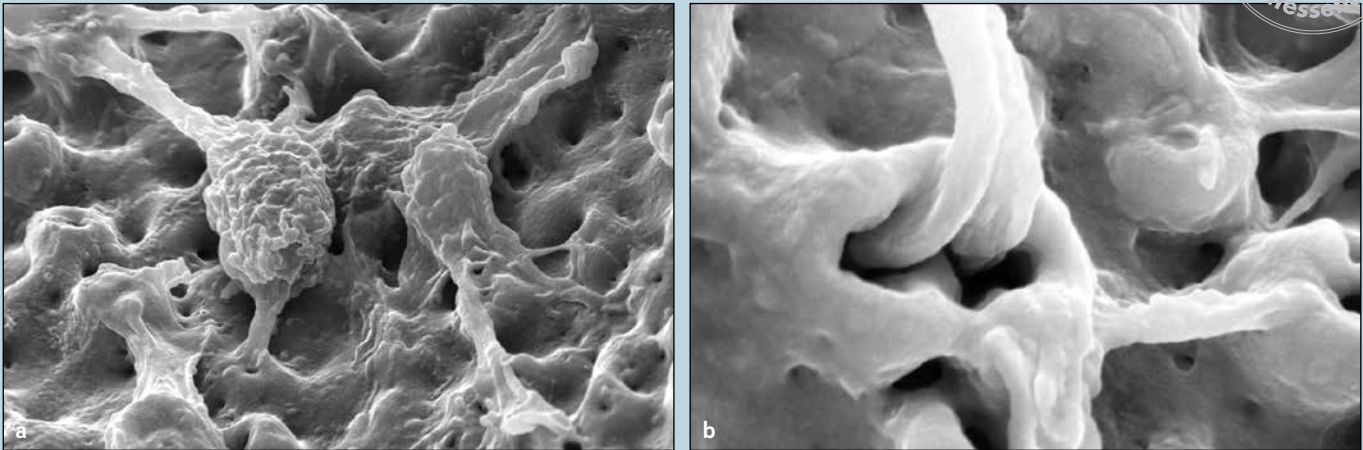
Fig 1-9 *(a and b)* The bone-depositing osteoblasts attach to the titanium surface using their pseudopodia and covering the orifices of the open pores. (Courtesy of Dr Peter Schüpbach, Langenthal, Switzerland.)

involves different biologic molecules, such as proteins of the extracellular matrix. These proteins interact with each other and induce translation signals to promote transcription factors and to regulate gene expression.[69]

Surface characteristics (eg, microstructure, surface chemistry, and free energy) also determine how biologic molecules will be adsorbed and in which orientation. This first contact between cells and material is allowed by these molecules, and this will affect the morphology of the osteoblasts and their capacity for proliferation and differentiation.[70] In the context of osseointegration, these bone matrix proteins are components of the bone/implant interface, and the cellular adhesion to the implant occurs indirectly via these proteins[71] (**Fig 1-9**).

Proliferation

Cellular proliferation is influenced by many factors. Among the main factors are cytokines and growth factors located around cells, hormones, growth factors present in the bloodstream, and physical or biochemical stimuli.[72,73]

Differentiation

Osteoblasts have to complete a differentiation process before producing bone matrix; these cells are required to acquire specific phenotypic characteristics of secreting cells.[74] Given a certain number of osteoblasts, from 65% to 85% are lost as a result of programmed cell death (ie, apoptosis), while only a small percentage survive and end their cycle as an osteocyte (14% in cortical bone and 29% in trabecular bone).[75] This differentiation

process is not spontaneous; evidence demonstrates that it is regulated by hormones, growth factors, cytokines, mechanical stimulation, and physical deformation.[76,77] The clot that is formed around the implant in the first hours after surgery will tend to mature over the following days, forming a granulation tissue that is rich in neutrophils and macrophages. The proliferation of small vessels and the production of growth factors by osteoid cells will allow the formation of connective tissue in the peri-implant area. Subsequently, the combined osteoclastic, fibroblastic, and osteoblastic actions will transform the connective tissue into an osteoid tissue, which will be replaced with the mature lamellar bone tissue after about 8 weeks.

The formation of new bone is divided into various stages, summarized as follows[6,43,47]:

1. Noncollagenic bone proteins absorb on the implant surface, especially osteopontin and bone sialoprotein along with proteoglycans.[46]
2. The first calcium phosphate crystals form, which begins the mineralization of the bone proteins.
3. A first mineralized state without collagen fibers is created that joins directly to the implant. This is called the *cement line*. It is about 0.5 µm thick and contains calcium, phosphorus, osteopontin, and bone sialoprotein.
4. The collagen fibers join the cement line to form a continuum with the marrow compartment. These fibers have no direct connection with the implant surface.[78]

The bone growth determined by an appositional process is regulated by polarized osteoblasts. As a result of matrix accumulation at their basal side, the cells passively drop out in a more apical direction. During the calcification process, osteoblasts succeed to migrate quickly and avoid being incorporated into the matrix; osteoblasts trapped in bone gaps are called *osteocytes*.[6,78]

Arrangement of newly formed bone

During the first postoperative weeks, the osteogenic response is high, with mitosis and differentiation of MSCs into osteogenic cells reaching its highest activity during the first 15 to 20 days. At first, woven bone tissue is formed with collagen fibers arranged in a completely random fashion, with low mineralization density and numerous irregularly organized osteocytes. The function of this immature bone is to restore the continuity between the walls of the surgical site and the implant surface. Its mechanical properties are lower than those of organized lamellar bone. The formation of woven bone allows for a bone anchor that corresponds to the biologic fixation of the implant; this process begins 10 to 14 days after surgery and is different from the primary stability, which is a purely mechanical fixation.[79]

The formation of new bone continues for another 6 weeks while the initial remodeling processes lead to a gradual adaptation of the newly formed bone. At 8 weeks, the neo-osteogenic activity is drastically reduced, while the remodeling and the morphostructural adaptation of newly formed bone reaches its peak. The bone tissue changes its structure, becoming more elaborate and acquiring a lamellar structure in addition to increasing its degree of mineralization[80–82] (**Figs 1-10** and **1-11**). 💬

Author's note

When biomechanical conditions stimulate the skeletal mass and the occlusal loads are properly distributed and transmitted to the implant, bone remodeling is initiated, leading to the formation of a lamellar bone layer along the entire surface of the implant.[81] The bone in contact with implant surface undergoes morphologic adaptation to stress and mechanical loading.[82] This is confirmed by the presence of medullary spaces containing osteoblasts, osteoclasts, MSCs, blood vessels, and lymph vessels. The remodeling region can be extended up to 1 mm from the implant surface (see Fig 1-10).[60,79]
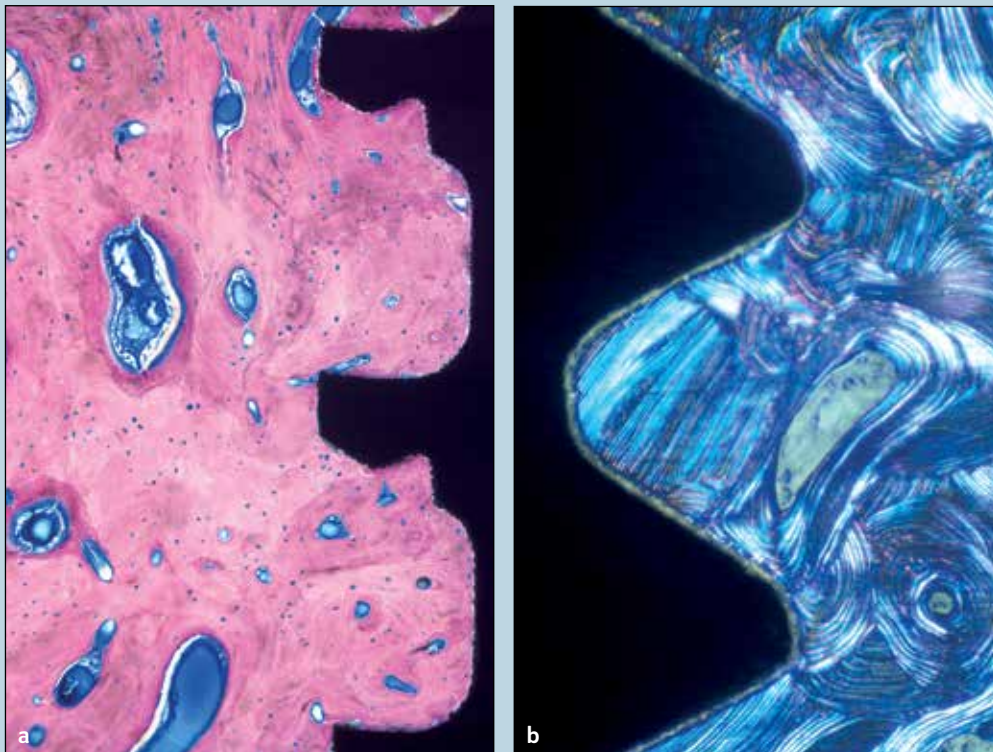
Fig 1-10 *(a and b)* Histologic and polarized light images show bone formation 6 months after implant placement. (Courtesy of Dr Peter Schüpbach, Langenthal, Switzerland.)
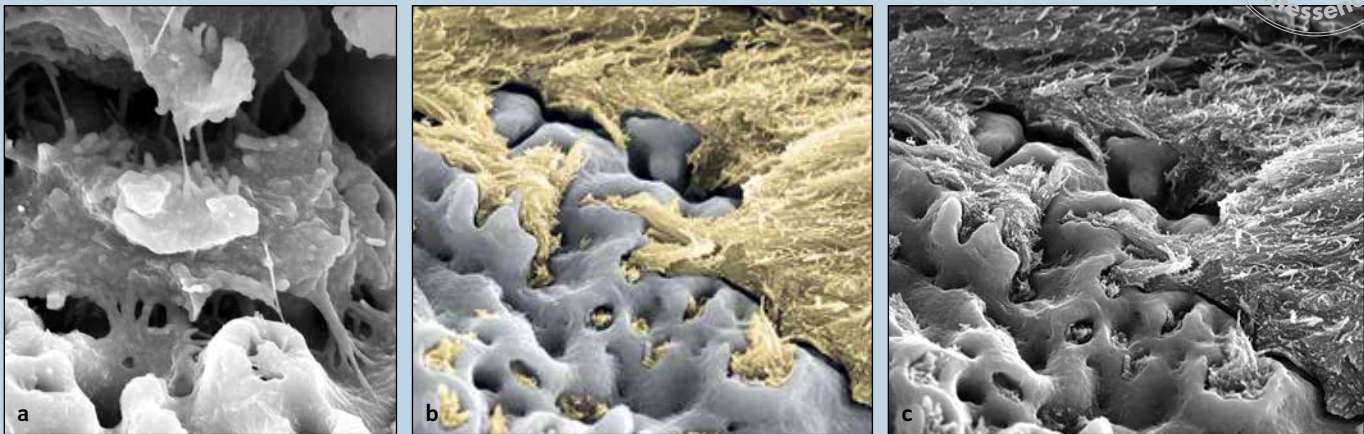
Fig 1-11 *(a to c)* Osteoconductive bone formation. The SEM images at 6 months after implant placement highlight the interaction between the newly formed bone and the TiUnite surface. The bone was removed to expose the implant surface. Note the presence of bone anchored in the orifices of the pores. (Courtesy of Dr Peter Schüpbach, Langenthal, Switzerland.)

Implant Morphology and Bone Healing Dynamics

It is known that the initial or primary stability is given by pure mechanical interlock between bone and implant without any biologic boundary.[83] 💬 The clinician generally evaluates the level of this primary stability based on the implant insertion torque. The torque, expressed in Ncm, reflects the stress level at the bone/implant interface added to the friction forces generated during seating.[34] It is generally assumed that the bone is an elastic tissue and that there is a linear relationship between implant stability and bone deformation.[34] In reality, stability decreases if microfractures converge into a macrofracture, and bone necrosis can be a consequence of vascular damage and ischemia.[84] Both microfracture formation and bone necrosis by compression are evident at different levels when there is a difference between the outer diameter of the implant threads and the inner diameter of the osteotomy drill.[33]

Author's note

Davies[45] described how the success of immediate implant loading is based on three factors: *(1)* obtaining primary stability, ensuring that the micromobility of the implant is avoided during and immediately after positioning; *(2)* having good secondary stability (commonly called *biologic stability*) based on osteogenesis in the peri-implant area; and *(3)* being able to control bone resorption resulting from abnormal forces that destabilize the implant during the healing period.

In a recent publication, Coelho and Jimbo[33] analyzed how the relationship between implant macrogeometry and osteotomy size could drive the osseointegration process. According to the authors, it is not advisable to achieve high levels of torque because the excessive deformation not only leads to a decrease in biomechanical stability, but depending on implant thread design, it may cause adverse biologic effects, resulting in a degree of bone compression.[33]

This type of scenario is well illustrated in an animal model (dog mandible) where an implant with V-shaped threads was placed in a site prepared with a drill with a diameter equivalent to the inner part of the threads.[33] The histologic image shows the continuity of the bone/implant interface, which represents a mechanical index of the connection between the two components, with a high level of primary stability within 2 weeks (**Fig 1-12a**). There are microfractures due to stress concentration at the tips of the threads and bone remodeling as a result of tissue necrosis. After 4 weeks, a remodeling area emerges due to the union of bone remodeling sites created after necrosis by compression and formation of microfractures (**Fig 1-12b**). In a time between 2 and 4 weeks, primary stability decreases because of bone resorption; the resorbed volume will be filled with new woven bone that will reestablish the contact with the implant surface (ie, secondary stability). According to this scheme of osseointegration that Coelho and Jimbo[33] define as *interfacial remodeling*, the bone that surrounds this type of implant is mature lamellar bone with few small marrow spaces.

By placing implants in sites made with a drill with a diameter equivalent to the external part of the threads, empty spaces were created between the implant and the osteotomy walls,
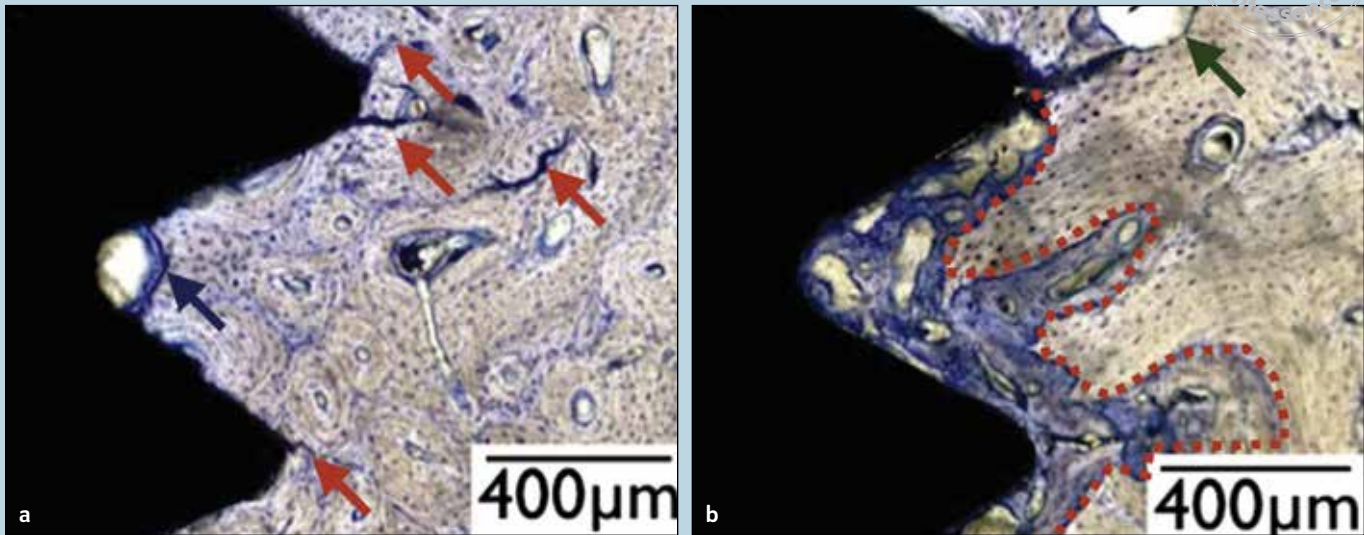
Fig 1-12 Optical micrographs of V-threaded implants placed in sites surgically instrumented to the inner diameter of the implant thread in vivo in a beagle dog model. *(a)* At 2 weeks in vivo, the almost continuous bone/implant interface reveals mechanical interlocking between components, which is responsible for primary stability. The *red arrows* depict microcracks at regions where the yield strength of bone has been exceeded due to high stress concentration; the *blue arrow* depicts initial remodeling taking place between the implant threads due to compression necrosis. *(b)* At 4 weeks, substantial remodeling has occurred at the interface, where cell-mediated processes resorbed the region encompassed between the *dashed line* and the implant. The *green arrow* shows a remodeling site at the extension of a microcrack. (Reprinted with permission from Coelho and Jimbo.[33])

leading to healing that is referred to as *intramembranous-like* healing.[58] These areas, called *healing chambers*, will be filled with a blood clot and will not contribute to primary stability but will play a key role in secondary stability.[85,86] In these healing chambers, the bone formation process begins according to a model of intramembranous ossification that results in direct bone formation on the implant surface without removal of necrotic bone. The woven bone will be replaced with lamellar bone that surrounds the osteons.[85] Although this model does not require high levels of primary stability, good fixation in the bone can be guaranteed by the implant apex. It is therefore possible to have a stable blood clot inside the healing chambers to start osteogenesis.[87,88]

Studies were conducted using implants with an external thread design to ensure primary stability while the internal part and the osteotomy size allows for the formation of healing chambers. In fact, there is no bone resorption in the healing chambers, but only the process of immature bone formation that can compensate for the loss of primary stability due to the bone compression zone located in the implant thread extremities.[89]

However, instead of altering the preparation of the osteotomy to accommodate the implant threads, it is better to have an implant morphology that promotes hybrid healing, with a thread design that ensures primary stability. This allows for a combination of compact lamellar bone structure (due to the interfacial remodeling) together with bone with a haversian-like structure due to the intramembranous-like healing. Currently, there are not many implants with this configuration, so there is no available long-term evaluation of this hybrid osseointegration model.[90]

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