Bone and Soft Tissue

Augmentation in Implantology

Fouad Khoury

Bone and Soft Tissue Augmentation in Implantology

With contributions from:
R. Gruber, Th. Hanser, Ph. Keeve, Ch. Khoury, J. Neugebauer, J. E. Zöller

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Foreword

The replacement of failed and missing teeth with dental implants is a common and well-accepted treatment modality. The success and long-term stability of dental implants is directly related to the quantity and quality of the supporting bone and surrounding soft tissue. When there is a lack of adequate bone volume for implant placement, a variety of bone augmentation procedures and materials have been proposed to develop the site. Although no single technique or biomaterial is optimal for every clinical situation, autogenous bone continues to be considered the gold standard of graft materials, and this text exemplifies this mantra.

Prof. Dr. Fouad Khoury is a world-renowned authority in the fields of oral surgery and dental implantology. He is a unique blend of gifted clinician and inspiring teacher. Prof. Khoury is Chairman and Director of the Privatklinik Schloss Schellenstein in Olsberg, Germany, and Professor in the Department of Oral and Maxillofacial Surgery at the University of Muenster.

Prof. Khoury is a skilled and exceptional surgeon who has dedicated his career to developing innovative techniques using autogenous bone for augmentation of the deficient ridge. His knowledge of bone biology spurred the development of the split cortical bone block protocol, often referred to as the ‘Khoury bone plate’ technique. This novel approach has been well proven as a very predictable method for the three-dimensional reconstruction of the maxilla and mandible. Prof. Khoury’s perspective on the importance of autogenous bone led to his development of other bone grafting procedures such as the bone core technique and the bony lid approach. His clinical philosophy has also stressed that successful bone augmentation requires impeccable soft tissue management.

This outstanding new book presents techniques for more routine treatment as well as some of the most challenging cases a clinician might encounter.

Prof. Khoury has assembled a team of respected academicians and expert clinicians to complete the text. A comprehensive understanding of bone biology is fundamental to developing a rationale for clinical decisions. Prof. Reinhard Gruber has done a wonderful job laying the foundation by explaining the biology of bone regeneration and the unique characteristics of autogenous bone. The book continues with clinical topics written by Dr. Thomas Hanser, Dr. Philip Keeve, Prof. Charles Khoury, Prof. Joerg Neugebauer, and Prof. Joachim Zoeller, including diagnosis and treatment planning, soft tissue management, autogenous bone harvesting, complex implant-supported rehabilitation, risk factors, and complications. The procedures are well documented in a clear and precise manner with high-quality photographs and extensive references. Many of the chapters address the interdisciplinary aspects of treatment, which is critical in managing more complex cases.

Prof. Khoury is one of the most generous and humble teachers I have encountered in dentistry. For decades he has not only thoughtfully treated patients but shared his vast knowledge and experience with students and clinicians around the world in classrooms and conferences. He has also been devoted to documentation and long-term follow up of his cases to scientifically support his philosophy of treatment. This text is just one example of his lifetime commitment and dedication to teaching.

It is been a distinct honor to get to know Prof. Khoury over the years as an esteemed colleague and friend. We have shared a similar perspective on the importance of autologous tissue for predictable augmentation and long-term outcomes.

I would like to thank and congratulate Prof. Khoury and his co-authors for their contributions and this achievement. This superb text will serve as an invaluable reference for students and faculty as well as clinicians in the treatment of their implant patients. We are indeed fortunate that Prof. Khoury and his team have shared their expertise in this new third edition.

Craig M. Misch, DDS, MDS
May 2021

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Foreword of the first edition

Implant dentistry has evolved into a highly predictable clinical procedure in routine cases where the available bone is of adequate height and width. However, this condition is not met by all of our patients. Yet even patients with an inadequate bone supply to support implants now want – even expect – improved function and better esthetics.

This superb textbook presents treatment techniques both for routine cases and for some of the most difficult cases a dentist is likely to encounter. Dr. Fouad Khoury is one of the elite clinicians in oral and maxillofacial surgery. He is a true talent. He is supremely knowledgeable about every clinical aspect of transplantation, and his approach is impeccably scientific. He is a rare blend of superb clinician and gifted teacher.

For this book, Dr. Khoury was able to enlist the assistance of a wonderful group of teachers and academics. They have done an excellent job of sharing their knowledge and experience. They have described their treatment procedures in a clear and precise manner, including extensive references at the end of each chapter. In addition, many of the chapters address the interdisciplinary aspects of treatment – which deserves particular praise, since too many clinicians tend to be locked into their own specialist's approach to their patients' problems. We should remember to take a step back now and then and look at a therapy as a unified whole, not just at a sequence of treatment steps, important as they may be.

Dr. Khoury is one of the most innovative surgeons that I know. For decades, he has been at the forefront of new and creative ideas to help his patients. He has also been kind enough to share these innovations with the rest of the world. This book is just one example of his lifetime commitment to teaching.

He and his co-authors are to be congratulated for this outstanding effort. It is the work of a lifetime put down on paper for all of us to look at, think about, and – most importantly – use in the treatment of our patients. By sharing with us their thoughts about what works and what does not, Dr. Khoury and his team have truly advanced the cause of dentistry. We are grateful and thank them for all of their hard work.

Dennis P. Tarnow, DDS
2006

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Preface

Oral rehabilitation supported by dental implants is today an important column of restorative dentistry. Since the first scientific-based publications in the early 1960s, many improvements in materials and techniques, especially in the augmentative field, have occurred. Increasing patient demand for perfect esthetic and functional rehabilitations, even in difficult anatomical situations, has led to the development of different methods that today allow for the fulfillment of almost all patient desires for a restoration that not only mimics the original anatomical situation, but gives an even better long-term result.

During the past 30 years, different techniques and materials have been recommended for the reconstruction of alveolar defects such as autogenous, allogenic or alloplastic bone grafts. Although the actual evolution of allogenic, xenogenic, and alloplastic materials, in combination with guided tissue regeneration techniques, is progressing from day to day, reproducibility and predictable long-term prognoses are still limited in comparison with autogenous bone, which is still the gold standard. The main problem of xenografts and allografts, especially in block form, is their poor ability for revascularization. This leads to several early as well as late complications and failures in the contaminated oral cavity.

Compared with other bone substitutes, the superiority of autogenous bone has been demonstrated on a biologic, immunologic, and even medicolegal basis. Due to graft morphology, autogenous bone has additional mechanical (cortical) and osteogenic (cancellous) properties, allowing early revascularization and functional remodeling, with low complication rates that are unequalled by any allograft, xenograft, or alloplastic material.

Through better understanding of the biologic processes of bone healing, including cell interaction, vascular supply, and bone remodeling, and in combination with some modifications of the surgical procedures, it is possible today to offer an implant-supported restoration to almost all patients. Alveolar bone is reconstructed in a safe and reproducible manner, even in cases of severe bone loss, so that, following prosthetic planning, a secure and correct implant insertion can be performed. Long-term results of such implants inserted in regenerated bone are providing similar success rates to implants inserted in non-grafted bone.

Different techniques and modifications for augmentation with intraorally harvested bone grafts have been developed over the past three decades with predictable long-term results. These techniques cover almost all situations, starting with a minimally invasive approach with locally harvested bone grafts up to the extremely complicated 3D reconstruction of the whole maxilla and/or mandible.

This is the third book I have edited on bone augmentation in oral implantology. The first one was published in 2006 in English, and the second came out in 2009/2010 in more than 10

languages. In this new edition on bone augmentation and soft tissue management in oral implantology, the focus is principally on the techniques that were developed and modified at our hospital over the past three decades and documented long term by our team.

The first chapter deals with the biology of bone healing especially after grafting procedures, and the second with descriptions of diagnostics and treatment planning. Soft tissue management in combination with bone augmentation is a very important topic with a great influence on the success of the grafting procedure. For this reason, the third chapter plays an exceptional role in the new edition, with important step-by-step details of the different techniques. The central topic and most important part of the book is, of course, the fourth chapter on safe bone harvesting and predictable grafting procedures for all kinds of bone deficiencies, starting with minimally invasive techniques for augmentation of small bony defects up to the extensive bone augmentation of severe 3D bone loss. All the techniques are demonstrated step by step with numerous clinical images, allowing a good and easy understanding of the described methods. Documented long-term results of the different techniques, up to 27 years postoperatively, are presented as they appear, with both radiographic and clinical images. The book contains a special chapter with the focus on our restorative concept for the treatment of patients with complex restorations in combination with extensive bone grafting procedures, which also explains the procedures step by step, from the temporary until the definitive restoration. The last chapter discusses the possible risks and complications, in combination with the grafting procedures explaining how to deal with such risks as well as the possibilities of how to prevent or to treat complications.

In this new edition I would like to present our clinical knowledge based on biologic principles as well as our long-term experience, for those interested in extending their clinical skills and scientific background in order to offer their patients the best possible treatment in terms of bone and soft tissue augmentation.

Acknowledgments

Firstly, thank you to all my contributors for their excellent cooperation and the high quality of their work. In addition, I would like to thank all my alumni, not only for their help in the treatment of complex cases but also in the precise documentation of the long-term results, including superb-quality clinical images. In particular, I would like to single out my co-worker, Dr. Thomas Hanser, for his friendship and unwavering loyalty. Over the past 26 years I have had about 38 postgraduate students and residents from different countries following our oral surgery program. These alumni as well as the actual co-workers and residents are: Dr. Friedrich Pape (head of the Restorative Department in Olsberg and responsible for most of the prosthetically treated cases presented in this book), Dr. Frank Spiegelberg, PD Dr. Arndt Happe, Dr. Alessandro Ponte (Turin, Italy & Lugano, Switzerland), Dr. Klaus Engelke, Dr. Stefan Bihl, Dr. Frank Berger, Dr. Jochen Tunkel, Dr. Luca de Stavola (Padova, Italy), Dr. Pierre Keller (Strasbourg, France), Dr. Herman Hidajat, Dr. Jenny Schmidt, Dr Şerif Küçük, Dr. Frank Zastrow, Dr. Joel Nettey-Marbel, Dr. Ayoub Alsifawo (Libya), Dr. Alexander Friedberg, Dr. Ingmar Braun, Dr. Stefano Trasarti (Teramo, Italy), Dr. Romain Doliveux (Lyon, France), Dr. Marco Vuko Tokic (Croatia), Thuy-Duong

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Finally, the most important thanks are for my wife, Michaela, and my children, Chantal, Elias, and Chérine, for their love, great support, and endless understanding.

Fouad Khoury
Olsberg, Easter 2021

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Biology of bone regeneration in augmentative procedures

Reinhard Gruber

1.1 Introduction

Regenerative dentistry critically depends on the functional understanding of bone biology – to be precise, bone development, bone modeling and remodeling and bone regeneration – in a physiologic but also in a pathologic and pharmacologic context. Bone biology also describes the cellular and molecular regulation behind Wolff's law (form follows function), which was later refined by Frost's Mechanostat theory.[44] Bone biology is a molecular and cellular system that is essential for mammalian evolution. Besides being a framework connecting to tendons and muscles and for protecting the bone marrow, the skeleton is a storage for calcium and phosphate that is transported via the umbilical vein and later through the mother's milk into the fetus and newborn. Understanding the delicate interplay of bone-

forming cells and bone-resorbing cells – which act in concert with the osteocyte located within the bone matrix, the blood vessels providing support for the respective progenitors, and the cells originally dedicated to the immune system – provides one part of the information necessary for progress in medicine.

The concert has to be orchestrated, which is, in the context of bone biology, the cell-to-cell communication involving the classical path. This path can roughly be divided into local and systemic regulation. Local regulation includes cell communication via cytoplamatic connections or the release of signaling molecules, with particular receptors on the respective target cells. Systemic regulation refers to the endocrine system, whereby hormones or growth factors are released and transported via the bloodstream to target cells elsewhere in the body. It is fascinating to imagine all the different levels – molecular, cellular, tissue, and organ – to be coordinated, with the same aim of homeostasis. In a broader sense, not only does homeostasis maintain the tissue (which would be bone remodeling), it is also the mechanism to regain homeostasis after injury, thus bone regeneration. However, the delicate cellular and molecular mechanisms aiming for homeostasis are sensitive to change; for instance, the drop of steroid hormones during menopause, which causes not only enhanced but also disbalanced bone remodeling and ultimately leads to bone loss and postmenopausal osteoporosis. The mechanical integrity, particularly of the trabecular bone, is rapidly impaired, and fragility fractures of the vertebra and the hip become clinical hallmarks of the disease.[107] Postmenopausal osteoporosis is but one example of how bone homeostasis undergoes a catabolic shift that, together with age-related changes, leads to a progression of bone loss over time.

The main focus of this chapter, however, is to provide an explanation of autograft consolidation, and to discuss the clinical success of this therapy at the molecular and cellular levels. With an emphasis on bone augmentation, the chapter is intended to supplement the essential information on bone regeneration that has been obtained from histologic and biomechanical analyses.

It is a well-accepted fact that osteoblasts form the bone[40] and osteoclasts resorb it.[12,121] The osteocytes are important in that they are the masters of regulation in bone remodeling.[33] The blood vessels are also important as they serve as a source of renewal and, in particular, as a transport medium for the precursor cells of osteoblasts and osteoclasts;[78,134] they are also key in terms of inflammation, and are therefore relevant in pathologic conditions such as inflammatory osteolysis.[55,84] In this context, classical questions are addressed in the chapter, such as the evidence that autografts are considered “osteoconductive, osteogenic and osteoinductive,”[98] and the possible mechanisms of graft resorption.

1.2 Cells of bone remodeling

Three cell types are characteristic of bone tissue and are responsible for bone formation, maintenance, remodeling, and repair. However, bone biology and bone metabolism comprise

a complexity of interactions involving many factors, including growth proteins and many humeral messages and events that are not described in this chapter. One main goal of the chapter is to provide an update on the essential activity of the bone-forming cells (osteoblasts) and the bone-resorbing cells (osteoclasts), with special attention paid to the osteocytes and their important role in the maintenance of bone structure.

1.2.1 Osteoblasts

These cells originate from pluripotent mesenchymal stem cells through the activation of a series of transcription factors[62] partially involving members of the bone morphogenetic protein superfamily.[81,99] Osteoblasts are present in layers on the bone surface. In all active bone-formation sites, they are responsible for extracellular matrix production (osteoid) and subsequent mineralization. Osteoblasts are polarized cells with a mineral-facing side through which the matrix is extruded. Once osteoid production stops, some osteoblasts are trapped in the extracellular matrix and differentiate into osteocytes, which are located in the bone lacunae. On the one hand, neurocranial bones,[21] including the mandible (except the mandibular condyle) and maxilla as well as part of the clavicle, are formed by membranous ossification. This is a direct ossification without a cartilaginous phase, where differentiated osteoblasts lead to osseous matrix formation through mesodermal and ectomesodermal cellular condensation. On the other hand, the appendicular and axial skeleton follows an endochondral ossification route. A temporary cartilaginous scaffold is produced by chondrocytes, which mature and hypertrophy in a second stage. In a third stage, this cartilaginous matrix becomes mineralized. Finally, a vascularization is established that allows, at first, the arrival of osteoclasts (or chondroclasts), which lead to the resorption of the calcified cartilaginous matrix and, following that, the differentiation of osteoblasts that will replace the cartilaginous scaffold by a bony matrix. This matrix will lead to the formation of the trabecular structure of the long bones.[91]

Osteoblasts can produce three types of bone: woven bone, primary parallel-fibered bone, and lamellar bone. The difference between these bone types is related to the orientation of the collagen fibrils: In woven bone, the fibrils are three-dimensionally and randomly distributed due to the rapidity of osteoid deposition and mineralization (Fig 1-1). Compared with mature lamellar bone, this bone is more elastic and mechanically less consistent due to the low level of mineralization and the lack of a specific orientation of the collagen fibers. In adults, this type of bone is produced during healing processes, and it is the only bone able to grow in the absence of a pre-existing mineralized tissue. Woven bone forms ridges and roots between and around the blood vessels (Fig 1-2). Primary parallel-fibered bone is characterized by a more parallel distribution of the collagen fibrils, and is typically produced during periosteal and endosteal bone apposition. The mechanical properties are as weak as those of woven bone. Lamellar bone is a well-organized mineralized tissue. Collagen fibrils are distributed in parallel layers that have a thickness of 3 to 5 µm. Osteoid production is slow (1 to 2 µm per day) compared with woven bone, and it takes about 10 days to be mineralized at a well-defined mineralization front. Lamellar bone needs a pre-existing bone surface to be produced by osteoblasts, which means that, unlike woven bone, it is not able to bridge gaps.

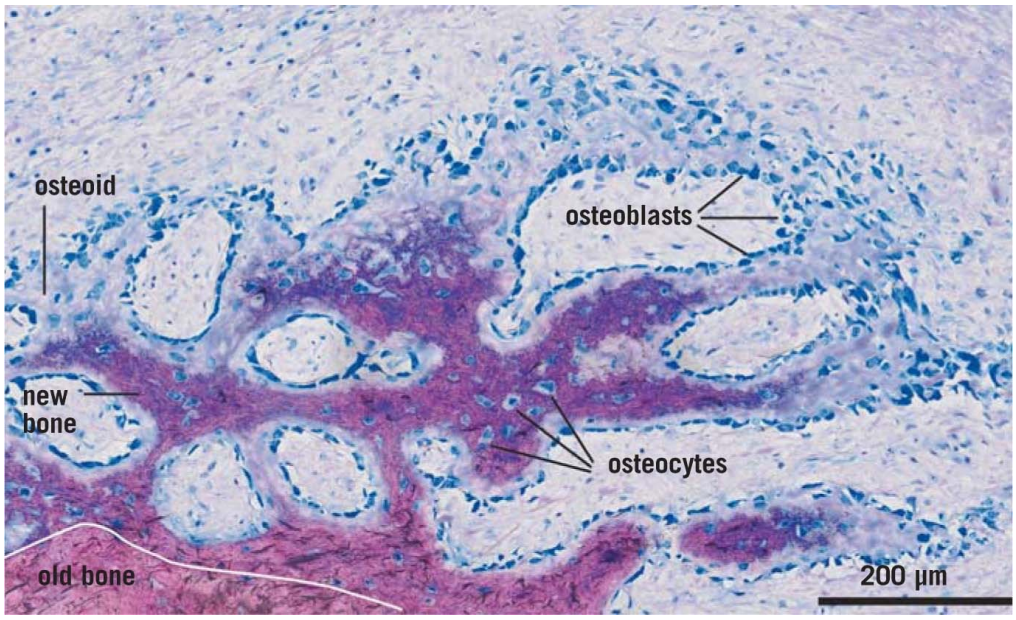

Fig 1-1 Osteoblasts produce bone on the surface of a host bone. Bone formation occurs on the surface of existing bone (pink). New bone (dark purple) is lined by seams of osteoblasts and arranged in osteonal structures. Osteoid (barely stained) is bone that is not yet mineralized. The direction of new bone formation can be anticipated by the sprouting of extension into the defect area. [The image is of pig bone.]

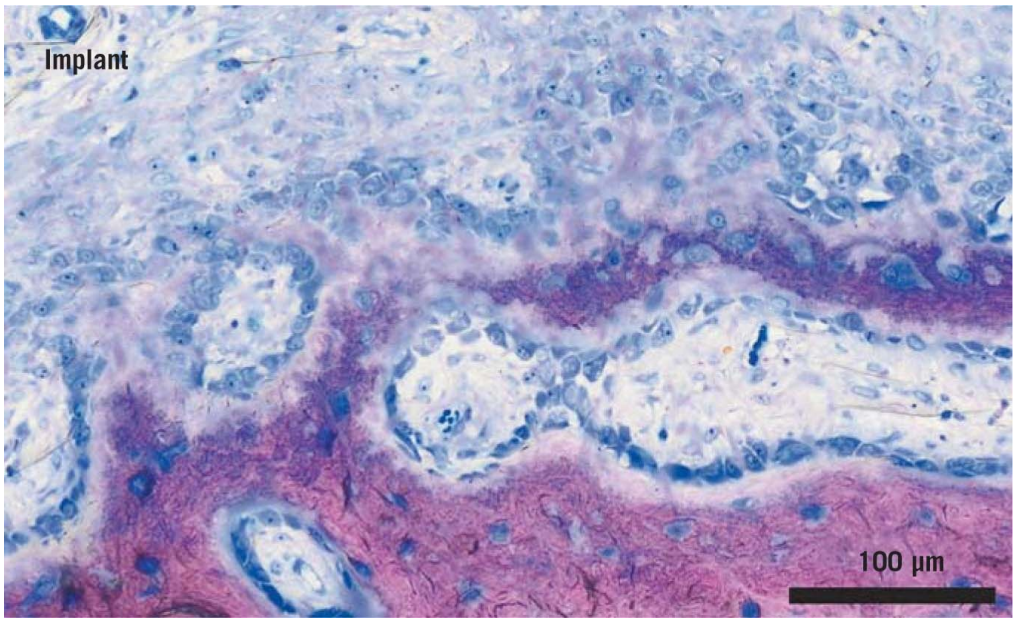

Fig 2-1 Osteoblast seams during the early stages of bone formation. Bone formation is the consequence of osteoblast activity. Osteoblasts dominate the scene, and non-mineralized bone (osteoid) is visible. [The image is of pig bone.]

When not active in osteoid production, osteoblasts can differentiate into bone-lining cells. This particular conformation determines a flat distribution of osteoblasts over the bone surface, creating a barrier-like layer between the bone and the extracellular space that seems to be responsible for ion exchange. The bone lining cells may also be responsible for bone resorption through two mechanisms: the first is determined by cell contraction and subsequent bone surface exposition; the second is defined by the direct secretion of osteoclast activating factors.

1.2.2 Osteocytes

Osteocytes are characterized by a slower metabolism than osteoblasts and present elongations of the cytoplasmic membrane that connect osteocytes to each other and to the surface cells through gap junctions, creating a three-dimensional canalicular network in the mineralized tissue that is particularly impressive in the osteons (Fig 1-3). The diffusion of nutrients and ions, otherwise impossible, is guaranteed by this cell network. A limit in diffusion through the canalicular system exists, which is approximately 100 µm. This is also the mean wall thickness of osteons in the cortical bone and also the packets in trabecular bone. The osteocytes, which control the effector cells (the osteoclasts and osteoblasts),[7,10,33] require a long lifespan because they are embedded in lacunae within the mineralized matrix, and are connected via dendritic processes that run through the canaliculi. The dense, interconnected network that spans the entire skeleton also connects to blood vessels and to the cells on the bone surface, e.g. the lining cells, osteoblasts, and osteoclasts. As recently summarized,[15] 1 mm^3 of bone contains about 20,000 to 30,000 osteocytes, each having 100 dendritic processes and a radius of approximately 70 nm. Around 40 billion (10^9) osteocytes with 20 trillion (10^{12}) connections and a total length of dendritic processes of 200,000 km can be calculated for the entire skeleton. The surface area and the volume of the lacuno-canalicular network are around 200 m^2 and 40 cm^3, respectively. Osteocytes are not only interconnected via their dendritic processes but are surrounded by a liquid that connects them to the overall circulation. Osteocytes are obviously predestined to control bone homeostasis at the local and systemic levels. For example, osteocytes are the cells that almost exclusively produce sclerostin, an inhibitor of the Wingless-related integration site (Wnt) signaling pathway.[129,130] The molecular function becomes obvious when one considers bone overgrowth, including the jaw and facial bones of sclerosteosis and van Buchem disease, which are caused by the loss of sclerostin expression and secretion, respectively.[128,130] Mouse models lacking sclerostin also display systemic high bone mass, and increased alveolar bone and cementum.[77,82] Osteocytes are also a main source of RANKL required for physiologic bone remodeling and in pathologic situations, including ovariectomy,[45,94] secondary hyperparathyroidism[140] or glucocorticoid excess.[92] Mice lacking osteocyte-derived RANKL even resist the bone loss caused by tail suspension.[93] Recently, osteocyte-derived RANKL was considered relevant in inflammatory osteolysis[51] and orthodontic tooth movement.[109] Thus, osteocytes control bone formation and bone resorption during good health and during disease, including their expression of sclerostin and RANKL.

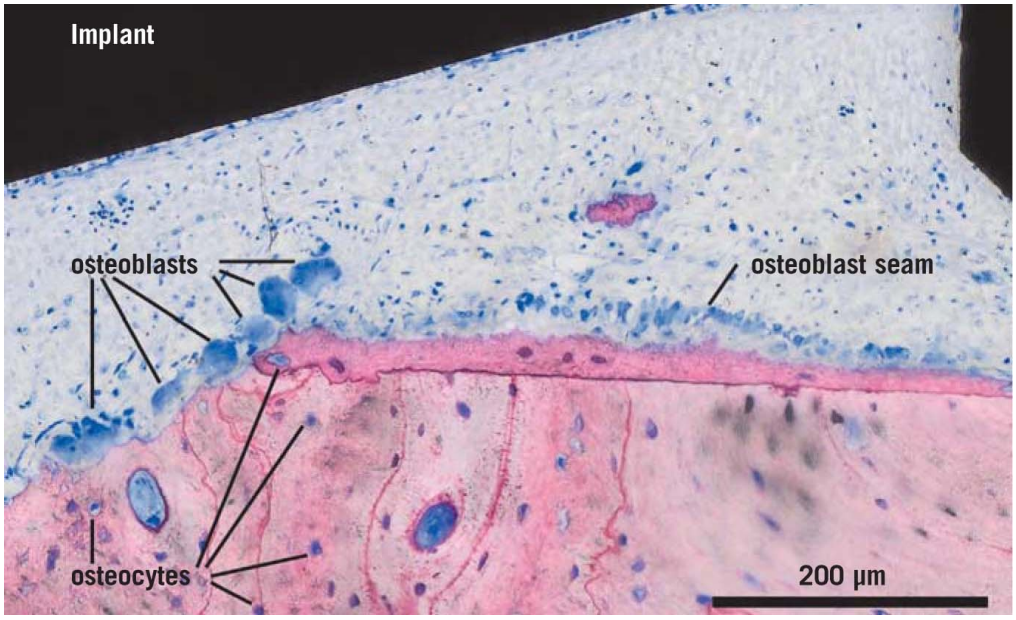

Fig 3-1 Osteoclasts (boneresorbing cells), osteoblasts (bone-producing cells), and osteocytes. Osteoclasts are multinucleated cells that are exclusively capable of resorbing bone. In this image, which is a detail taken from Fig 1-7, a group of osteoclasts is resorbing bone next to a seam of osteoblasts, which are producing new bone. An osteoid seam is visible below the osteoblasts. Osteocytes are embedded in the bone. [The image is of pig bone.]

1.2.3 Osteoclasts

Osteoclasts and osteoblasts are partners in the bone remodeling process – osteoblasts are the bone-building and osteoclasts the bone-resorbing cells (Fig 1-4a and b). Osteoclasts are therefore specialized in the breakdown of calcified tissue. Hematopoietic cells, particularly those of the monocyte lineage, are the pool of progenitors that have the potential to become osteoclasts; otherwise, they develop into macrophages or dendritic cells with a focus on the immune system. The molecular signature to drive osteoclastogenesis was discovered almost two decades ago, with the introduction of the RANKL-OPG system, the agonist, and the respective antagonist.[23,61,118] Mouse models that lack RANKL[73] or the respective receptor RANK[38] develop severe osteopetrosis, indicated by the lack of a bone-marrow cavity and non-disrupted teeth. In contrast, mice lacking RANKL-OPG acquire a fulminant osteoporosis.[14,111] RANKL was considered the ‘bottleneck’ of osteoclastogenesis. Mature osteoclasts are characterized by the sealing zone that sticks the osteoclasts to the mineralized bone surface, surrounding that extensively folded ‘ruffled border,’ where the protons (to lower the pH) and the proteases (to digest the collagen, mainly cathepsin K) are transported into the space facing the naked bone matrix.[121] Osteoclasts are considered to be of “great beauty”[18] and are not simply “bone eaters”[27] as they contribute to bone formation and also interact with the hematopoietic system, including the stem cell niche and adaptive immune cells.

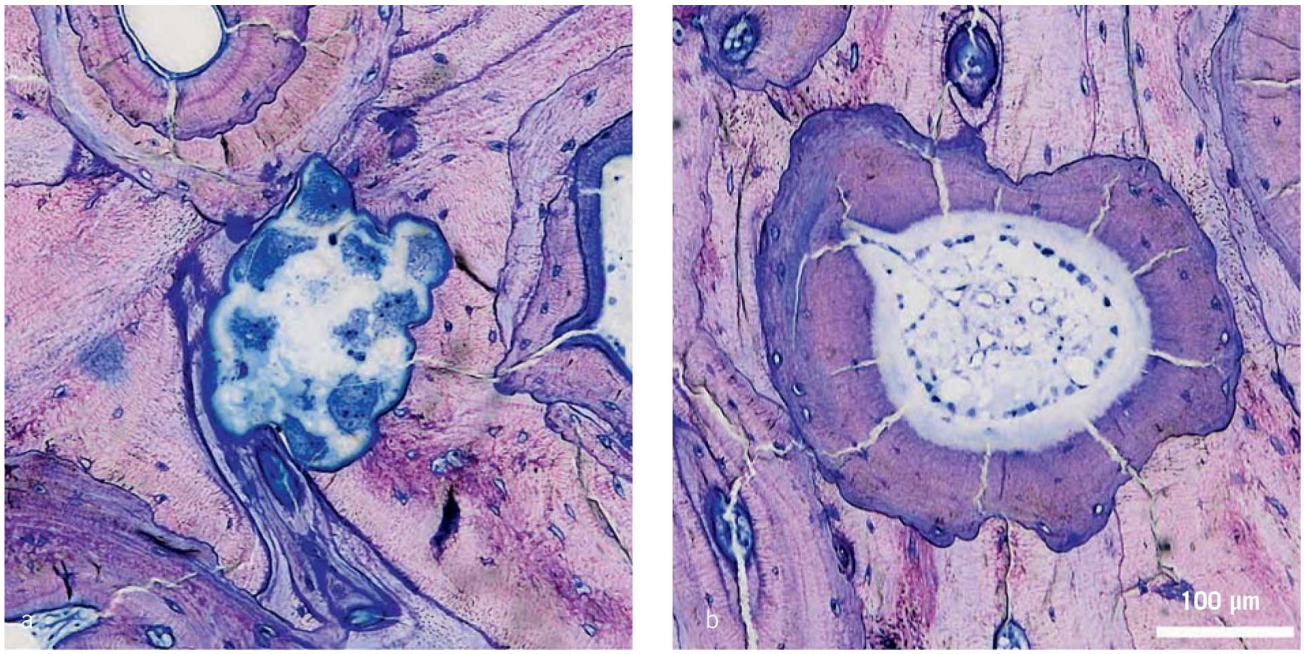

Fig 1-4 Creation of osteons by basic multicellular compartments (BMU). The BMU defines the site of bone remodeling. (a) Tunneling of cortical bone by multinucleated osteoclasts. (b) This image is characteristic for the activity of bone forming osteoblasts with an osteoid layer, rebuilding the concentric structure of osteons. [The image is of pig bone.]

The main physiologic function of osteoclasts is to participate in bone remodeling. Localized in Howship's lacunae, which represent the active resorption sites on a bone surface, osteoclasts are indicated as multinucleated cells staining positive for tartrate-resistant acid phosphatase. The acidophil cytoplasm contains vacuoles, which indicate resorption. In trabecular bone, osteoclast resorption does not usually exceed 70 µm before a team of osteoblasts fills the space with new bone. Howship's lacunae are part of the bone remodeling compartment (BRC) canopy.[35] In cortical bone, however, the basic multicellular unit (BMU) defines the site of bone remodeling.[106] Here, osteoclasts produce a tunnel in the cortical bone that is closed in concentric layers of new bone by the bone-forming osteoblasts with a blood vessel in the center, culminating in the characteristic histologic picture of the osteons in a transversal section (Fig 1-5). Even though the two remodeling compartments are not identical in structure, there is the common principle of the coupling: when osteoclastic bone resorption has ceased, osteoblastic bone formation is initiated. Preosteoclasts are not only important for bone renewal and remodeling but also for bone revascularization,[137] thereby possibly supporting the sprouting of blood vessels at the site of bone regeneration.

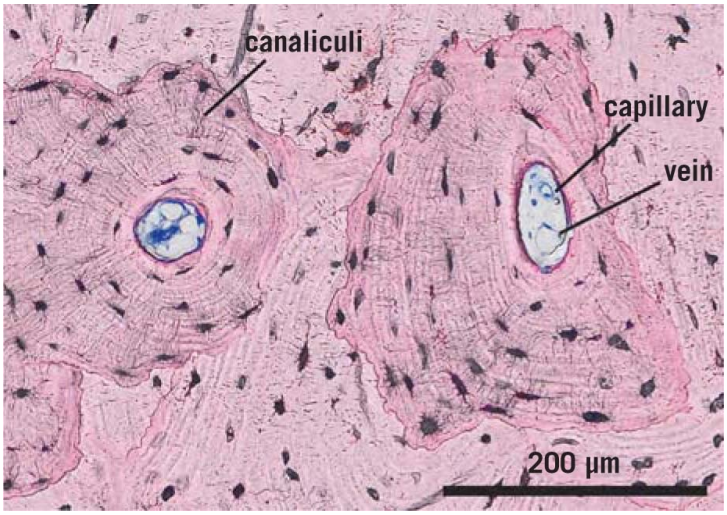

Fig 1-5 Osteon with osteocytes being connected via their canaliculi. The osteon is a functional bone unit consisting of a central canal filled with soft tissue, with bone lamellae arranged concentrically around it. They can be found in the substantia compacta of the bone. Osteocytes are interconnected via canaliculi. They are in contact via canaliculi with the lining cells in the central channel. [The image is of human bone, from an implant extraction.]

1.3 Biology of bone regeneration

Bone regeneration is another important aspect of bone biology. Bone regeneration works perfectly in the sense that no scar tissue is formed, which contrasts with the classical skin wound healing in adults, where the defect is left with a matrix rich in collagen but poor in cells. This is summarized in excellent reviews on bone regeneration, particularly in fracture healing[30,42] and wound healing.[90,113,143] Both events start with the formation of a blood clot, where the coagulation cascade of proteases culminates in the formation of thrombin, which cleaves fibrinogen. The fibrin itself assembles into a transient extracellular matrix, where platelets are activated and form aggregates, together with erythrocytes. Growth factors and other molecules are released, attracting neutrophils into the blood clot to clean the defect site. Macrophages appear later in the blood clot. To make space for the granulation tissue, which is characterized by the sprouting of blood capillaries into the new tissue and the concomitant appearance of fibroblastic cells, fibrinolysis is initiated. The invading cells release activators for plasminogen being stored in the blood clot – it is plasmin that cleaves the fibrin matrix. Interestingly, mouse models lacking fibrinogen allow bone regeneration,[141] while those lacking plasminogen show impaired bone regeneration.[64] These findings highlight the importance of fibrinolysis over the formation of the fibrin matrix.

Mouse models have also helped in the understanding of the importance of macrophages in bone regeneration, as they were shown to be in wound healing, early on. The depletion of macrophages and the genetic modification of the cells to erase their activity culminate in impaired bone regeneration, including intramembranous ossification, which is the more relevant path in regenerative dentistry compared with the endochondral ossification that is typically observed in fracture healing.[95,135] However, the role of macrophages is not

restricted to a defect situation. For example, macrophages form a canopy structure over mature osteoblasts during bone remodeling, suggesting that they interact via juxtacrine and a paracrine mechanism that remains to be fully elucidated.[25] The clinical implication of this fundamental principle in regenerative dentistry is unclear, but it opens a wide arena for research that may involve biomaterials. Mouse models have also provided evidence that at least a transient inflammation is required for bone regeneration, as, for example, the knockout of TNFα[24,48] and COX-2[142] caused impaired bone regeneration. Moreover, in bones lacking bone morphogenetic protein 2 (BMP-2), the earliest steps of fracture healing seem to be blocked,[125] and it is possible that the local inflammation controls the expression of BMP-2, at least in vitro.[46] To what extent macrophages are involved in the inflammation required for bone regeneration has not yet been investigated. Also, here, the clinical relevance of these observations should be interpreted with care. For example, painkillers should not be a great concern in regenerative dentistry as they do not completely block cyclooxygenases and are only used temporarily.[49] Bone regeneration is not influenced or jeopardized when inhibitors of TNFα are used,[122] as in a situation of chronic inflammation, including rheumatoid arthritis and colitis ulcers. Thus, findings from the extreme situation of a gene knockout or enhanced expression in mouse models should be interpreted carefully in the clinical context.

Mouse models also support the role of BMP-2 during bone regeneration.[125] Molecular screening approaches have revealed a long list of growth and differentiation factors that are differentially expressed during bone regeneration, in particular fracture healing, that play a major role in bone formation.[54] For example, BMP-4[126] and BMP-7[127] have no effect on fracture healing, but Wnt signaling is crucial for bone regeneration, based on observing with a sclerostin antibody and sclerostin knockout models.[4] The Hedgehog signaling pathway also plays a critical role in osteoblasts during fracture repair.[6] While it is obviously the orchestrated interplay of a large spectrum of local and systemic signals that drives osteoblastogenesis, and thus bone regeneration, there are growth factors such as BMP-2 that are not only supportive but also essential for proper bone regeneration, and thus likely also for graft consolidation. However, considering the complex interplay of immune cells, endothelial cells, osteocytes, and osteoclasts in controlling bone formation, many molecular mechanisms remain to be discovered.

Histology has provided insights into the defect sites, showing that osteoclasts are already active a few days after the injury, and that bone formation by osteoblasts is clearly visible 10 days after implant insertion in a pig model.[131] The new bone grows fairly rapidly, at approximately 10 μm per day, and sprouts into the defect area. Then, lamellar bone is formed on the surface of the woven bone, which overall is independent of osteoclasts and is thus strictly in an anabolic phase until bone remodeling is initiated. Finally, the woven bone and the primary lamellar bone are replaced by secondary lamellar bone, which is the final stage of bone regeneration, and bone remolding takes over. What histology convincingly demonstrates is that the new bone grows into an area rich in blood vessels, but without touching them.[131] Considering the three choices of osteoblasts – to become an osteocyte, to

become a lining cell, or to die – a supply of new osteoblasts to drive bone regeneration seems mandatory. The close proximity of osteoblasts has always pointed toward blood vessels as the source of the mesenchymal progenitor cells, but evidence was scarce. Today, advanced mouse models have supported this hypothesis, e.g. by showing that only a certain type of endothelial cells (H-type) is associated with osteogenic precursors, which resemble pericytes but are perhaps a distinct population.[78,134] Blood vessels in the growing long bones are rich in osteogenic precursors, and are predetermined as they express the differentiating marker osterix.[78] Blood vessels in the bone marrow, however, do not carry this cell population. It is reasonable to suggest, under the premise that (to some extent) bone regeneration recaptures bone development, that these osteogenic blood vessels also sprout into the defects after implant insertion or bone augmentation. Moreover, Prx1-Cre mouse models support the role of the periosteum as a rich source of osteogenic cells. These cells can efficiently contribute to cartilage and bone formation upon injury.[41] This knowledge now has to be translated into higher animals and its clinical relevance determined.

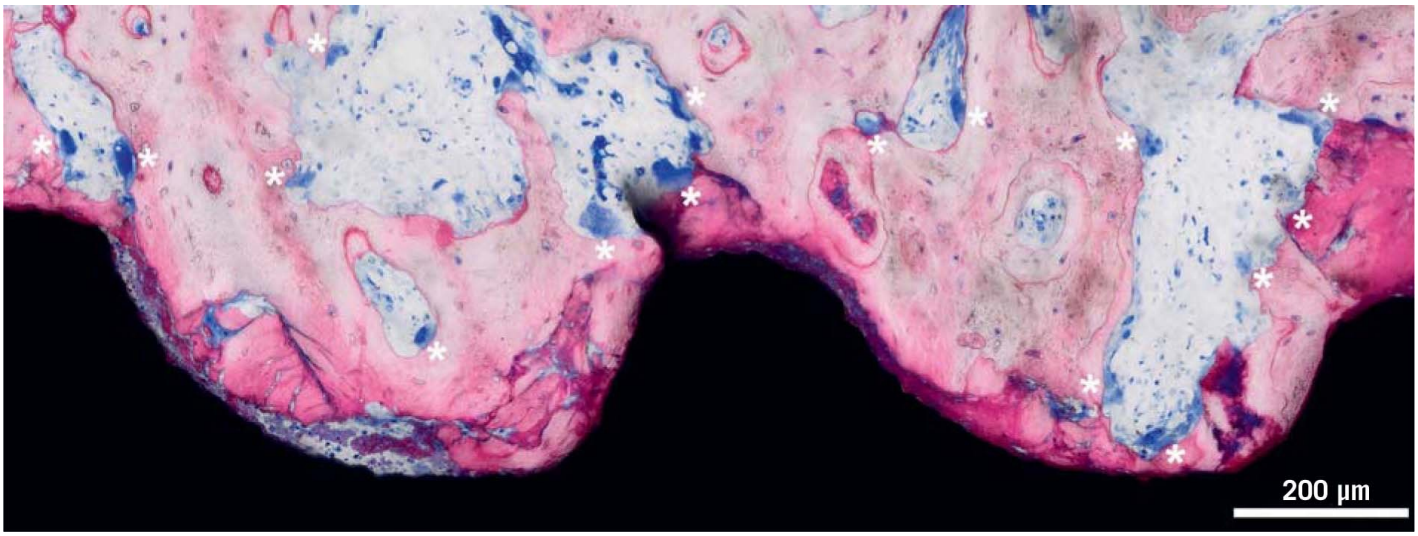

Fig 1-6 Dental implant after 5 days of osseointegration in a pig jaw, from a study by Vasak et al.[131] Five days after implant placement, close to the implant surface, the bone is fragmented, squeezed, and heat damaged (dark pink). Osteocytes in the vicinity are dead and dying. Osteoclasts (white asterisks) are digging bone channels, sprouting from existing bone canals (osteons) to reach and resorb the damaged bone. They are about to reach the most damaged bone close to the implant and will soon remove it.

If the overall hypothesis is correct, the formation of this subtype of endothelial cells carrying the osteogenic cells is essential for bone regeneration, and thus also for regenerative dentistry. However, since the pioneer findings with parabiosis experiments,[22] there is good evidence that blood vessels provide the progenitors of osteoclasts. Here, the bone marrow is irradiated and thus osteoclastogenesis is impaired; however, it is regained when the circulation is connected to a vital mouse, so that osteoclast progenitors have to be carried via the bloodstream. Taken together, the blood vessels are key for osteoblastogenesis and osteoclastogenesis – and consequently also for bone regeneration.

1.3.1 Osseointegration of dental implants

It is known from preclinical histologic investigations in minipig[131] and mandibular canines,[9] but also by measuring implant stability in a clinical setting,[108,132] that within the first week, resorption of the peri-implant bone dominates the scene, before bone formation takes over (Fig 1-6). This early catabolic process is required for the removal of micro-damaged necrotic bone, which is characterized by dying osteocytes. After around 1 week, the osteoclasts have disappeared, leaving behind an osteophilic surface onto which new bone is deposited (Fig 1-7).[9,131] Small defects, as they occur between the local bone and the threads of the implants, are bridged with new bone. These relatively small distances are known as jumping distances.[11] Primary woven bone formation shows a typical picture, with blood vessels in the center of an open ring of new bone (Fig 1-8). This image supports the assumption that the origin of the cells required for bone formation is based on pericytic progenitor cells of sprouting blood vessels.[78,134] This bone is immature (woven bone).[9] Subsequently, lamellar bone will strengthen the woven bone that later undergoes modeling and remodeling.

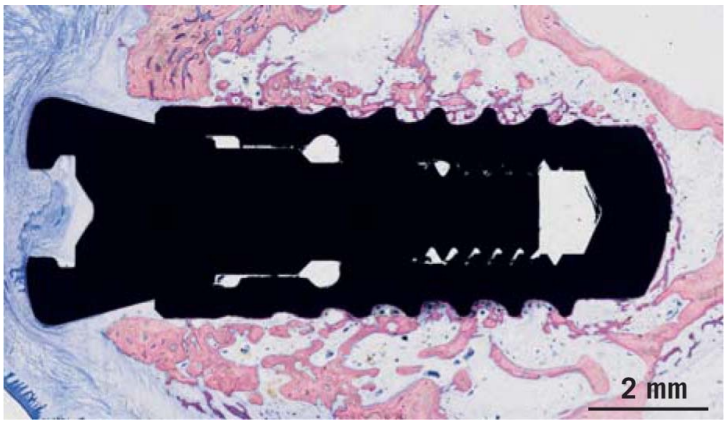

Fig 1-7 Dental implant after 10 days of osseointegration in a pig jaw, from a study by Vasak et al.[131] Ten days after implant placement, feeble trabeculae of new bone have already replaced the damaged old bone. New bone continues to grow. Batches of osteoclasts are resorbing the remaining damaged bone.

Modeling refers to the functional adjustments based on the reaction of the bone to biomechanical stimuli according to Wolff's law and Frost's Mechanostat theory.[44] We are beginning to understand today how resident bone cells perceive and translate mechanical energy into biologic signals. These signals transiently uncouple the remodeling equilibrium of osteoblasts and osteoclasts; otherwise, no structural change of bone anatomy is possible.[96] Remodeling, then, ensures the preservation of bone quality and long-term implant success. According to current hypotheses, the necrotic bone areas created during loading are resorbed by osteoclasts and are immediately replaced by osteoblasts, which was originally postulated by Frost[44] and has now been proven to involve the apoptotic and necrotic death of osteocytes.[65,66] Osseointegration is therefore not only the transition from mechanical primary instability to biologic secondary stability due to bone regeneration;[86] it also requires the continual maintenance of bone quality through remodeling. Bone regeneration and bone remodeling are not necessarily subjected to the same regulatory mechanisms; for example, bone formation during early fracture healing can take place without the resorptive activity of osteoclasts,[50,85] while bone remodeling is strictly based on the coupled effect of osteoclasts

and osteoblasts.[112] What is true for osseointegration is also observed during graft consolidation – the osseointegration of autografts.

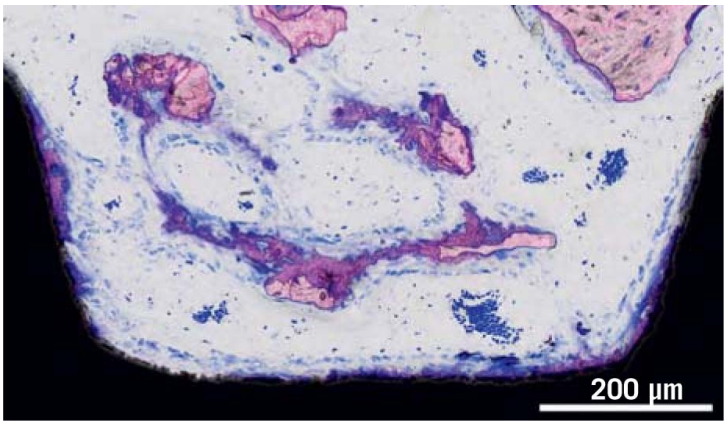

Fig 1-8 Dental implant after 10 days of osseointegration in a pig jaw, from a study by Vasak et al.[131] Dynamics of early bone formation in the grooves of an implant. New bone (purple) is growing on the implant surface as well as on fragments of old bone that is not resorbed (light pink). Erythrocytes (dark blue) indicate the presence of blood vessels.

1.3.2 Autogenous bone grafts

Even though there is a long tradition of considering autologous bone a gold standard, this claim needs to be specified. Bone transplantation dates back to 1879, when a bone allograft was performed on a 3-year-old boy affected by a huge humeral bone loss.[36] Reviews such as the one by Albee in 1930[2] are worth reading from an orthopedic perspective.[2] From back in the pioneer days to today, the primary intention of bone grafting was to allow the replacement of missing bone in defects of critical size.[103] In implant dentistry, starting in the 1980s, bone grafts harvested from the ilium and the mandible were used to reverse alveolar atrophy of the maxilla and mandible.[124] At that time, bone regeneration with autografts was also being compared to those filled with bone substitutes.

Preclinical research in pig mandibular defects convincingly showed that, after 2 weeks, almost twice as much new bone formation had occurred in the presence of autologous bone chips compared with bone substitutes;[16,59,60] however, this does not necessarily mean that autograft bone chips support bone formation. In the same model, when defects were foiled with corticocancellous blocks particulated by a bone mill, bone scraper, piezosurgery, and bone slurry, bone formation at 1 week was restricted to the borders of the defect, making a total of 3% to 4% of new bone; no bone formation was observed in the center of the defect.[100] Bone chips that filled around 20% to 30% of the area were significantly covered by osteoclasts.[100] After 2 weeks, bone formation had increased, covering 20% to 30% of the defect area, while within only 1 week, 20% to 40% of the bone chips were resorbed.[100] This dynamic phase of graft resorption followed by extensive bone formation continues after 4 and 8 weeks, albeit slowing down overall. The low resorption and the favorable osteogenic potential of autographs is supported by the research of the editor of this book.

1.3.2.1 Bony lid technique

Already in 1987, Khoury reported his clinical data on the bony lid technique for the apical root resection of mandibular molars.[71] In another study, he reported his prospective data on this technique in pre-implant and implant surgery.[67] The bony lid is a cortical bone plate obtained by the cutting and luxation of parts of the mandible (see Chapter 4). The cortical bony lid can also be split into two halves that are used as a bony sheet (stabilized by micro screws) that holds the bone particles in place, thereby molding the augmentation and implantation site (see Chapter 4). At the re-entry 3 months later, the average width of the alveolar crest after placing the bony lid showed a loss of only 0.5 mm, which is around 7% of the original dimension, suggesting good volume stability.

1.3.2.2 Split bone block (SBB) technique

Based on the principles of the bony lid technique, Khoury went on to harvest monocortical bone blocks with the MicroSaw, especially from the retromolar area.[69] The bone blocks were longitudinally split and thinned with a bone scraper, gaining at the same time a significant quantity of autogenous bone chips. The thin bone blocks were then stabilized at a distance from the alveolar crest with micro screws to recreate alveolar ridges with sufficient volume and thickness, especially for vertical bone augmentation, and allowing for later implant placement in the prosthetically required position. The space between the thin bone blocks and the remaining alveolar crest was filled with the scraped autogenous bone chips. After 3 months, the implants were inserted into the grafted area[70,72] (see Chapter 4). After 3 months of healing, the grafted area was exposed, and the height and width of the grafted area measured. At the same time, bone cores from the planned implant site were removed for histology and histomorphometry using trephine burs (Fig 1-9). The mean bone resorption was 3.9% in the vertical and 7.2% in the horizontal dimension at the time of implant insertion in the case of 3D vertical augmentation in the posterior maxilla. After 10 years of observation, the mean vertical bone resorption measured on the radiographs was 8.3%. The core biopsies obtained prior to implant placement in the two-stage approach show larger (Fig 1-10a to c) and smaller (Fig 1-11a to c) bone chips, which now are integrated into the new bone. Noticeably, the bone surface is not occupied by multinucleated cells, and new bone formation is obvious, making the augmented area ideal for supporting the process of osseointegration of dental implants. This explains the long-term stability of the vertical grafted area with the osseointegrated implants.

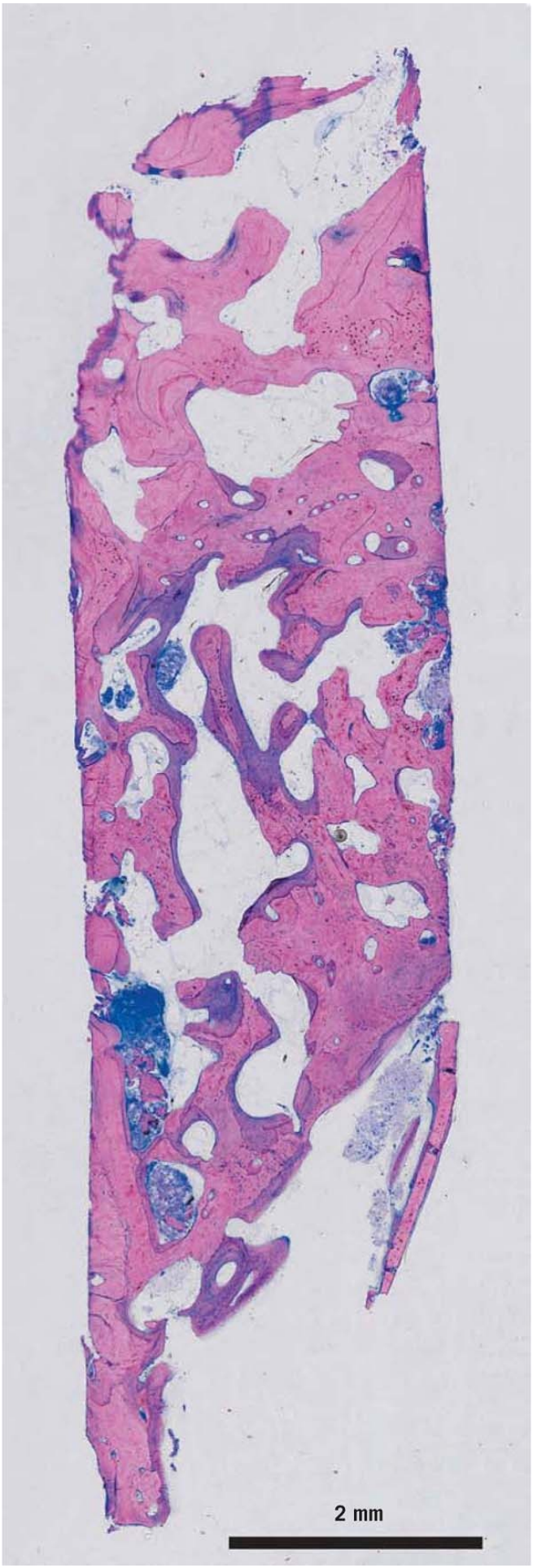
2 mm

Fig 1-9 Biopsy from the split bone block (SBB) technique. The space between the thin bone blocks and the remaining alveolar crest was filled with the scraped autogenous bone chips. After 3 months, the implants were inserted in the grafted area.[70,72] After 3 months of healing, bone cores from the planned implant site were removed for histology. In this image, the new bone is stained purple, while the old pristine bone and the transplanted bone chips are pink.

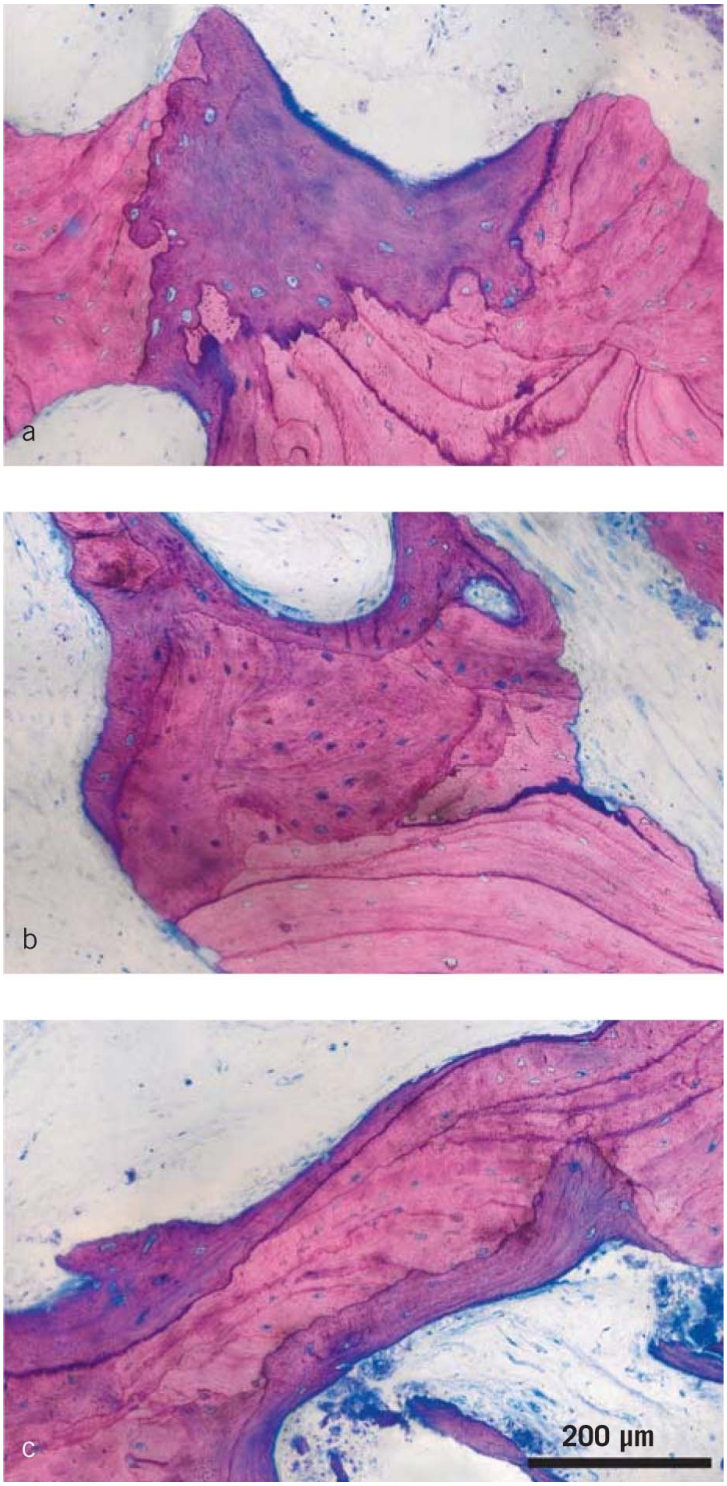

Fig 1-10a to c New bone formation on the surface of transplanted bone chips. In the SBB technique, scraped autogenous bone chips fill the space between the cortical bone blocks. After 3 months, healing bone cores from the future implant site were removed. The new bone is stained purple, while the transplanted bone chips are pink. Note the cement lines of the transplanted bone, which are signs of previous bone remodeling. Osteocyte lacunae are either empty or filled.

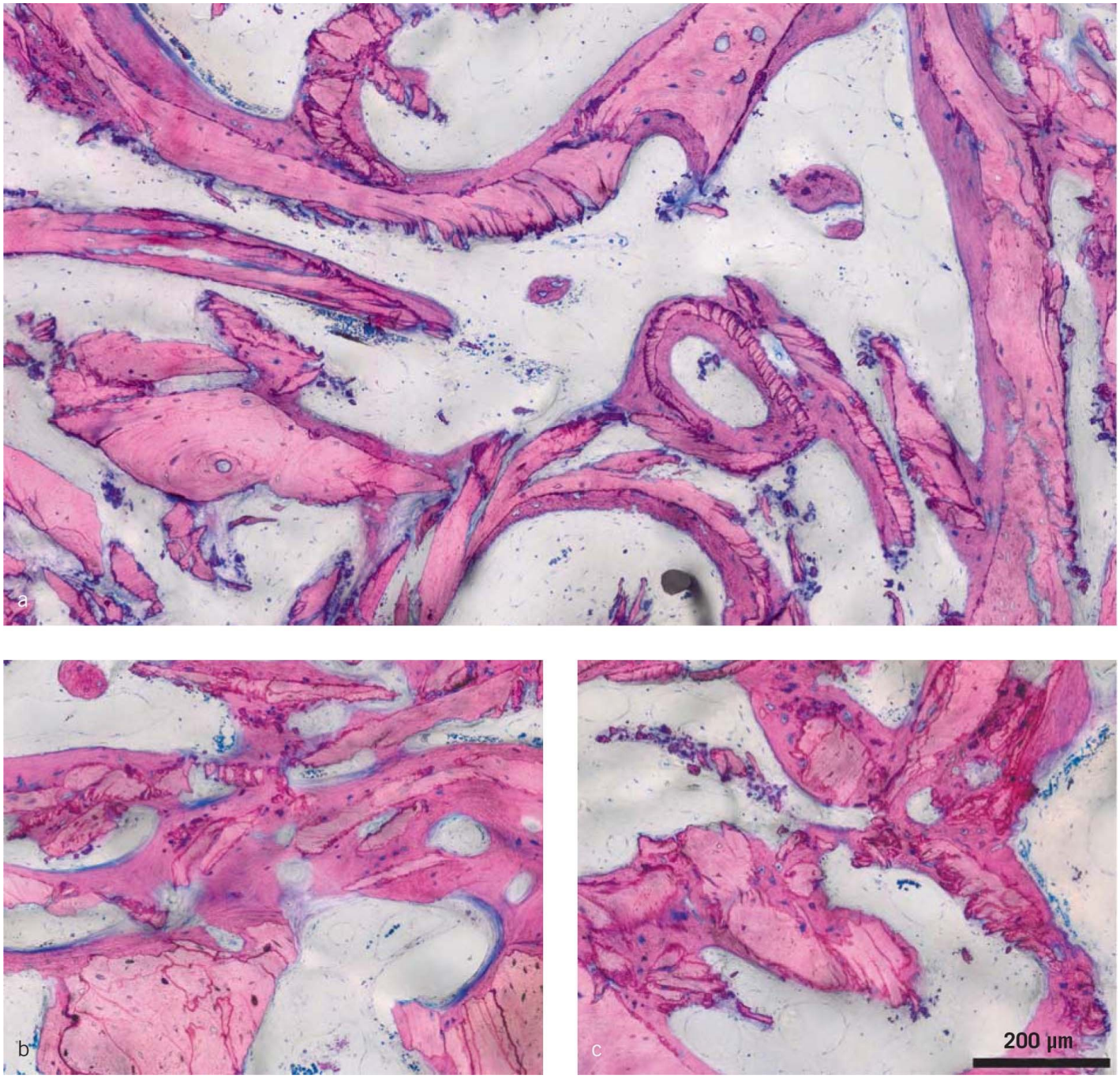

Fig 1-11a to c New bone formation on the surface of transplanted bone chips. Scraped bone chips can have various shapes and may even resemble bone dust. In the SBB technique, after 3 months of healing, the bone chips are covered by new bone and no obvious signs of resorption are visible.

1.3.2.3 Bone core technique

For small augmentations, the bone core technique is recommended. A bone core is harvested using trephine burs of different diameters, but on average a 3.5-mm external and a 2.5-mm internal diameter (see Chapter 4). The bone cores are used together with bone chips to augment the bone immediately after implant placement. This trabecular bone core can be used analogous to the cortical bone plate, providing a small bony sheet for the bone particles, again requiring stabilization with micro screws. After 3 months of healing, the implants and the grafted bone are exposed, and the width of the grafted area measured. Bone cores grafted completely inside the bony contours demonstrated no resorption 3 months postoperatively,

while in most cases bone cores grafted partially outside the bony contours showed partial resorption of the bone outside the bony contours.[67] Similar to the bony lid technique, at the re-entry 3 months later the average width of the area reconstructed with the trabecular bone core only lost 0.3 mm, which is around 13% of the original dimension, again suggesting good volume stability. What we can learn from this approach is that, in a clinical scenario, the resorption of cortical bone plates as well as trabecular bone cores is low, and that bone chips are well integrated into the newly formed bone after 3 months.[67-69] Taken together, autografts in this particular indication allow and may even support the occurrence of natural bone formation originating from the host bone and maybe also from the transplanted autografts. In addition, and interestingly, the augmented volume remains rather stable, with around 7% to 13% resorption after 3 months.

Bone resorption also occurs after tooth extraction, as reported in canine models[5] and clinical cases,[104] and when the facial bony wall is thin it even disappears, probably due to the lack of vascular supply.[26] The questions are as exciting as they are important: 1) Why are transplanted autographs resorbed? 2) Why does this resorption occur partially but not completely, depending on the size and anatomy of the autograft? 3) Why is it difficult to predict the extent of resorption?

There are certainly many reasons for bone resorption – some are known (e.g. the influence of muscle activity), while others are as yet unknown. In case of human sinus augmentation with pure autogenous grafts, around 40% of bone volume is lost within 6 months, probably through the respiratory pressure on the sinus mucosa covering the grafted and non-mechanical resistant trabecular bone,[31,47,101] similar to a canine model.[102] In alveolar cleft patients, transplanted iliac bone showed comparable bone resorption rates of less than 40% within 6 months.[39,136] On a cellular level, the resorption of autologous bone chips by osteoclasts within 1 week is particularly obvious in the pig mandibular defect mentioned above.[100] It seems that the resorption of transplanted bone that undergoes necrosis is prone to resorption – similar to local bone areas, with microcracks that undergo fatigue damage and are replaced by remodeling.[107]

1.4 Autograft resorption

There must be at least one mechanism that controls the resorption of the transplanted bone. One possible explanation could be the function of osteocytes, which are ubiquitously present in the bone, forming a coherent network.[15] Osteocytes can control the formation of boneresorbing cells by expressing RANKL,[89,138,139] a central agonist of osteoclastogenesis.[118] In addition, there is increasing evidence from mouse research that dying osteocytes significantly promote osteoclastogenesis.[120] The resorption of alveolar bone upon tooth extraction, implant placement, and early stages of graft consolidation after bone transplantation may also be associated with osteocytes. In all cases, the bone tissue is

separated from the blood vessels, and therefore the oxygen and nutritional supply of the osteocytes by passive diffusion is limited or even impossible. Consequently, osteocytes die, and, by a molecular mechanism, promote the expression of RANKL by the adjacent osteocytes that, in turn, can initiate osteoclastogenesis.[65,66] Molecules released by dying osteocytes can also increase the sensitivity of osteoclast progenitors to RANKL via a C-type lectin receptor. Importantly, unloading-induced bone loss also requires the dying osteocytes to enhance bone resorption via their expression of RANKL.[17] Accordingly, bone resorption, presumably also in dentistry, is bound to dying osteocytes and does not progress uncontrolled. However, it is reasonable to suggest that dying osteocytes can not only transiently push osteoclastogenic resorption, but also the reparation process, through new bone formation as a normal physiologic reaction of remodeling. Thus, the initial boost of bone resorption that occurs at implant sites[131] and upon bone grafting[100] is followed by the attraction of osteogenic progenitor cells that become bone-forming osteoblasts on the surface of the host bone, the autografts, and also on biomaterials, including dental implants.[131]

Elegant preclinical studies in mouse models support the hypothesis through experiments in which the apoptosis of the osteocytes were analyzed after the preparation of an implant bed, e.g. drilling tools create a zone of dead and dying osteocytes around the osteotomy[29] that is increased as a function of the insertion torque.[19] The pharmacologic suppression of apoptosis can also reduce bone atrophy upon extraction in a rat model.[105] Thus, the strategy exists to develop low-invasive drill designs that initiate low heat and mechanical friction, with the overall goal of preserving osteocyte viability.[1,28] In a bovine femora, test drills can reach 47°C, particularly after repeated use,[20] which is similar to experiments performed with polyurethane foam blocks,[43] a temperature that causes osteocyte damage and RANKL expression in a rat model.[37] Cutting energy is converted into heat.[80] Bone chips produced by drilling[80] presumably follow the dying osteocytes – RANKL expression axis and are removed by osteoclasts before the osteoconductive properties come into play. It therefore seems relevant to pay special attention to atraumatic procedures when placing implants, extracting teeth, and probably also removing bone grafts, with the overall aim of maintaining the vitality of osteocytes. For example, at the time of implant insertion in free fibula or iliac crest bone grafts, most of the biopsies showed partial or total necrotic bone.[58] There is also limited atrophy of free fibular grafts after mandibular reconstruction.[57,110] The question is raised: How much vital bone is necessary for the survival of the graft?

1.5 Osteoconductive characteristics of autografts

According to the textbooks, autologous bone has the following properties: “osteoconductive, osteogenic, and osteoinductive.”[3] Osteoconductive is the term used to describe the property of new bone being able to form on the surface.[3] Therefore, osteoconductive materials can not only serve as a guide rail for bone regeneration in a defect of critical size, but also in bone

augmentation. It is also a term, albeit unusual, for the property of implant surfaces that allows for the deposition of new bone without the formation of a fibrous layer.[3,34] Osteoconductivity therefore first requires a surface. Once the transplanted bone has been partially resorbed, the remaining bone surface again becomes osteoconductive.[100] Transplanted bone that remains after the initial resorption phase serves as a guide splint. Clinically, it is therefore common to dimension autologous bone, taking into account partial resorption. The reason why autologous bone clearly allows more bone formation than bone substitutes in the first weeks after transplantation in a pig mandibular defect[16] remains a matter of speculation, but it is not particularly surprising that osteoblasts and their mesenchymal progenitors like the mineralized surface that they have produced themselves. In summary, the property osteoconductive can be confirmed for autologous bone through histology.

1.6 Osteogenic properties of autografts

Autografts contain viable osteoprogenitor cells, in contrast to allografts and bone substitutes of xenogeneic and synthetic origin. By definition, osteogenic means that the cells brought along during transplantation actively participate in bone formation, i.e. osteogenic precursor cells of the mesenchymal line differentiate into osteoblasts after transplantation and form new bone. Numerous in vitro studies have shown that osteogenic cells can be generated from explant cultures of bone grafts, particularly from trabecular but also from cortical bone.[56,115] The key experiment that proved osteogenicity related to transplantation at ectopic sites. This research took place in the 1970s, when Gray and Elves transplanted isografts from the ilium[52] and femur diaphysis,[53] e.g. into the back of rats. They showed bone formation after 2 weeks, mainly originating from the transplanted endosteal and periosteal cells. Once the cells were removed by enzymatic digestion or through boiling, the osteogenic capacity was nil, suggesting that the osteocytes could not replace the cells on the surface and that the bone matrix alone could not induce bone formation.

In a xenogeneic transplantation model, 5 mm^3 of human morselized cancellous bone from the proximal femur was transplanted into immunodeficient mice that received radiation, and depletion of macrophage and natural killer cells. Consistently, after 8 weeks, new bone was produced by human bone cells rather than from the induction of host mesenchymal cells into mouse osteoblasts.[13] Bone transplants, however, underwent resorption and necrosis in untreated immunodeficient mice, considering that macrophages could developed into osteoclasts.[13] Also, in a goat model, ectopic transplantation of 1 cm^3 of femur condylar corticocancellous bone was transplanted in the paraspinal muscle. Both the block grafts and the respective bone chips showed ectopic new bone formation after 12 weeks. Upon freeze thawing, block grafts maintained a weak osteogenic potential, while the respective bone chips were resorbed,[75] probably because only a few osteogenic cells can survive under such conditions.[114] Preclinical research in goats showed that it requires a well-nourished

environment for the transplanted osteogenic cells to contribute to bone formation.[74] Mouse models further revealed that perivascular cells located within transcortical channels contributed to osteoblast formation and bone tube closure in a cortical bone transplantation model.[97,123]

Recent evidence further suggested that, at least in a mouse model, the interval between autograft harvesting and transplantation affected its viability and bone-forming capacity.[119] Immediately after autograft harvesting, apoptotic cells were barely detectable, but already within 5 minutes the number of apoptotic cells had nearly tripled.[119] The time between harvesting and transplantation also affected the osteogenic potential of an autograft upon transplantation.[119] Overall, autografts resemble the osteogenic potential of tissue engineering constructs, showing ectopic bone formation; however, when in small-sized constructs, only around 20 to 70 mm^3 in mice[79] and in goats.[76] Importantly, however, the orthotopic transplantation could not reveal any benefit of cell-based therapies with respect to bone formation at the defect site.[76] Thus, beside the fact that osteogenic cells can basically survive transplantation and are a source of osteoblasts at ectopic sites, the overall contribution of the transplanted cells to graft consolidation is yet to be investigated. Nevertheless, our biopsies suggest that the new bone originates from the transplanted bone chips, with new, nascent bone bridging the space between the transplanted bone particles (Fig 1-12).

1.7 Osteoinductive properties of autografts

The postulated osteoinductive effect attributed to autografts is questionable. By definition, the unlimited osteoinductive effect of autografts can only be proven by ectopic bone formation outside the skeletal system, and not only in or on the bone. Osteoinductive refers to demineralized bone but also dentin matrix, both of which can trigger new bone formation after implantation, e.g. in the muscle of a rat.[63] This demineralized bone matrix ultimately leads to the isolation and molecular characterization of bone morphogenetic proteins (BMPs). It is not widely known that the isolation of BMPs requires 5 to 20 kg of bone to obtain sufficient protein for purification testing, including in vitro osteogenic differentiation and in vivo osteoinductive bone formation.[8,83,133] However, there is no evidence for ectopic bone regeneration after transplantation of bone chips in a muscle; in fact, it is the opposite – that the bone chips are resorbed without the induction of new bone by host-derived induced osteoblasts.[13]

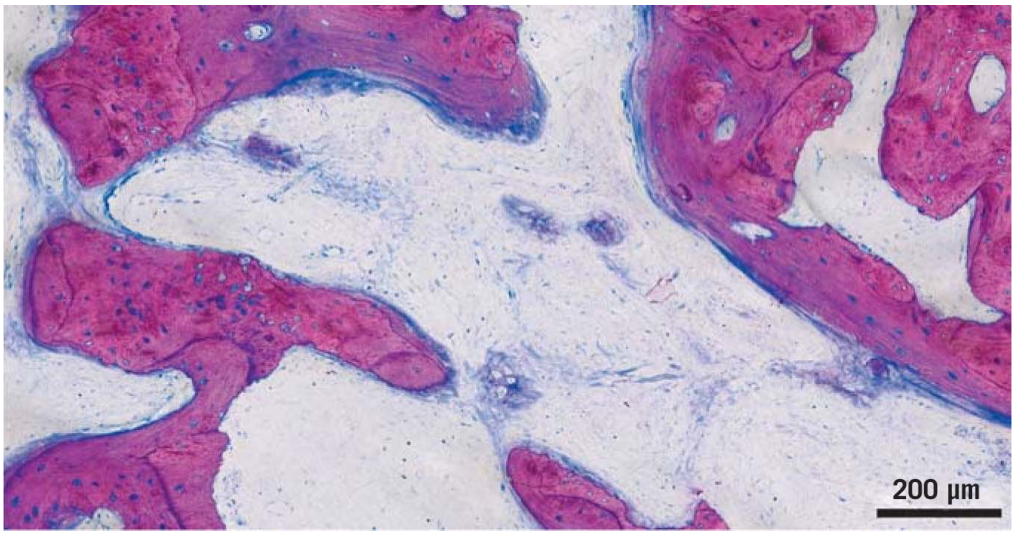

Fig 1-12 New bone formation on the surface of transplanted bone chips. In the SBB technique, after 3 months, healing areas of nascent bone formation are detectable. The structure of future bone formation can already be anticipated. Even though the origin of the bone is not defined, it seems that bone formation originates from the transplanted osteogenic cells.

When implanted into the muscle pouches of beagle dogs, bone grafts resorbed quickly, while alloplasts and a synthetic biphasic calcium phosphate showed minor signs of ectopic bone formation.[87] Also, in Wistar rats, autologous bone chips from a corticocancellous bone block grafted in a muscle were entirely resorbed after 6 weeks.[88] If native bone chips were actually unlimitedly osteoinductive, it would mean that, were bone chips to enter the soft tissue, new bone would be formed there. This side effect of ectopic bone formation in soft tissue would be clinically undesirable. However, there is evidence that, at least during bone remodeling, osteoclasts release TGF-βb1 from the bone matrix, which recruits mesenchymal progenitors to the remodeling sites.[32] It was recently confirmed that TGF-β1 released by acid lysis of bone is a major regulator of gene expression in mesenchymal cells in vitro.[117] Moreover, acid bone lysates delayed bone formation in a rat calvaria defect model.[116] Since the accumulation of these results makes a major involvement of BMPs in graft consolidation unlikely, and proposes that TGF-β1 supports the immigration of progenitor cells, the idea of the osteoinductive properties of autografts needs to revisited, and has to be limited only to the support of bone formation in direct contact with bone tissue.

1.8 Summary

In summary, the surgical approaches outlined in Chapter 4 of this book – the bony lid technique, the SBB technique, and the bone core technique[67,68] – nicely reflect the basic principles of successful bone healing introduced in this chapter, which are that:

1. Autografts have favorable osteoconductive properties, allowing bone to form on the surface.
2. Once harvested and used immediately, autografts can exert osteogenic properties where the transplanted cells might contribute to bone formation.

3. The osteoinductive properties of autografts are questionable, and it is desirable to avoid ectopic bone formation at soft tissue sites.

Nevertheless, the resorption of autografts releases growth factors that might support graft consolidation. The amount of resorption can be clinically controlled under certain indications, including the biologic approaches presented in this book.

The prerequisites for successful graft consolidation are mechanically stable conditions in a well-vascularized area with vital bone walls as the origin of the newly formed bone. The definitions of a gold standard should mainly be seen clinically, and defined for each indication, since experimental animal research is mostly based on a short observation time of only a few weeks. It therefore seems worthwhile to resume experimental work on the autogenous bone experiments of the pioneers, ultimately in search of molecular and cellular explanations for the definition of a gold standard.

Acknowledgments

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2

Diagnosis and planning of the augmentation procedure

2.1 Introduction

The aim of implant prosthetic rehabilitation is the integration of fixed or removable dental prostheses. Therefore, it is necessary to set up a treatment plan that considers the individual findings according to the result expected by the patient. It is important to define the surgical, prosthetic, and dental technical effort to achieve a functional and esthetic result. The amount of surgical effort required depends on the available bone and soft tissue. This effort is necessary both before and during implant insertion in order to achieve a long-term stable prosthetic result. To achieve an optimal result, detailed planning is as important as a complication-free reconstruction of the atrophied jaw and prosthetically oriented implant placement, which requires proper training in all treatment steps.[93]

The planning of the position, number, and dimension of the implants represents the essential step for a successful restoration from an esthetic and functional point of view. The

prosthetic aspects have to be considered and the available bone evaluated. Today, implants can be inserted from a prosthetic point of view as far as possible using various grafting techniques.[81] Nevertheless, it is necessary to take precise account of the anatomical landmarks at the time of implant placement,[44] otherwise insufficient bony coverage of the implant surface can lead to complications such as peri-implantitis shortly after the final prosthetic delivery.[29] Further restrictions in terms of the functionality of the prosthetic restoration result from implant positions that require a non-physiologic tooth shape with a limited esthetic result (Fig 2-1a to d) or do not allow for sufficient hygiene maintenance (Fig 2-2a to g).[94]

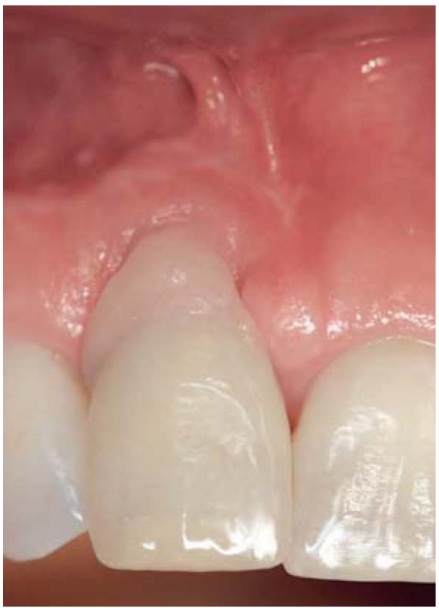


Fig 2-1a Long crown after deep implant placement without considering a two-stage grafting procedure.

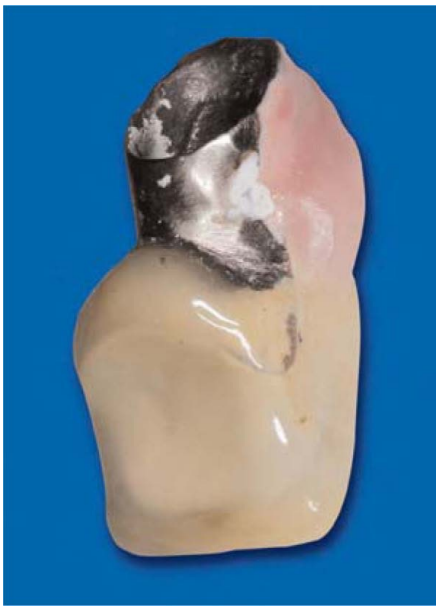


Fig 2-1b Non-physiologic crown shape with limited oral hygiene options.

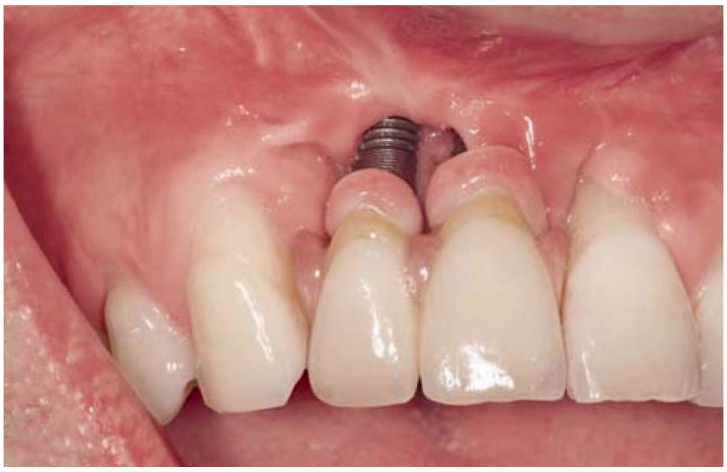


Fig 2-1c Failed implant restoration in the maxillary anterior area.

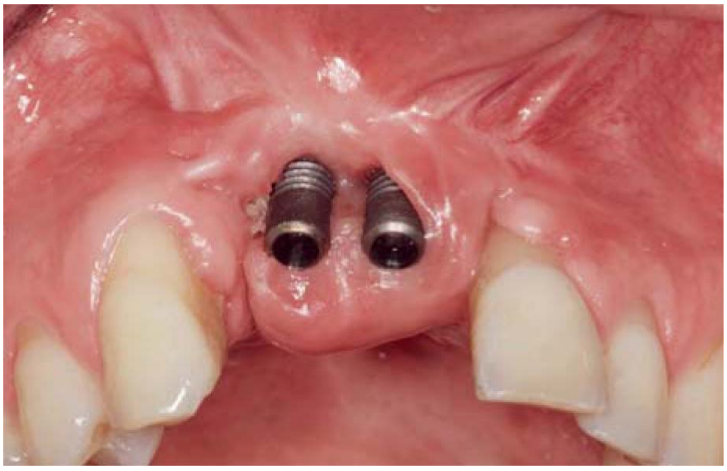


Fig 2-1d Clinical situation after removal of the crowns.

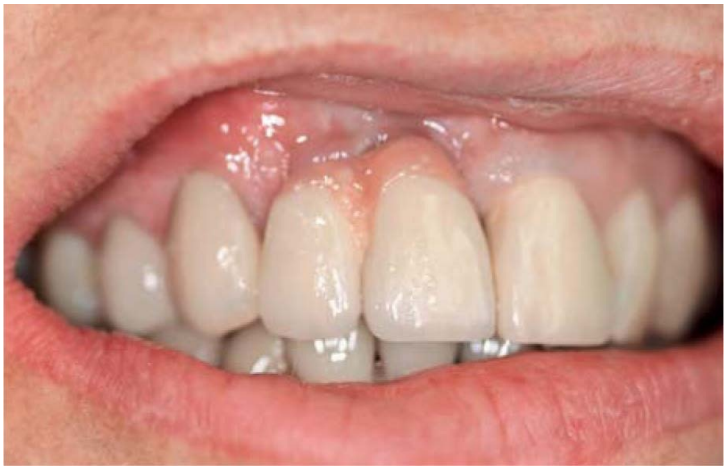


Fig 2-2a Clinical aspect of an unesthetic and unhygienic restoration.

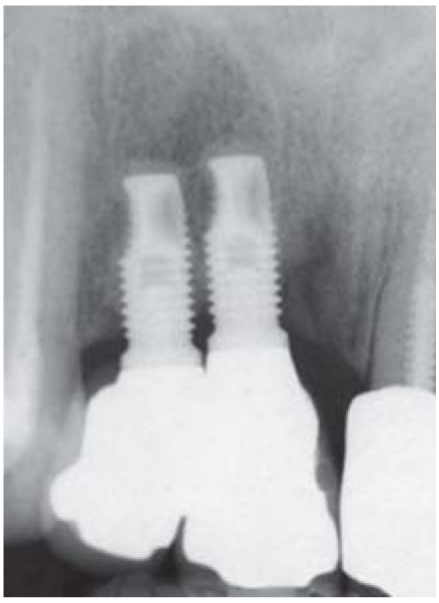


Fig 2-2b Minimal implant distance as the cause of an unacceptable result.

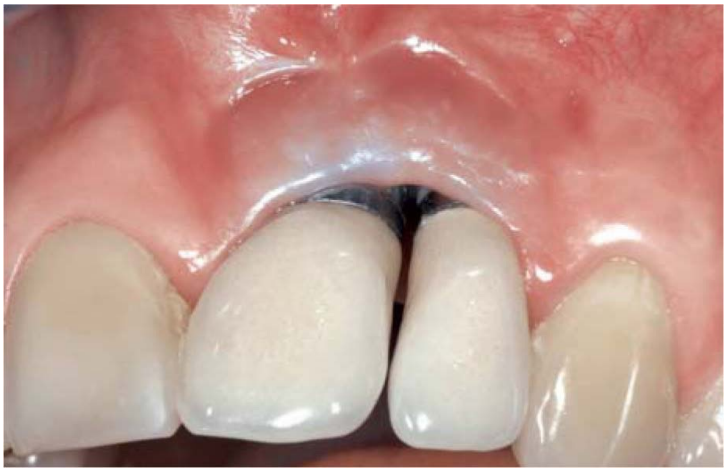


Fig 2-2c Direct contact of two implants prevents the formation of interimplant soft tissue.

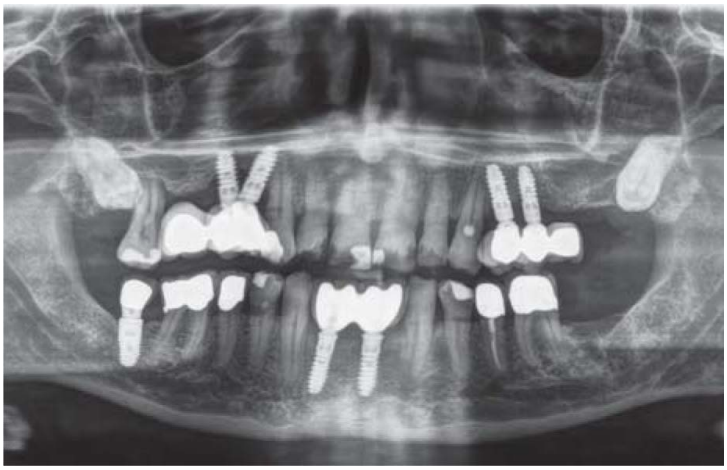


Fig 2-2d Panoramic radiograph documenting bad implant planning especially in the right maxilla, leading to peri-implant bone loss.

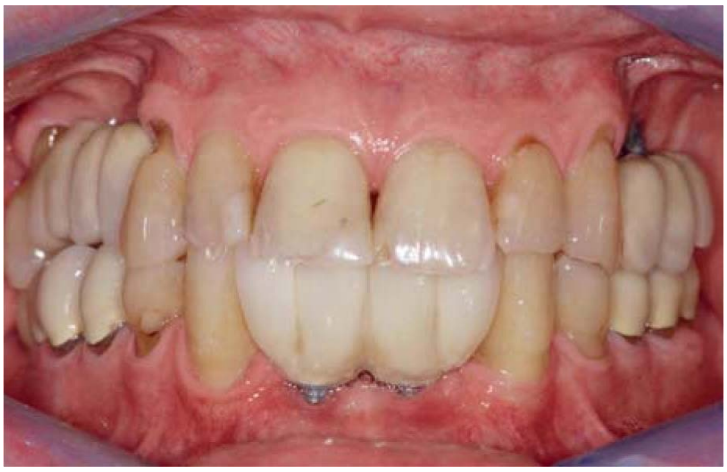


Fig 2-2e Clinical aspect of Figure 2-2d, documenting unesthetic and unhygienic restorations due to bad implant positions.

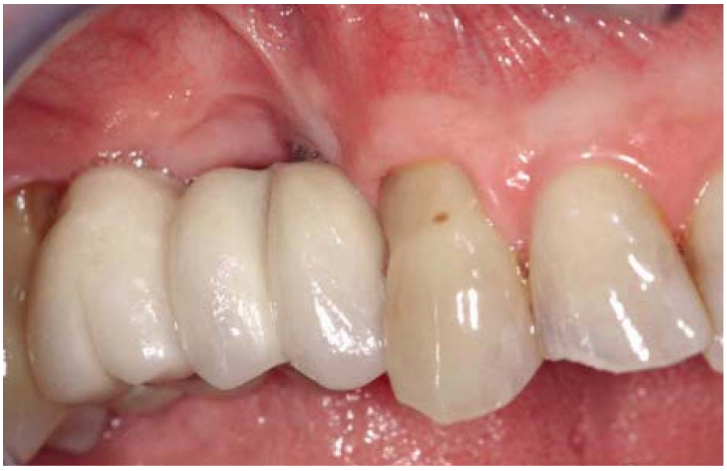


Fig 2-2f Clinical situation in the right maxilla offering inadequate cleaning possibility.

2.2 Patient consultation

Depending on the patient's expectations and willingness to cooperate, it is necessary to precisely define the aim of the treatment. Clarify right from the start in detail the various available grafting techniques and their suitability for the specific patient. Also, alternative methods should be considered such as diameter-reduced or ultrashort and tilted implant placement to avoid grafting procedures.[69,77] To achieve the best possible patient cooperation and satisfaction, it is not sufficient to only explain the intra- and postoperative surgical risks. Patients need information about the overall treatment duration, costs involved, and possible alternative procedures.[77] During the course of clarifying the implant prosthetic treatment requirements and procedures, it may happen that the patient's original expectations change once the realization sinks in that the time involved, the material costs, the surgical procedure itself or the increased risks of surgery, especially in the presence of systemic disease, are too much for the patient.

Especially in patients with alveolar crest defects, it is important to describe the entire

treatment at the beginning. To achieve high patient satisfaction, it is vital to match the patient's expectations and the necessary treatment steps as closely as possible.[8]

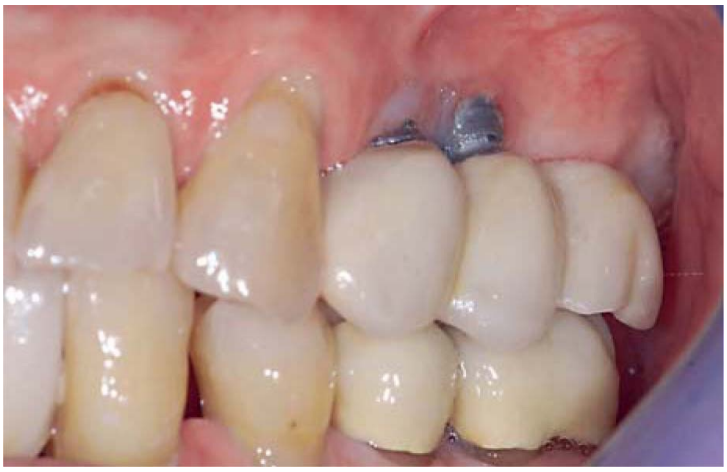


Fig 2-2g Clinical situation in the left maxilla showing exposed implant neck due to lack of bone and soft tissue.

For the definition of the selected therapy, special attention should be paid to the motivation of the patient in an extensive implant prosthetic treatment in order to achieve good cooperation in the long-lasting and intensive course of therapy. Important information about the patient's motivation is provided by the cause of the tooth loss and the patient's attitude toward it (Fig 2-3a and b). The possibilities of the prosthetic design also depend on the awareness of the patient regarding hygiene. Depending on the patient's oral hygiene status, the choice between fixed, conditionally removable, and removable prostheses should be differentiated.

2.3 Anamnesis

In addition to the general conditions, the medication, the presence of allergies, the consumption of psychoactive drugs, and the patient's attitude to antibiotic medication should be surveyed as part of the medical history. In particular, there is a tendency of differentiated patients to reject a postoperative antibiotic medication, which can lead to an increased complication rate, especially when using heterologous grafting materials.

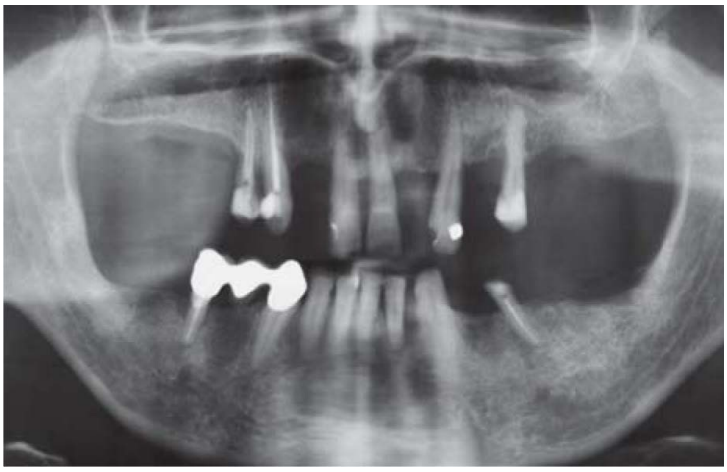


Fig 2-3a Periodontally compromised dentition with non-restorable teeth in the maxilla and a pronounced gagging reflex.

2.3.1 Nicotine consumption

Patients often show early tooth loss due to nicotine use. This situation should be rehabilitated by correspondingly extensive therapies with a fixed prosthesis.[52] Tobacco smoke passing through the oral cavity contains a mixture of hazardous substances that has cytotoxic and carcinogenic effects. This leads to a degeneration of the soft tissue, with a reduced perfusion and vascular supply, which, in a similar way to diabetes mellitus, can lead to surgical or long-term complications in implant therapy.[46]

If patients show complete or partial tooth loss with pronounced or severe alveolar ridge atrophy at the end of the fourth decade of life, an evaluation of the interleukin-1 polymorphism can be made. This is synergistically known in smokers for chronic periodontal disease. At the same time, these patients also have an increased risk of peri-implantitis.[11,32] In order to clarify the long-term prognosis, simple swab tests are now commercially available that allow the pain-free diagnosis of an IL-1 mutation by polymerase chain reaction (PCR)-based methods.

In case of heavy nicotine consumption (more than 10 cigarettes per day), the extensive use of xenogenic bone substitute materials in combination with membrane techniques should be avoided, as wound healing complications are more likely to occur due to reduced vascularization and therefore loss of the augmented areas.[6]

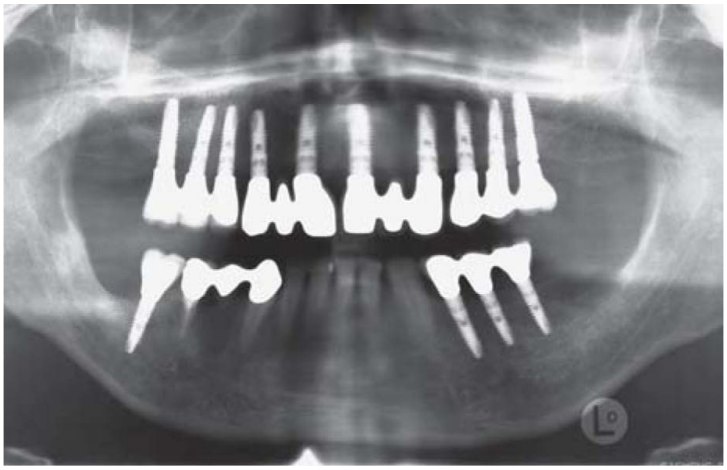
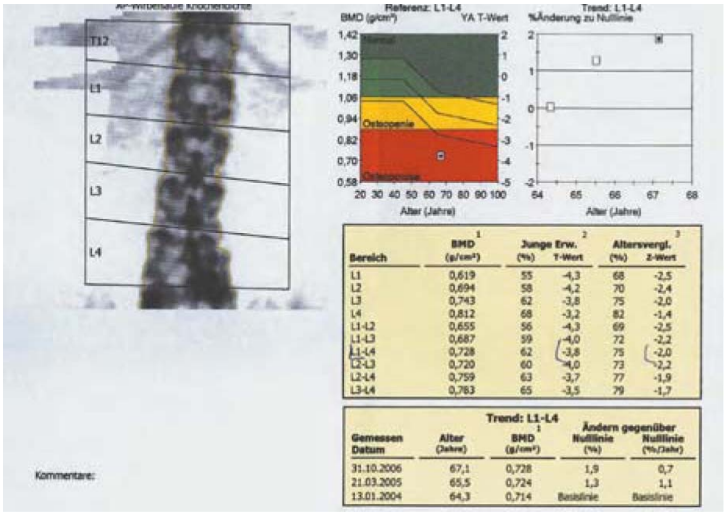


Fig 2-3b Situation after an implant prosthetic restoration with three-unit FPDs after extensive reconstruction of the alveolar crest by autogenous grafting procedure.

Nicotine use is not a contraindication for bone augmentation, but patients should be aware of the overall increased risk of complications.[3] For the surgical procedure, the focus should be on minimally invasive methods such as the tunnel technique or the vestibular incision technique (see Chapter 8 on risks and complications).

2.3.2 General medical findings

Among general medical conditions, diseases with a direct impact on bone metabolism are still the greatest risk group for implant therapy, especially in combination with bone grafting. Most patients in western society do not exercise enough and many of them suffer from degeneration of the skeletal system, especially due to hormonal changes and advanced age. Today, osteoporosis is considered to be one of the most severe diseases, with the risk of life-threatening vertebral body factors[35] (Fig 2-4a). Hints that the blood levels of cholecalciferol (vitamin D) is low are soft bone structures in preoperative radiographs or increased bone resorption.[19] In such cases, medication is administered, which is specified in three different stages.[36] The least risky and most beneficial for implant placement consists of calcium and vitamin D supplements. Newer drug approaches follow the application of strontium preparations, which have a positive effect on bone metabolism, as bone resorption is inhibited, and the formation of new bone is promoted. In such instances, however, negative phenomena can occur in the area of the oral mucosa, which can then lead to peri-implant mucosal changes if the medication continues (Fig 2-4b).



Bereich	BMD (g/cm²)	Junge Erw. (%)	Junge Erw. T-Wert	Altersvergl. (%)	Altersvergl. Z-Wert
L1	0,619	55	-4,3	68	-2,5
L2	0,694	58	-4,2	70	-2,4
L3	0,743	62	-3,8	75	-2,0
L4	0,812	68	-3,2	82	-1,4
L1-L2	0,655	56	-4,3	69	-2,5
L1-L3	0,687	59	-4,0	72	-2,2
L1-L4	0,728	62	-3,8	75	-2,0
L2-L3	0,720	60	-4,0	73	-2,2
L2-L4	0,759	63	-3,7	77	-1,9
L3-L4	0,783	65	-3,5	79	-1,7

Trend: L1-L4

Gemessen Datum	Alter (Jahre)	BMD (g/cm²)	Ändern gegenüber Nulllinie (%)	Nulllinie (%/Jahr)
31.10.2006	67,1	0,728	1,9	0,7
21.03.2005	65,5	0,724	1,3	1,1
13.01.2004	64,3	0,714	Basislinie	Basislinie

Fig 2-4a Densitometry in case of osteoporosis with below-average bone density values in the area of the spine.

2.3.2.1 Antiresorptive therapy

To inhibit osteoclast activity, antiresorptive therapy using bisphosphonate or RANKL inhibitors is available.[83] The range of increased performance bisphosphonate drugs has increased in the past few decades. In addition, the human RANKL antibody Denosumab (Prolia) was approved in 2010 for the treatment of postmenopausal osteoporosis. As a

subcutaneously administered drug, it extends the possibility of individualized osteoporosis medication, also interfering in bone metabolism.[87]

To reduce the risk of occurrence of osseous disseminations, e.g. in patients with breast and prostate carcinomas and with multiple myeloma, a high dose of bisphosphonates is given. For these tumors, a high rate of new disease (antiresorptive drug-related osteonecrosis of the jaw – ARONJ) is continually observed every year.[31] Usually, intravenously administered bisphosphonate therapy, which is used curatively as well as palliatively, means a reduction in the consequences of the oncological disease for these patients, since further metastasis growth in the bone is reduced.[31] Since metastasis needs the help of the osteoclasts to remove bone, allowing for their growth, the strong inhibition of the osteoclasts will stop bone resorption: metastasis cannot grow inside the bone any longer.

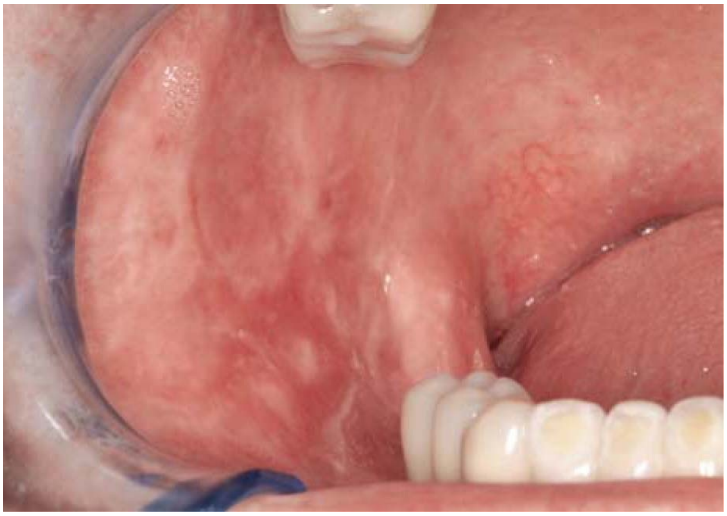


Fig 2-4b Aphthoid mucosal lesion on the planum buccale and on the fixed mucosa on the alveolar ridge in osteoporosis-induced strontium therapy (Protelos).

Due to the change in bone metabolism, a careful dental examination is recommended to perform invasive dentoalveolar surgery prior to medication in order to avoid osteonecrosis in the oral cavity.

Osteoporosis is a disease that shows an increasing prevalence with increasing life expectancy, especially in females. If left untreated, it leads to a significant impairment of the quality of life of those affected. In Germany, a prevalence of 6.3 million people with osteoporosis is assumed, with an incidence of 885,000 new cases per year.[35] Bisphosphonate therapy for osteoporosis is administered through a weekly oral intake or a quarterly or yearly intravenous injection that lead to a stabilization of the skeletal system. A short-term intake of bisphosphonates shows no increased risk of osteonecrosis. After an intake of the medication for longer than 3 years, a higher prevalence of osteonecrosis as well as other general medical side effects are evidenced.[80] Classic open wound healing is absolutely contraindicated, especially after tooth extraction, due to extremely high risk of infection. In addition, after other dentoalveolar surgery, reduced bone regeneration is observed, and the risk for sequestration of the infected bone can occur[31] (Fig 2-5a and b).

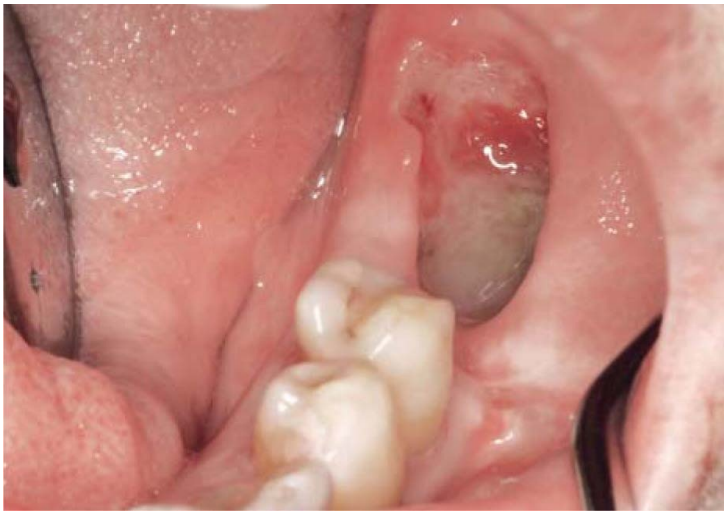


Fig 2-5a Bisphosphate-induced osteonecrosis in plasmacytoma with colonization of multi-resistant hemolyzing streptococci.

In this context, a few years ago, the systemic intake of bisphosphonates for the treatment of oncological disease or in osteoporosis was an absolute contraindication. Clinical experience shows that this contraindication needs to be reevaluated.[16,25] Bisphosphonate medication interferes with the physiology of bone metabolism, thereby limiting the function of the osteoclasts responsible for the bone resorption and remodeling processes.[89] Accordingly, the indication for techniques that require high osteoclastic activity for the remodeling must especially be reevaluated. In this case, techniques that involve the transplantation of autologous spongiosa are preferable to those that transplant purely cortical bone or xenogeneic bone substitute material that requires higher resorption kinetics to achieve a stable implant site.[20]

Fig 2-5b CBCT evaluation of the available bone with contraindications for augmentation and implant therapy due to osteonecrosis of the jaw (ONJ).

For oncology therapy with regular infusions ranging from a few months to a few years, implant placement should be avoided.[31] Even with long-term oral administration or intravenous administration in the form of so-called ‘depot injections’ of these preparations, the critical limit is set at 3 years. To avoid bisphosphonate-induced bone necrosis in patients

receiving treatment for osteoporosis, a very strict indication for augmentation and implant therapy is recommended for these patients.[31,34]

Since the success of implant therapy with bisphosphonate therapy is controversial,[42,87] the extent of treatment should be determined on an individual basis, depending on the patient's health and dental history.

2.3.2.2 Specific antibody therapy

Nowadays, a large number of antibody therapies are successfully used for cancer treatment, even in the advanced stages, and are sometimes administered continually to avoid cancer progression. This can significantly improve the survival rates of these patients. Although these therapies are not without side effects, there are fewer compared with conventional chemotherapy. Therapies include the administration of high-dose cortisone, which is utilized to stabilize the patient. However, even in cases where such treatments are given only for a short period of time, they can negatively influence the prognosis of treated teeth as well as the healing of bone postsurgery due to their intervention in the calcium balance. Therefore, tooth loss that is due to tumor treatment, bone metabolism, and the capacity for wound healing should be clarified specifically, as is the case with patients undergoing antiresorptive therapy.[10]

2.3.2.3 Albert Schoenberg's disease

This hereditary osteopathy, known as marble bone disease, shows a massive compression of cancellous bone and medullary spaces of the regular bone tissue caused by a genetic defect of the osteoclast function. Strong bone apposition without sufficiently simultaneous bone resorption compresses the medullary spaces so severely that hardly any vascularization remains possible. The bone then looks extremely white, like marble. Radiologically, the eponymous marble-like change in bone structure is also known as osteopetrosis. It also shows developmental disorders of the teeth, with enamel hypoplasia and crown and root malformations. High-grade sclerosis results in an increased risk of fracture of the entire skeleton, with a poor healing tendency of the bone, so that implant or augmentation therapy is absolutely contraindicated.[65] With this condition, single case reports show a high risk of osteomyelitis after implant placement.[61]

2.3.2.4 Osteitis deformans (Paget's disease)

This is a chronic generalized or monostotic bone disorder of an unknown cause that occurs predominantly in the 6th and 7th decade of life in males. In contrast to Albert Schoenberg's disease, the cortical bone is transformed into a fine-meshed cancellous bone, the medullary spaces of which are filled with fibrous tissue.[15]

In addition to the rheumatic complaints, an increase in the circumference of the skull is characteristic, which in extreme cases presents as Leontiasis ossea (lion face) with a high skull cap, pronounced prominent zygomatic bones, increased eye relief, and distension of the maxilla. Radiologically, brightening and shading occur, resembling a cotton flake structure, and the affected bone is generally thickened. Nowadays, the bisphosphonates described

above are usually administered intravenously to stabilize the bone. Due to the altered bone metabolism, a strict indication for implant or augmentation therapy is recommended. The initial case reports show positive treatment outcomes, although there are as yet no long-term studies.[75,76,90] If necessary, modeling osteotomies can be performed to improve the prosthetic anchorage on the deformed alveolar process.

2.3.2.5 Medications

Today, many people self-medicate to improve their physical and psychologic wellbeing. These medications are often not declared at the anamnesis, even though they may have an impact on the outcome of implant therapy. How these medications impact implant therapy has not yet been evaluated for all medications, and many patients assume that their medication history is not relevant for the dentist. Patients receiving proton pump inhibitors (PPI) to treat gastritis or serotonin reuptake inhibitors to stabilize depression episodes exhibit higher rates of implant failure.[45] In these patients, the duration and number of drugs should be investigated before considering implant treatment.[45]

For other medications such as glucocorticoids and NSAIDs, conflicting results have been reported regarding their effect on implant treatment outcomes.[26] However, due to the risk of serve wound healing disturbances, the possibility of a drug holiday should be checked with the responsible physician regarding long-term or high-dose glucocorticoid treatment.

Table 2-1 ASA physical status classification system (last approved by the ASA House of Delegates on 15 October 2014)[40]

ASA PS classification	Definition	Examples (including, but not limited to)
ASA I	A normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only, without substantive functional limitations. Examples include (but are not limited to): current smoker, social drinker of alcohol, pregnancy, obesity, well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitation; one or more moderate to severe diseases. Examples include (but are not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥ 40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (> 3 months) of MI, CVA, TIA or CAD/stents
ASA IV	A patient with severe systemic disease that is a constant threat to life	Examples include (but are not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected	Examples include (but are not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction

	to survive without the operation	
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

2.3.2.6 Cardiovascular diseases

Other general medical conditions only represent a contraindication to implant and augmentation therapy if the patient's life is threatened by the surgical procedure. Intraoperative cardiovascular complications induced by surgical stress should be reduced or even eliminated by perioperative monitoring.[13] Depending on their medical insurance system, it is recommended for patients with ASA Class III to receive dentoalveolar treatments as inpatient procedures (Table 2-1).[47] If surgical intervention is performed as an outpatient procedure, it must be ensured that postoperative home care is in place. In an infarct event, there is an absolute contraindication for elective implant prosthetic surgery in the first 6 months.

2.3.2.7 Hemorrhagic diathesis

When anticoagulant therapy is required, the risk of extensive intraoperative or postoperative bleeding is relevant (Fig 2-6). Anticoagulant therapies are not an absolute contraindication; however, depending on the indication, the risk of a suspended medication or changeover should be weighed against the associated benefits of planned implant and augmentation therapy.[82] When patients declare that they are taking one or more of the so-called blood thinners, it is crucial to find out the exact medication. In case of postoperative bleeding, it is important to know the exact mechanism and, if appropriate, to take into account the specific systemic treatment for the drug (Table 2-2). In some diseases such as atrial fibrillation and coronary artery stenting, double or even triple anticoagulant therapy is recommended.[78]

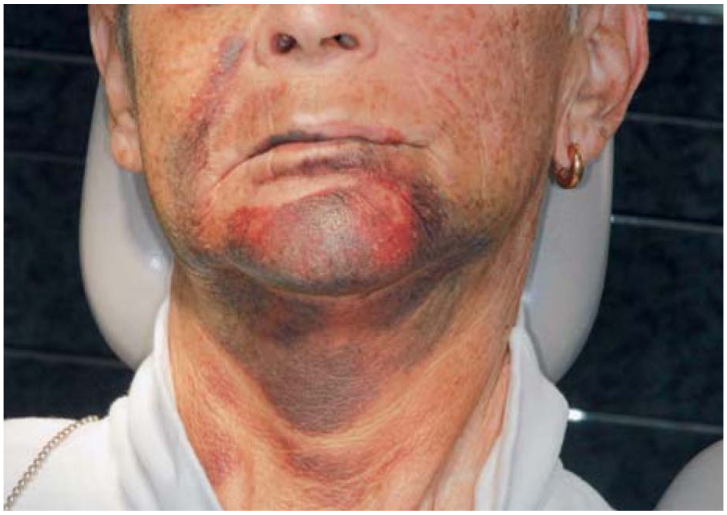


Fig 2-6 Intensive hematoma after surgery in patient under regular aspirin medication.

A distinction should be made between antiplatelet agents such as ASS or P2Y12-antagonists or plasma disorders (coumarins, heparin). While platelet aggregation inhibitors are essentially prophylactically formulated to prevent arterial thrombi in the event of heart attack risk, the plasmatic drugs, in addition to the prophylactic indication, are primarily used therapeutically in cardiac arrhythmias, heart valve replacement, and deep venous thrombosis. The latest developments are direct oral anticoagulants (DOAC/NOAC), which are classified as thrombin or factor-Xa inhibitors. The extent of anticoagulant therapy can also be partially recognized during the patient examination. If old hematomas are already recognizable on the legs or hands, this indicates that the anticoagulant therapy is very heavily adjusted or uncontrolled.

The relatively rare congenital disorders of blood clotting are known mostly as hemophilia A and B and von Willebrand-Jürgens syndrome. When this disease is present, important factors in the coagulation cascade (mostly factors 8 and 9) are almost absent or ineffective and can have reduced activity that can reach a severe level until < 1%. Depending on the remaining activity of the factor, surgery can be performed by substituting the appropriate factors.[41,51]

Consultation with the treating physician is recommended in all patients with hemorrhagic diathesis, as unauthorized conversion might present the risk of the complication of lethal thromboembolic. Therefore, it is important to decide with the responsible physician whether a change to subcutaneous heparin injections (‘bridging’) or intermittent paralysis of anticoagulant therapy is necessary. In the case of replacement medication, an uncontrolled change of the medication with the reduction of the dose of the previous therapy can already lead to serious complications. To reduce the risk of a lethal thrombosis, the general opinion today in cases of oral surgery is not to stop any kind of antithrombotic treatment and not to perform any bridging with heparin, even with platelet aggregation inhibitors such as clopidogrel, prasugrel, ticagrelor or ticlopidine. Heavy postoperative bleeding should be controlled with local surgical possibilities such as an atraumatic approach, avoiding cutting important blood vessels, the use of local hemostatic, and good wound closure with the use of compression plates (see Chapter 8 on complications).

2.3.2.8 Diabetes mellitus

While diabetes mellitus type 1, which is caused by absolute insulin deficiency, only shows a prevalence of 0.02% worldwide, the incidence of diabetes mellitus type 2 is rapidly increasing, especially in the social underclasses of industrialized countries. In a few years, a morbidity rate of 10% in these societies is expected.

In these patients, in addition to the risk of a wound-healing disorder after grafting procedures or implant placement, the risk of peri-implantitis also increases.[30,70] In the area of the oral cavity, diabetic microangiopathy reduces the regenerative capacity of the oral mucosa, since the nutrition of the tissue is reduced due to damage to the capillaries. This often leads to extensive tissue necrosis with exposure of the augmented area, with partial or complete loss of the augmentation.[85]

Table 2-2 Different anticoagulant medications and their doses

Group	Platelet aggregation inhibitors		Plasmatic disorder drugs			
			Coumarin derivative	Heparin	'Non-vitamin K antagonist' oral anticoagulants (**NOAC**s)	
Pharmaceutical mechanism	**Thromboxane-inhibitors**	**P2Y12-inhibitors**	**Vitamin K antagonist**	**Antithrombin III inhibitor**	**Direct factor IIa inhibitor**	**Direct factor Xa inhibitor**
Pharmaceutical substance • Trademark	Acetylsalicylic acid • ASS Dipyridamole • Persantine	Thienopyridines Clopidogrel[1] • Iscover Prasugrel[1] • Efient *3rd generation ADP receptor inhibitors* Cyclopentyl-triazolopyrim-idine Ticagrelor[2] • Brilique • Possia Cangrelor[1] • Kengrexal	Phenprocoumon • Marcumar Warfarin • Coumadin Acenocoumarol • Sinthrome	Enoxaparin • Clexane • Lovenox Certoparin • Mono-Embolex Dalteparin • Fragmin Nadroparin • Fraxiparin Reviparin • Clivarin Tinzaparin • Innohep	Dabigatran • Pradaxa	Rivaroxaban[3] • Xarelto Apixaban[3] • Eliquis Edoxaban • Lixiana Betrixaban • Bevyxxa
Antidote	None available, experimental Desmopressin • Minirin	[1]None available [2]Antibody fragment PB2452 • Bentracimab	Vitamin K	Protamine sulfate	Idaruciz-umab • Praxbind	[3]Andexanet alfa • Ondexxya
Duration of effectiveness	7–10 days			1 day		
Risk of bleeding	Moderate		Middle to high Dose dependent		High	
Minor dentoalveolar surgery	No risk	No risk	INR < 2.5	24 h after last intake	12–24 h drug holiday	
		No risk	INR < 3.5	4–6 h after last intake		
Moderate oral surgery	No risk	No risk	INR < 3.0	24 h after last intake	12–24 h drug holiday	
				4–6 h after last intake		
Severe grafting procedures	No risk	Moderate risk	INR < 2.5	24 h after last intake	24–36 h drug holiday	
Hospital-ization necessary if:	Combination of ASS, P2Y12H, and/or NOAC must be continued and cannot be reduced to monotherapy		INR > 3.5 without possibility of reduction	No medication pause possible		
Special consider-ations	Fix-combinations available: ASS and Clopidogrel • DuoPlavin				Longer pause in case of renal insufficiency	

Since the circulation is restricted, the soft tissue seal of the osseointegrated implants, which is otherwise well accepted in endosseous implants, can already be disturbed during superficial bacterial colonization, so that the peri-implant bone is subject to infection. The medical treatment of the disease takes place according to the long-term blood sugar value of

the glycohemoglobin or HbA1c, the value of which should be below 6%, which corresponds to a value of 120 mg/dl for the acute blood glucose value. From a value of 8%, the risk of healing complications and periodontal disease increases,[80] so that the indication should be carefully checked.[54] If, in the further course of the disease there are no signs of any disruption of the long-term blood glucose value, the prognosis for implant restorations is good.[29] Some studies show no increased failure rates in patients with diabetes in a two-step approach in case of bone augmentation, with appropriate patient guidance and a good maintenance program.[14, 22]

2.3.2.9 Other metabolic diseases

The possibilities of implant therapy are limited by other metabolic diseases that directly or indirectly influence bone regeneration. Here, the diseases of the parathyroid gland should be mentioned because, through hyperparathyroidism, a reduced calcium storage in the bone occurs, which leads to osteoporosis.[48]

The administration of glucocorticoids has become established in several autoimmune diseases today. Cortisone therapy may lead to increased calcium excretion and thus to osteoporosis or a diabetic metabolic condition. This means *per se* that there are some risks involved in implant treatment in the case of a disturbance of secondary cortical activity (Addison's disease), but also in long-term treated bronchial asthma, neurodermatitis, autoimmune diseases such as Crohn's disease, and ulcerative colitis.[4,12] However, the decision to undergo implant treatment should be made according to the individual risk profile, taking into consideration the duration and intensity of the cortisone therapy.

2.4 Specific findings

For implant planning, the extra- and intraoral assessment is carried out to best determine the relevant factors for the necessary prosthetic rehabilitation. Not only should the missing teeth and the patient's desire to restore them be in the foreground of the treatment, but also the functional and esthetic outcome of the entire functioning of the oral system.

2.4.1 Genetic findings

Current development in the field of human genetics is providing an increasing amount of information about genetic developmental disorders. For the development of teeth and the periodontal ligament, ectodermal disorders are mainly relevant.[17] In ectodermal dysplasia, disorders occur on multiple structures that develop from the outer cotyledon. In addition to the hair, nails, and skin, the teeth are also affected. Only very few teeth are present (oligodontia or hypodontia) in the first and the second dentition (mostly canines), in combination with some rudimentary teeth (Fig 2-7a to c). In oligodontia, the existing teeth are often microdontic, so that the prosthetic value is limited. Due to the development-related

lack of teeth, the alveolar ridge is also underdeveloped in volume (Fig 2-7d), but the existing structures compensate for the missing bone supply with a dense bone quality. When planning a restoration, special attention must be paid to the existing available space and the growth pattern, so that pretreatment often requires many years of cooperation with the attending orthodontist (Fig 2-7e to n).[64]

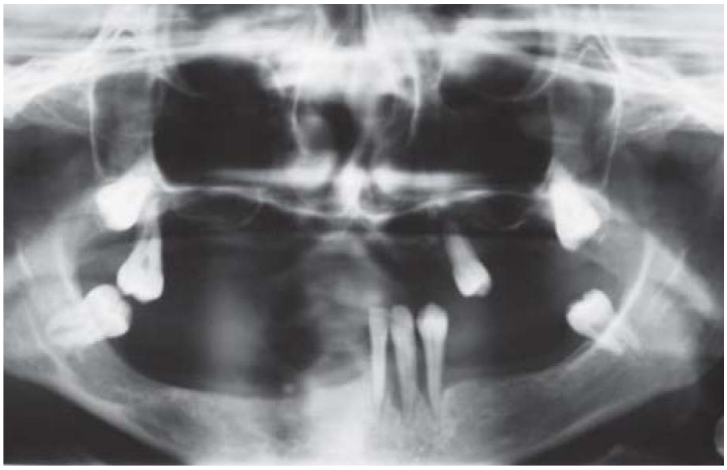


Fig 2-7a Panoramic view of a 28-year-old female patient with a mild form of ectodermal dysplasia.

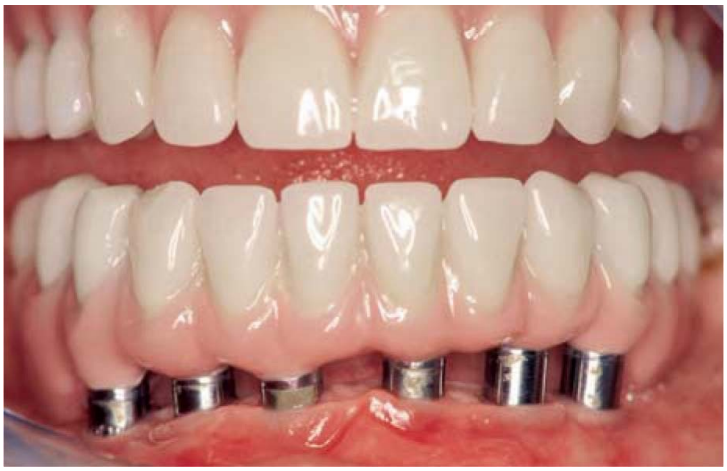


Fig 2-7b Clinical situation 12 years after bone grafting and implant restoration in the mandible.

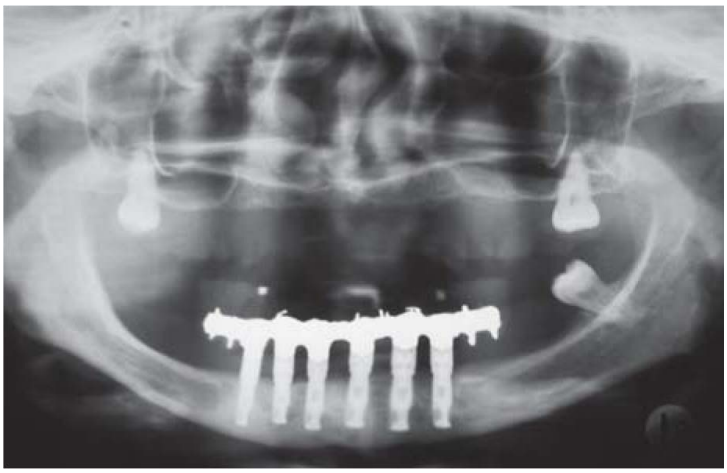


Fig 2-7c Radiologic control 12 years postoperatively.

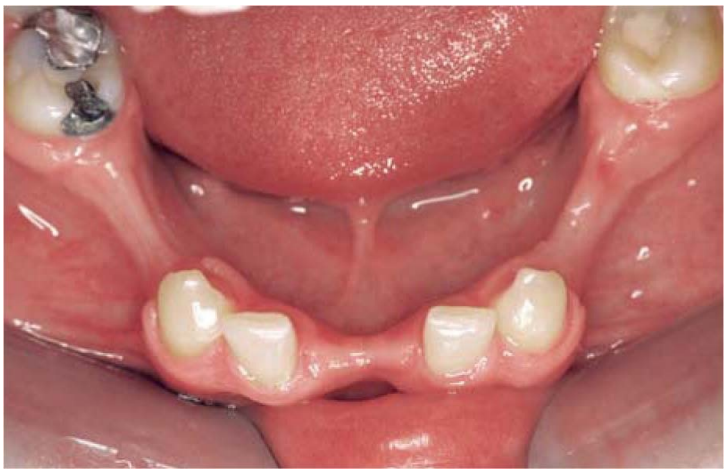


Fig 2-7d Severe bone atrophy with hypodontia.

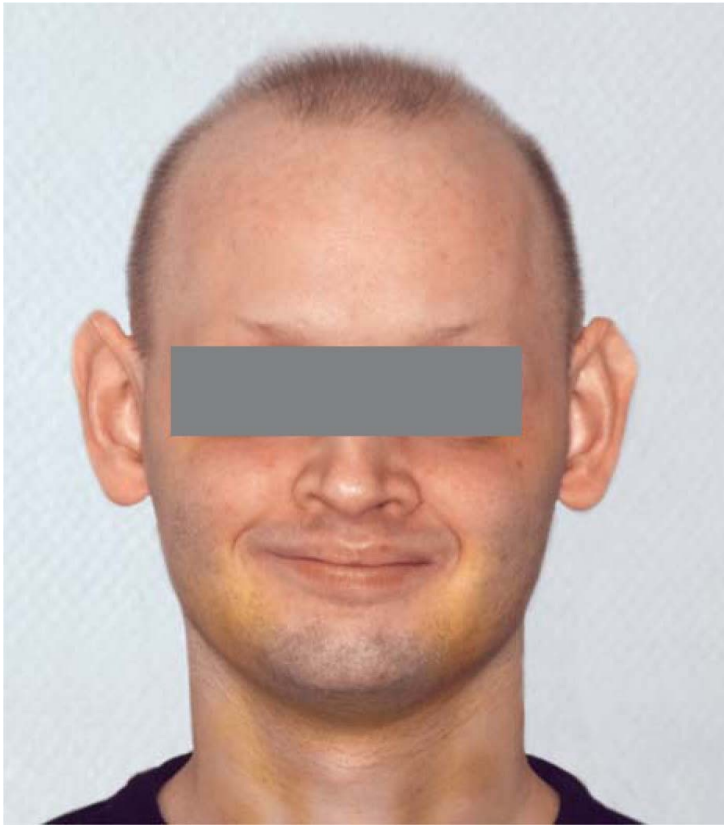


Fig 2-7e Typical appearance of a patient with moderate ectodermal dysplasia.

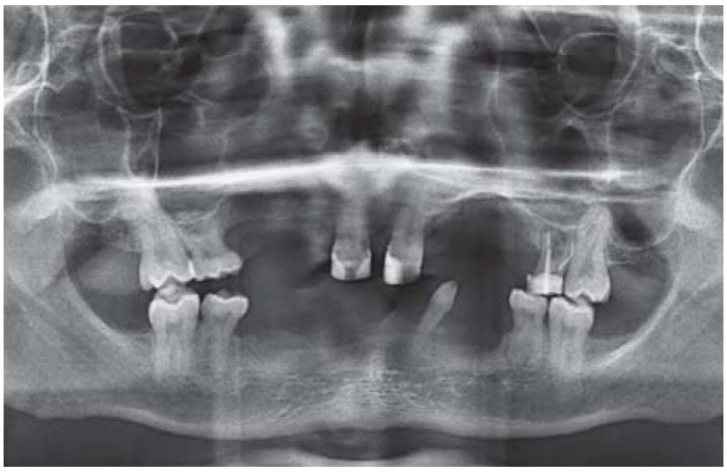


Fig 2-7f Panoramic radiograph revealing the absence of many teeth.

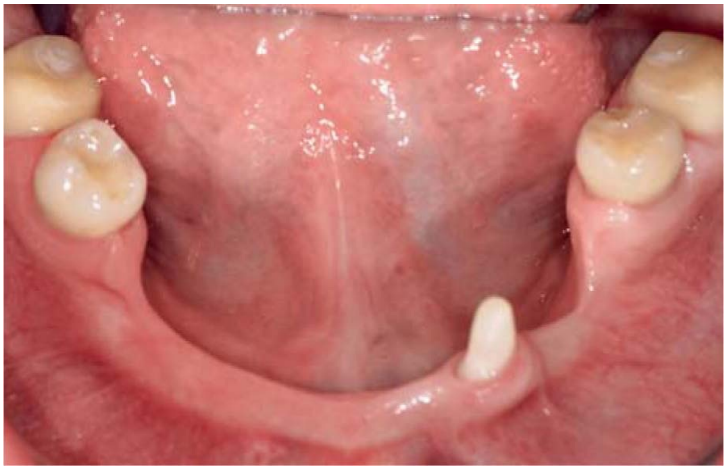


Fig 2-7g Clinical situation of the mandible with hypodontia and severe bone atrophy.

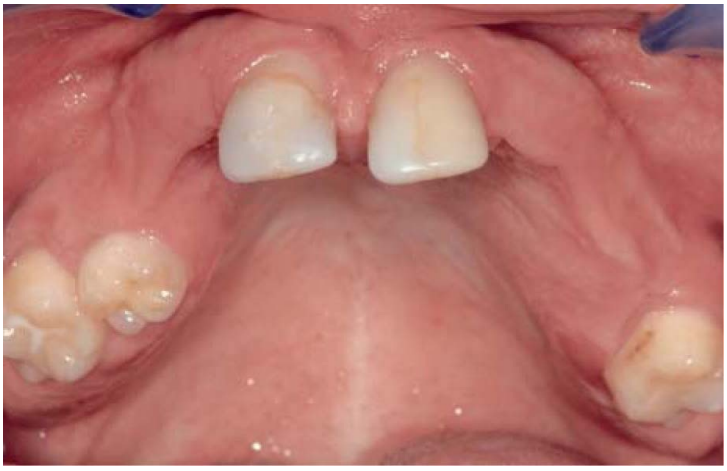


Fig 2-7h Clinical aspect of the maxilla.

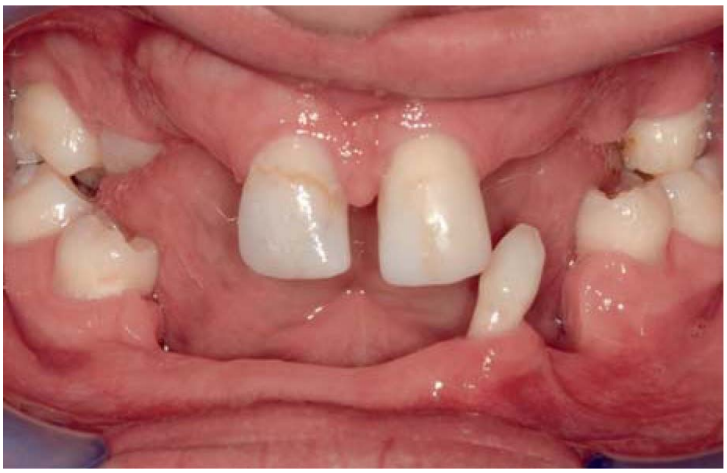


Fig 2-7i Absence of a physiologic VDO due to missing occlusal support.

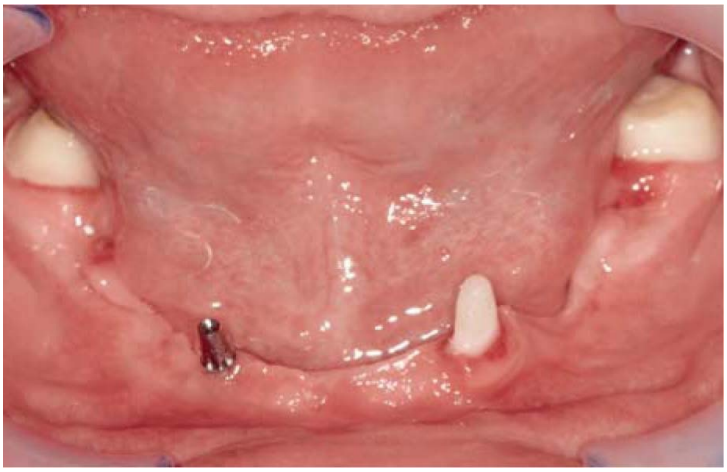


Fig 2-7j The remaining teeth are prepared to support a fixed temporary restoration. In addition, a temporary implant is inserted in the right mandible.

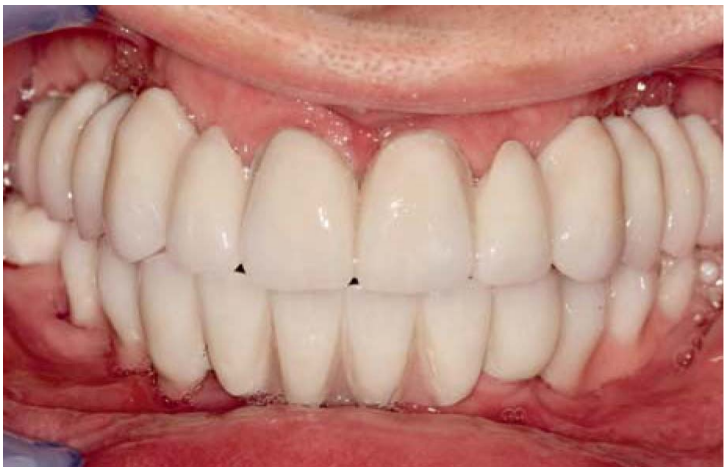


Fig 2-7k A fixed temporary restoration for the correction of the VDO.

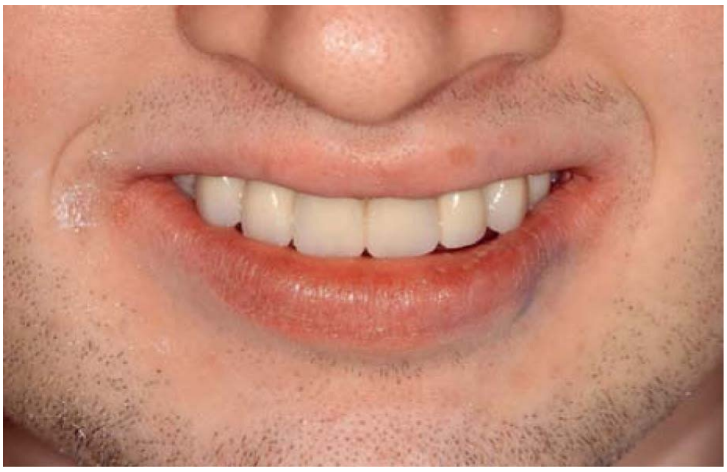


Fig 2-7l The temporary restoration offers good lip support, improving the esthetics.

In the very rare autosomal recessive inherited Papillon-Lefèvre syndrome, the periodontal findings show severe periodontitis, leading to early loss of primary teeth usually up to the 4th year of life, and permanent teeth up to the 14th year. This exceptional periodontal disease presents a pronounced atrophy of the alveolar processes, which requires augmentative pretreatment.[86]

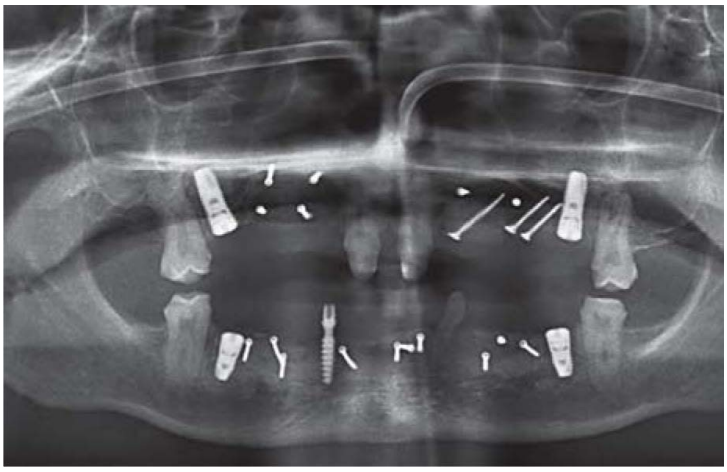


Fig 2-7m Multiple bone block augmentation to reconstruct the missing bone.

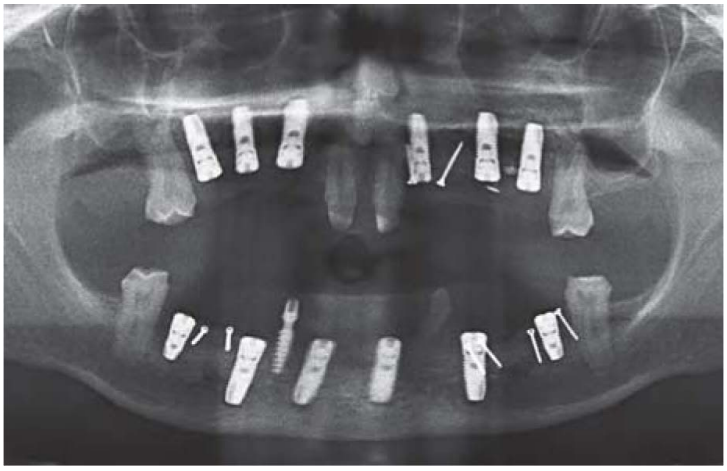


Fig 2-7n Radiograph control after insertion of the remaining implants in the grafted bone.