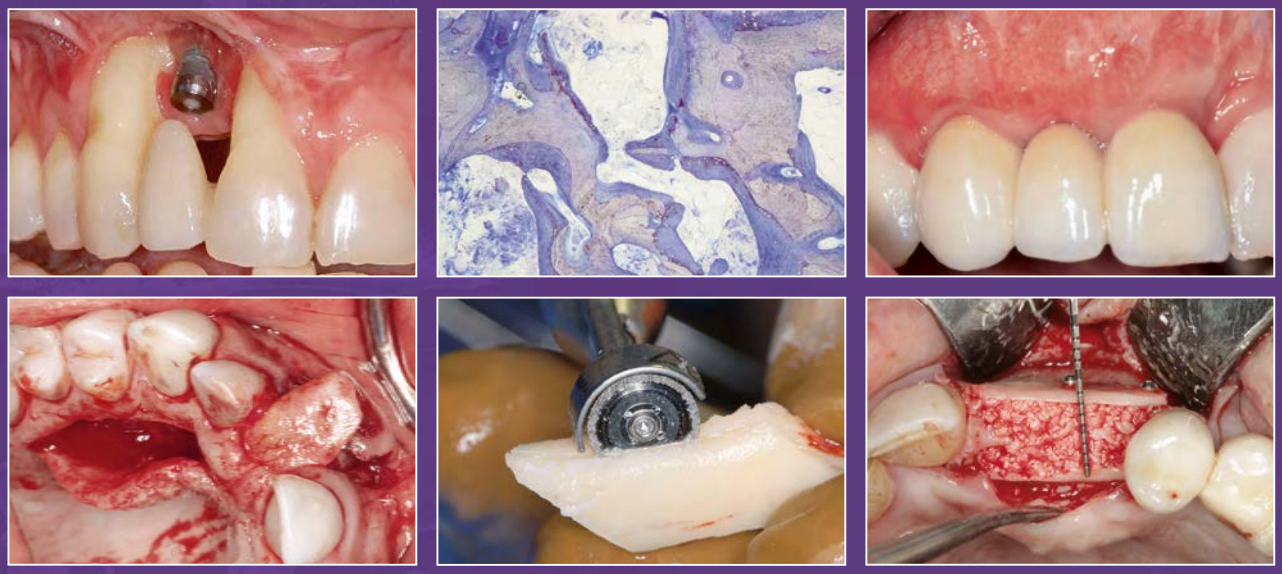
Fouad Khoury

Bone and Soft Tissue Augmentation in Implantology



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

QUINTESSENCE PUBLISHING

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

QUINTESSENCE PUBLISHING

Berlin | Chicago | Tokyo
Barcelona | London | Milan | Mexico City | Moscow | Paris | Prague | Seoul | Warsaw
Beijing | Istanbul | Sao Paulo | Zagreb

A CIP record for this book is available from the British Library.
ISBN: 978-3-86867-591-7

QUINTESSENCE PUBLISHING DEUTSCHLAND

Quintessenz Verlags-GmbH
Ifenpfad 2–4
12107 Berlin
Germany
www.quintessence-publishing.com

Quintessence Publishing Co Ltd
Grafton Road, New Malden
Surrey KT3 3AB
United Kingdom
www.quintessence-publishing.com

Editing: Avril du Plessis,
Quintessenz Verlags-GmbH, Berlin, Germany
Layout and Production:
Quintessenz Verlags-GmbH, Berlin, Germany

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

Private Practice in Oral and Maxillofacial Surgery and Prosthodontics
Misch Implant Dentistry, Sarasota, FL

Clinical Associate Professor
University of Michigan, School of Dentistry
University of Alabama at Birmingham, School of Dentistry
University of Pennsylvania, School of Dental Medicine
University of Florida, College of Dentistry

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

Professor and Chairman
Department of Periodontology and
Implant Dentistry
New York University College of Dentistry

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 Do-Quang (Netherlands), Dr. Jan Jansohn, Dr. David Wiss (Vienna, Austria), Dr. Michael Berthold, Dr. Elisabeth Schmidtmayer, Dr. Philip Keeve, Dr. Valentin Loriod (Besançon, France), Dr. Erik Faragó (Budapest, Hungry), Dr. Christopher Schmid, Dr. Andrea Savo (Rome, Italy), Dr. Oliver Dresbach, Dr. Kathrin Spindler, Dr. Alexander Zastera, Dr. Sarah Römer, and Dr. Jan Wildenhof. Special thanks to my previous co-workers, Dr. Carsten Becker, for his help with the digital transformation of analog figures as well as for the excellent illustrations of some surgical techniques (see Chapter 3), and Dr. Tobias Terpelle, for his tremendous support for the chapter on restorative

procedures. In addition, I would like to thank the whole team of the Privatklinik Schloss Schellenstein in Olsberg for their help and loyalty during the past three decades.

Thanks also to the further Director of the Department of Cranio-Maxillofacial Surgery, University Hospital Münster, Prof. Dr. mult. Ulrich Joos, as well as to the actual Director, Prof. Dr. Dr. Johannes Kleinheinz, for their scientific support.

My sincere thanks go to the entire team at Quintessence Publishing, especially Dr. Horst W. Haase, Mr. Christian Haase, Mr. Johannes Wolters, and Mrs. Anita Hattenbach, for their support and patience over the years. Many thanks also to Mrs. Avril du Plessis for the excellent correction and editing as well as to Mrs. Ina Steinbrück for the perfect layout.

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

Editors and Contributors

Editor

KHOURY Fouad, DMD, PhD
Director
Privatklinik Schloss Schellenstein
Olsberg, Germany;
Professor
Department of Cranio-Maxillofacial Surgery
University Hospital Münster, Germany

Contributors (in alphabetical order)

GRUBER Reinhard, DMD, PhD
Professor and Chair
Department of Oral Biology
School of Dentistry
Medical University of Vienna, Austria

HANSER Thomas, DMD, M.Sc.
Deputy Director
Privatklinik Schloss Schellenstein
Olsberg, Germany;
Senior Academic Lecturer
Department of Postgraduate Education
Goethe University Frankfurt, Germany

KEEVE Philip L., DMD, M.Sc.
Private Office for Periodontology and Oral Surgery
Hameln, Germany

KHOURY Charles, DDS, DES, CES, M.Sc.
Professor
Department of Prosthodontics
School of Dentistry
St. Joseph University, Beirut, Lebanon

NEUGEBAUER Joerg, DMD, PhD
Professor
Steinbeis University Berlin, Transfer-Institut, Management of Dental and Oral Medicine;
Senior Academic Lecturer
Interdisciplinary Department for Oral Surgery and Implantology
Department of Craniomaxillofacial and Plastic Surgery
University of Cologne, Germany;
Senior Oral Surgeon
Group Office for Implantology, Dr. Bayer and colleagues, Landsberg am Lech, Germany

ZOELLER Joachim, MD, DMD, PhD
Professor and Chairman
Interdisciplinary Department for Oral Surgery and Implantology
Department of Craniomaxillofacial and Plastic Surgery
University of Cologne, Germany

Table of Contents

1 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.

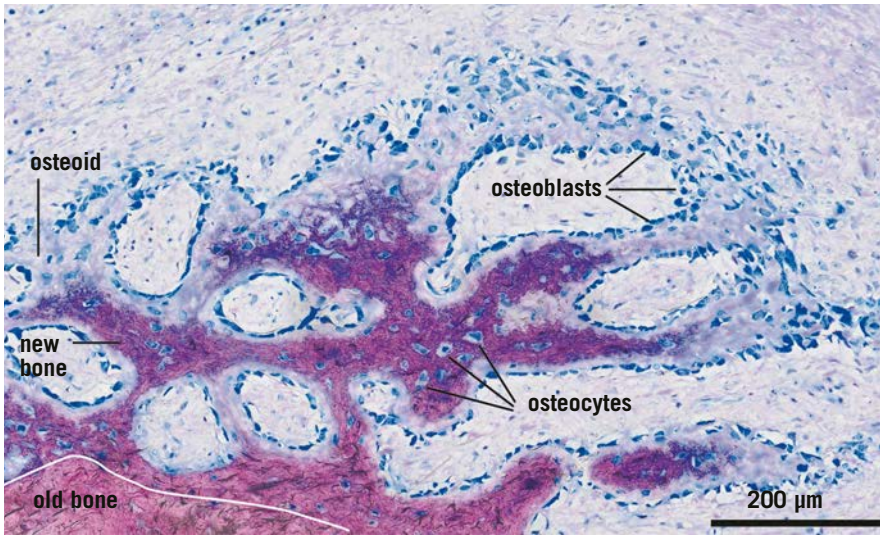


Fig 1-1 Osteoblasts produce bone on the surface of a host bone. Bone formation occurs on the surface of existing bone (pink). New bone (dark purple) is lined by seams of osteoblasts and arranged in osteonal structures. Osteoid (barely stained) is bone that is not yet mineralized. The direction of new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

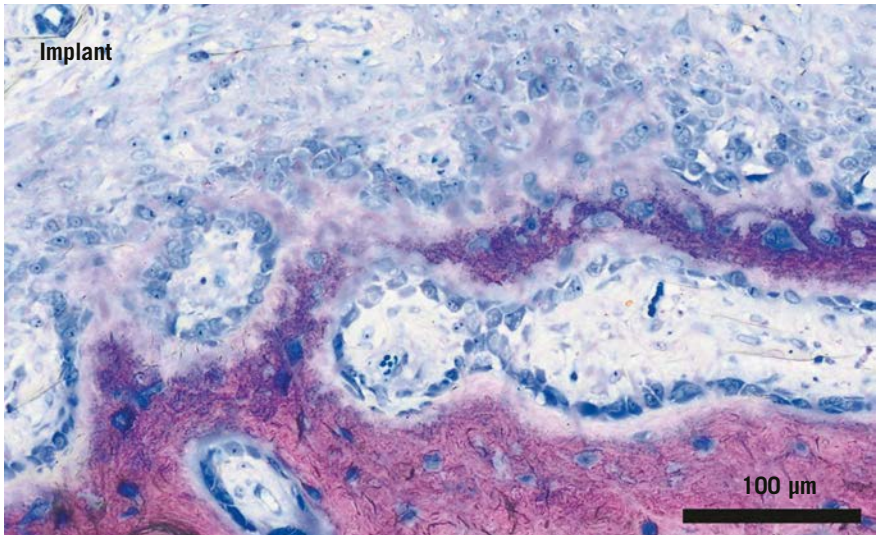


Fig 1-2 Osteoblast seams during the early stages of bone formation. Bone formation is the consequence of osteoblast activity. Osteoblasts dominate the scene, and non-mineralized bone (osteoid) is visible. [The image is of pig bone.]

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,

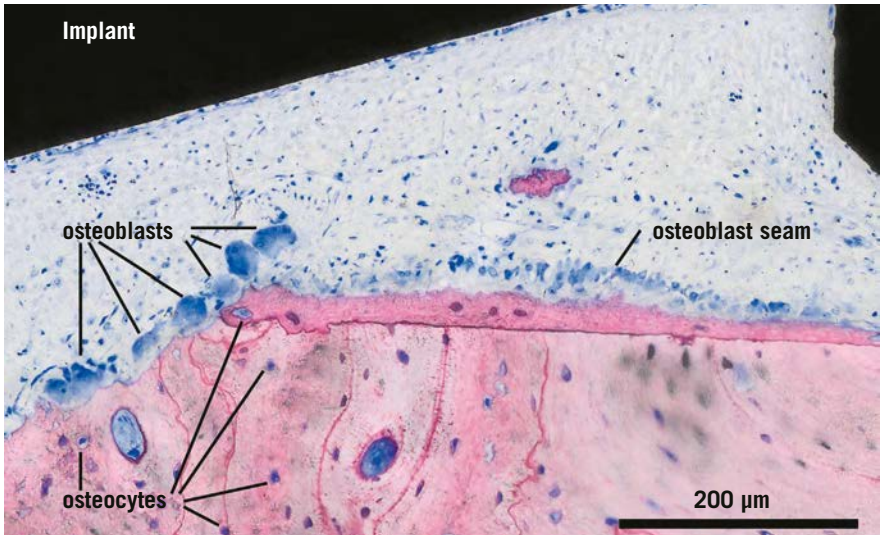


Fig 1-3 Osteoclasts (bone-resorbing cells), osteoblasts (bone-producing cells), and osteocytes. Osteoclasts are multinucleated cells that are exclusively capable of resorbing bone. In this image, which is a detail taken from Fig 1-7, a group of osteoclasts is resorbing bone next to a seam of osteoblasts, 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.]

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.

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

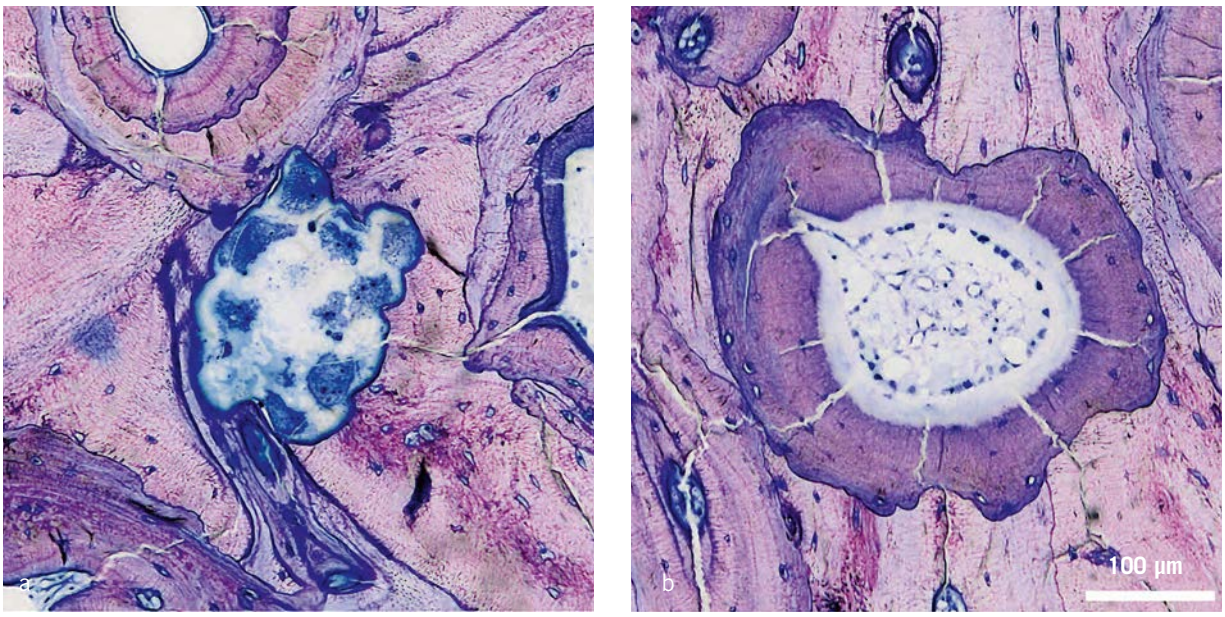


Fig 1-4 Creation of osteons by basic multicellular compartments (BMU). The BMU defines the site of bone remodeling. (a) Tunneling of cortical bone by multinucleated osteoclasts. (b) This image is characteristic for the activity of bone forming osteoblasts with an osteoid layer, rebuilding the concentric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

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.

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

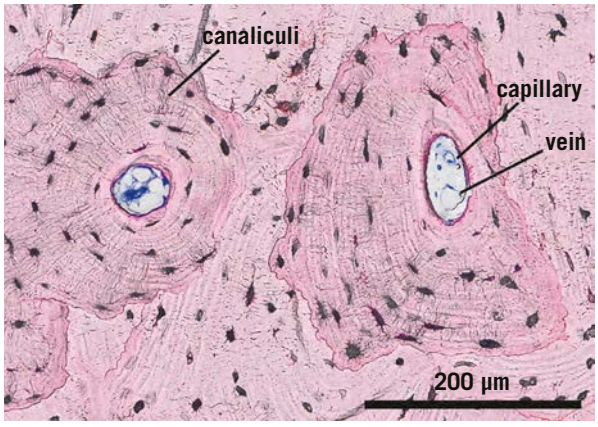


Fig 1-5 Osteon with osteocytes being connected via their canaliculi. The osteon is a functional bone unit consisting of a central canal filled with soft tissue, with bone lamellae arranged concentrically around it. They can be found in the substantia compacta of the bone. Osteocytes are interconnected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

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.

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