Next-Generation Biomaterials for Bone & Periodontal Regeneration

Edited by
Richard J. Miron, DDS, BMSc, MSc, PhD, Dr med dent
Yufeng Zhang, MD, DDS, PhD

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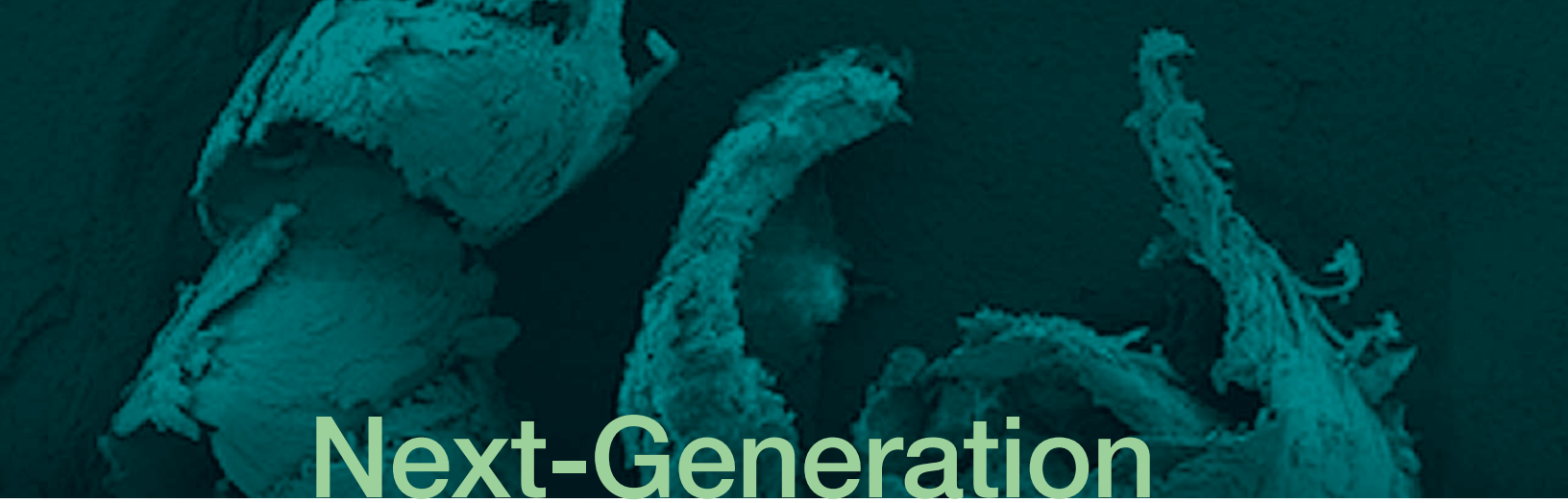

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Edited by

Richard J. Miron, DDS, BMSc, MSc, PhD, Dr med dent
Visiting Faculty
Department of Periodontology
School of Dental Medicine
University of Bern
Bern, Switzerland

Yufeng Zhang, MD, DDS, PhD
Professor
Department of Dental Implantology
School of Stomatology
Wuhan University
Wuhan, China

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Contents

Dedication

Mentors are without question the most pivotal people in any young aspiring scientist's career. I was blessed to have grown up in the small city of North Bay, Ontario, in Northern Canada, where the director of our high school science program, Jean-Marc Filion, took a young group of scholars under his wing each and every year, exposing them to the wonders of science through diverse science fair projects. He spent countless hours mentoring us, teaching us to accurately design experiments; to answer hypotheses; to think independently, critically, and ethically; to write scientifically; and to communicate our findings elegantly. We trained for hours and successfully represented this tiny little high school on both national and international levels. I'm frequently asked what it takes to succeed in academics, and the answer is simple: outstanding mentors.

I remember the day I first walked into the Filion science laboratory. I was 13 years old, 5 feet tall, and looked straight up to Room 325. Not knowing what to expect, I was happily greeted by a smiling, joyous man and entered a world of opportunities that I could never have imagined at such a young age. Like young athletes who are specifically taught to develop and master their craft as early as possible in their lives, I began a series of experiments in the arena of life sciences that opened an array of scholarship opportunities and future collaborations that have since pioneered my career in the sciences.

My favorite memory of Dr Filion was the day of his retirement party. Families and staff had gathered to discuss what remains one of the most prolific careers coming from my home city of North Bay, and while his curriculum vitae was decorated with numerous presidencies, titles, publications, awards, and honors, Dr Filion spoke not a single word of his lifelong achievements. Instead he spent the entire hour resonating with joy and discussing the careers of all the young people who had trained under his leadership. Not a word was spoken about any of his individual accolades; instead he expressed his true and sincere passion for mentoring young individuals to lead prolific careers in science, medicine, and research. As he once said so elegantly, he "found a way to gather wonderful people to do wonderful things to help create a much richer and rewarding life."

For those of you who have the opportunity to act as a mentor at any level, whether elementary school, high school, college, or university, I encourage you to consider the impact you can have on a young person's developing mind. Your selfless approach to teamwork, generous and countless hours spent mentoring, and love and dedication to your craft are certainly not unnoticed or forgotten. Never underestimate how important mentors are to young people.

In today's competitive world, great mentors are hard to come by, but their impact will extend far beyond the time each of them will spend on earth.

Dr Jean-Marc Filion passed away in 2017 at the age of 65 following complications from an unexpected heart attack. In honor of his legacy, 100% of the royalty proceeds from this book will be donated to Algonquin Secondary School in North Bay, Ontario, to create a scholarship program in his recognition for graduating students to attend college.

Preface

The use of biomaterials in dental medicine has become so widespread over the past few decades that an entire textbook is needed to address their use during bone and periodontal regeneration. As little as 40 years ago, the practice of dentistry did not embrace the various bone grafts, barrier membranes, or growth factors currently available in today's market. Over the years, exponential growth of each of these classes of biomaterials has delivered many new regenerative modalities and protocols for the improvement of patient care. As the number of new and innovative biomaterials continues to rise, many of them remain entirely foreign to practicing clinicians, and this book was designed to address this gap of knowledge by summarizing some of the groundbreaking research performed to date on this topic. Over 65 international authors have contributed to this textbook, each with different surgical backgrounds and expertise utilizing the various regenerative biomaterials presented throughout this book.

The first 10 chapters focus on the biologic background and applications of bone grafting materials utilized in dentistry. For each of these classes of biomaterials—including autografts, allografts, xenografts, and alloplasts—the pros and cons are discussed extensively with their appropriate clinical indications. In addition, next-generation biomaterials—including the recently developed osteoinductive synthetic bone grafts, 3D printed bone grafts, and novel bone adhesives used to facilitate bone-to-bone and bone-to-implant adhesion—are presented as future grafting options.

In chapter 11, the principles of guided tissue and bone regeneration are covered in detail with many recent advancements in barrier membrane technologies presented, including their uses and indications. Furthermore, a more natural approach utilizing platelet-rich fibrin is emphasized in chapter 12. Chapters 13 through 22 cover the increasing use of growth factors utilized in dentistry for bone regeneration, including the currently available FDA-approved bone morphogenetic protein 2 (BMP-2, Infuse Bone Graft [Medtronic]), as well as those utilized for periodontal regeneration, including enamel matrix derivative (EMD, Emdogain [Straumann]) and platelet-derived growth factor (GEM21, Osteohealth). While the use of such growth factors in daily dental practice remains in its infancy, it is generally accepted that they provide a prominent future avenue for regenerative medicine as the field continues to move toward more minimally invasive surgery. As such, the use of growth factors has been the focus of many research laboratories around the world investigating the impact of single or combined bioactive molecules for the regeneration of either soft or hard tissues. These include a liquid delivery system for EMD (Osteogain, Straumann), recombinant human BMP-9, recombinant human fibroblast growth factor 2, adenovirus delivery of growth factors (gene therapy), as well as the incorporation of various trace elements that induce bone/periodontal regeneration, including strontium (Sr), boron (Br), and magnesium (Mg), into biomaterials.

The final chapter of this textbook is perhaps the most important. It covers the selection criteria and decision-making process for clinicians and is designed to help select appropriate biomaterials for each specific regenerative protocol. These include important topics such as which bone graft to utilize for guided bone regeneration, sinus augmentation, as well as around dental implants under various clinical settings and loading protocols. Furthermore, the regenerative potentials of each growth factor are compared with clinical cases presented discussing their specific use in dentistry. Much like one implant diameter, size, and length cannot be utilized for each placed implant, neither can one bone grafting material or barrier membrane be utilized for all bone augmentation procedures. Similarly, it should neither be expected that one growth factor can fulfill the task of maximizing the regenerative outcomes in all clinical situations. This textbook aims to better address these issues and limitations in a simple and understandable manner to maximize the clinician's ability to utilize biomaterials in an appropriate, predictable, and evidence-based manner.

While the book is focused on covering gold-standard biomaterials utilized in dentistry today, it also introduces many of the next-generation biomaterials that will optimize future bone and periodontal regeneration. The inclusion of these materials will certainly facilitate and ease the practice of dentistry, and we anticipate updating this textbook in due time to provide more evidence-based protocols behind the currently utilized biomaterials and to introduce future biomaterials that will be made commercially available in upcoming years. As such, it is our hope that this book will benefit all surgically based dentists involved in regenerative dentistry by adding to their current knowledge base while also improving their ability to make rational, evidence-based decisions regarding the selection criteria of biomaterials utilized for bone and periodontal regenerative therapy.

I am very proud and honored to bring together this work from internationally recognized experts in this first edition of *Next-Generation Biomaterials for Bone & Periodontal Regeneration*. I sincerely hope you enjoy the read!

Acknowledgments

I want to start by thanking the co-editor of this textbook, Yufeng Zhang. Since meeting you nearly a decade ago, we have undertaken countless projects together, and it has been a sincere pleasure to work with you so closely. Our common and respective laboratories have done much of the preclinical research for the majority of the biomaterials discussed in this textbook, and we look forward to future collaboration with other colleagues and startup companies/pioneers to further evaluate biomaterials for bone and periodontal regeneration. This book project has been a ton of fun!

I also want to thank the contributing authors for their time, effort, and support during the completion of this major project. Each of you has had a tremendous impact on the use of biomaterials in regenerative dentistry, and your expertise, knowledge, and clinical guidelines and judgment have certainly enriched the quality of this textbook.

To all my mentors throughout my academic training, including Douglas Hamilton and Jeff Dixon at the University of Western Ontario, Canada; Anton Sculean, Dieter Bosshardt, Daniel Buser, and Reinhard Gruber at the University of Bern, Switzerland; and Fatiha Chandad at the University of Laval, Canada, I sincerely thank each and every one of you for your time and countless hours of encouragement during my years of study. Your never-ending mentorship and guidance have been a real blessing.

I want to personally thank two special authors who have each contributed majorly to numerous chapters in this textbook. To both Anton Sculean and Michael Pikos, leaders in periodontal and bone regeneration, respectively, I thank you tremendously for having provided countless well-documented cases that have complemented and improved this textbook. Your time and desire to share insightful clinical judgment and numerous guidelines have certainly enhanced the book. Your combined years of experience and knowledge have been highly regarded, valued, and appreciated.

To the team at Quintessence Publishing, especially Bryn Grisham, Director of Book Publications, and Leah Huffman, Senior Editor on this book, I personally thank you all for the opportunity to publish this work. The quality of your team at Quintessence Publishing and the attention to detail regarding the preparation of this manuscript have been nothing short of amazing. In every aspect, you've exceeded my expectations.

Lastly, I want to thank my parents and family for their support during these busy times. In particular, I thank Robin Miron for gathering and producing many figures and figure templates that were often created while on the road, in planes, or in the late hours of the evenings and weekends. Your efforts are certainly recognized. I also want to thank Yen Nguyen for reminding me to have a little more fun during the completion of this endless project.

Contributors

Alexandre-Amir Aalam, DDS
Clinical Assistant Professor
Herman Ostrow School of Dentistry
University of Southern California
Los Angeles, California, USA

Alina Krivitsky Aalam, DDS
Private Practice Limited to Periodontics and Implants
Los Angeles, California, USA

Mustafa Abd El Raouf, PhD
Faculty of Veterinary Medicine
Zagazig University
Zagazig, Egypt

Sarah Al-Maawi, DDS, PhD
Postdoctoral Research Fellow
FORM-Lab (Frankfurt Orofacial Regenerative Medicine)
University Hospital Frankfurt
Goethe University
Frankfurt am Main, Germany

Nicole B. Arweiler, DDS, PhD
Professor
Department of Periodontology
Philipps University of Marburg
Marburg, Germany

Albert Barroso Panella, DDS, MSc, PhD
Assistant Professor
Department of Oral and Maxillofacial Surgery
School of Dental Medicine
International University of Catalonia
Barcelona, Spain

Itzhak Binderman, DMD
Professor
Department of Oral Biology and Biomedical Engineering
School of Dental Medicine
Tel Aviv University
Tel Aviv, Israel

Mark Bishara, DDS
Private Practice
Bowmanville, Ontario, Canada

Dieter D. Bosshardt, PhD
Professor and Head of Oral Histology
Department of Periodontology
School of Dental Medicine
University of Bern
Bern, Switzerland

Michael Brown, BEng
R&D Program Manager
Launchpad Medical
Boston, Massachusetts, USA

Fatiha Chandad, PhD
Dean of Research
University of Laval
Quebec City, Quebec, Canada

Joseph Choukroun, MD
Private Practice
Nice, France

David L. Cochran, DDS, MSc, PhD, MMSci, Dr hc
Professor and Chair
Department of Periodontics
University of Texas Health Science Center at San Antonio
San Antonio, Texas, USA

Michel Dard, DDS, PhD
Professor
New York University College of Dentistry
New York, New York, USA

Ferdinando D'Avenia, DDS, MSc
Professor
Department of Periodontology
University Hospital of Parma
Parma, Italy

Joost de Bruijn, PhD
Professor
School of Engineering and Materials Science
Queen Mary University of London
London, England

James Deschner, Dr med dent
Professor and Director
Department of Periodontology and Operative Dentistry
University Medical Center of the Johannes Gutenberg University
Mainz, Germany

Ferenc Döri, DMD, PhD, Dr habil
Associate Professor
Department of Periodontology
Semmelweis University
Budapest, Hungary

Bruce R. Donoff, DMD, MD
Dean
Harvard School of Dental Medicine
Boston, Massachusetts, USA

Nikos Donos, DDS, MSc, PhD
Head and Chair of Periodontology
Director of Research
UCL Eastman Dental Institute
London, England

Jonathan Du Toit, DDS
Department of Periodontics and Oral Medicine
Faculty of Health Sciences
University of Pretoria
Pretoria, South Africa

Mariusz Duda, DMD, PhD
Private Practice
Katowice, Poland

Meizi Eliezer, DDS, PhD
Department of Periodontology
School of Dental Medicine
University of Bern
Bern, Switzerland

Tobias Fretwurst, Dr med dent
Oral Surgeon
Department of Oral and Maxillofacial Surgery
University of Freiburg
Freiburg, Germany

Stuart Froum, DDS
Adjunct Clinical Professor and Director of Clinical Research
Department of Periodontology and Implant Dentistry
New York University College of Dentistry

Private Practice
New York, New York, USA

Paul Fugazzotto, DDS, MSc
Private Practice Limited to Periodontics and Implants

Visiting Lecturer
Tufts University and Harvard School of Dental Medicine
Boston, Massachusetts, USA

Masako Fujioka-Kobayashi, DDS, PhD
Research Associate
Department of Cranio-Maxillofacial Surgery
University Hospital of Bern
University of Bern
Bern, Switzerland

Shahram Ghanaati, MD, DMD, PhD
Professor
Department for Oral, Cranio-Maxillofacial and Facial Plastic Surgery
FORM-Lab (Frankfurt Orofacial Regenerative Medicine)
University Hospital Frankfurt
Goethe University
Frankfurt am Main, Germany

Howard Gluckman, BDS, MChD (OMP)
Specialist in Periodontics, Implantology, and Oral Medicine
Director of Implant & Aesthetics Academy
Cape Town, South Africa

Andrea Grassi, DDS
Private Practice
Reggio Emilia, Italy

Reinhard Gruber, PhD
Professor
Department of Oral Biology
Medical University of Vienna
Vienna, Austria

Vincent Guillemette, DMD
Private Practice
Quebec City, Quebec, Canada

Gideon Hallel, DMD, MPA
Private Practice
Tel Aviv, Israel

Robert Horowitz, DDS
Professor
Department of Periodontology, Implant Dentistry and Oral Surgery
New York University College of Dentistry
New York, New York, USA

Angel Insua, DDS, MSc, PhD
Department of Periodontics and Oral Medicine
University of Michigan School of Dentistry
Ann Arbor, Michigan, USA

Søren Jepsen, DDS, MSc, PhD
Professor and Chair
Department of Periodontology, Operative and Preventive Dentistry
University of Bonn
Bonn, Germany

Adrian Kasaj, DDS, MSc, PhD
Professor
Department of Periodontology and Operative Dentistry
University Medical Center of the Johannes Gutenberg University
Mainz, Germany

George Kay, DMD, MMSc
Lecturer
Advanced Graduate Education
Division of Restorative Dentistry
Harvard School of Dental Medicine
Boston, Massachusetts, USA

Ismael Khouly, DDS, MSc, PhD
Associate Director of Periodontology & Implant Dentistry
Bluestone Center for Clinical Research

Clinical Assistant Professor
Department of Oral and Maxillofacial Surgery
New York University College of Dentistry
New York, New York, USA

Gregori Kurtzman, DDS
Private Practice
Silver Spring, Maryland, USA

Ye Ling, DDS, PhD
Professor
State Key Laboratory of Oral Diseases
National Clinical Research Center for Oral Diseases
West China Hospital of Stomatology
Sichuan University
Chengdu, China

Staale Petter Lyngstadaas, DDS, MSc, PhD
Professor and Head of Research
Institute of Clinical Dentistry
University of Oslo
Oslo, Norway

Richard J. Miron, DDS, BMSc, MSc, PhD, Dr med dent
Visiting Faculty
Department of Periodontology
School of Dental Medicine
University of Bern
Bern, Switzerland

Alberto Monje, DDS, MS
Director, Division of Periodontology
Clínica CICOM
Badajoz, Spain

Associate Professor
Department of Periodontology
International University of Catalonia
Barcelona, Spain

Toshiaki Nakamura, DDS, PhD
Senior Assistant Professor
Department of Periodontology
Kagoshima University Graduate School of Medical and Dental Sciences
Kagoshima, Japan

Kathia Nelson, DDS, MSc
Professor and Chair
Department of Oral and Maxillofacial Surgery
University of Freiburg
Freiburg, Germany

Carlos Nemcovsky, DDS, MSc, PhD
Professor
Department of Periodontology and Dental Implantology
Tel Aviv University
Tel Aviv, Israel

Dimitris Nikolidakis, DDS, MSc, PhD
Private Practice Limited to Periodontics
Heraklion, Greece

Kazuyuki Noguchi, DDS, PhD
Professor and Chair
Department of Periodontology
Kagoshima University Graduate School of Medical and Dental Sciences
Kagoshima, Japan

Michael A. Pikos, DDS, MSc
Director, Pikos Institute
Tampa, Florida, USA

Benjamin Pippenger, PhD
Research Associate
Preclinical & Translational Research
Institut Straumann AG
Basel, Switzerland

Alan Pollack, DDS
Private Practice
New York, New York, USA

Giulio Rasperini, DDS, MSc, PhD
Professor
Department of Biomedical Surgical and Dental Sciences
University of Milan
Milan, Italy

Nikola Saulacic, DDS, PhD
Research Associate
Department of Cranio-Maxillofacial Surgery
Faculty of Medicine
University of Bern
Bern, Switzerland

Patrick R. Schmidlin, Dr med dent habil
Professor and Head
Division of Periodontology and Peri-Implant Diseases
Clinic of Preventive Dentistry, Periodontology and Cariology
Center of Dental Medicine
University of Zurich
Zurich, Switzerland

Anton Sculean, Dr med dent, Dr hc, MS
Professor, Executive Director and Chairman
Department of Periodontology
School of Dental Medicine
University of Bern
Bern, Switzerland

Jordi Caballé Serrano, Dr med dent, MSc, PhD
Associate Professor
Department of Oral and Maxillofacial Surgery
School of Dental Medicine
International University of Catalonia
Barcelona, Spain

Associate Researcher
Department of Oral Surgery and Stomatology
School of Dental Medicine
University of Bern
Bern, Switzerland

Yoshinori Shirakata, DDS, PhD
Associate Professor
Department of Periodontology
Kagoshima University Graduate School of Medical and Dental Sciences
Kagoshima, Japan

Alain Simonpieri, DDS
Professor
Department of Oral Surgery
University Federico II Naples
Naples, Italy

Private Practice Limited to Periodontology and Implantology
Beausoleil and Marseille, France

Andreas Stavropoulos, DDS, MSc, PhD
Professor and Chair
Department of Periodontology
Malmö University
Malmö, Sweden

Leonardo Trombelli, DDS, MSc, PhD
Professor and Chair of Periodontology
Director, Research Centre for the Study of Periodontal and Peri-implant Diseases
University of Ferrara
Ferrara, Italy

Hom-Lay Wang, DDS, MSc, PhD
Collegiate Professor of Periodontics
Professor and Director of Graduate Periodontics
Department of Periodontics and Oral Medicine
University of Michigan School of Dentistry
Ann Arbor, Michigan, USA

Yulan Wang, DDS, PhD
Postdoctoral Research Fellow
Department of Dental Implantology
School of Stomatology
Wuhan University
Wuhan, China

Hudi Xu, DDS, PhD
Postdoctoral Research Fellow
Department of Dental Implantology
School of Stomatology
Wuhan University
Wuhan, China

Huipin Yuan, PhD
Professor
Complex Tissue Regeneration
MERLN Institute
Maastricht University
Maastricht, The Netherlands

Homayoun H. Zadeh, DDS, PhD
Associate Professor
Director, Postdoctoral Periodontology Program
Herman Ostrow School of Dentistry
University of Southern California
Los Angeles, California, USA

Xiaoxin Zhang, DDS, PhD
Postdoctoral Research Fellow
Department of Dental Implantology
School of Stomatology
Wuhan University
Wuhan, China

Yufeng Zhang, MD, DDS, PhD
Professor
Department of Dental Implantology
School of Stomatology
Wuhan University
Wuhan, China

Liwei Zheng, DDS, PhD
Professor
State Key Laboratory of Oral Diseases
National Clinical Research Center for Oral Diseases
West China Hospital of Stomatology
Sichuan University
Chengdu, China

Giovanni Zucchelli, DDS, MSc, PhD
Professor
Department of Biomedical and Neuromotor Sciences
University of Bologna
Bologna, Italy

01

The Regenerative Properties of Bone Grafts: A Comparison Between Autografts, Allografts, Xenografts, and Alloplasts

Richard J. Miron / Yufeng Zhang

Summary

The use of bone grafting materials in implant dentistry, periodontology, and oral surgery has become so widespread over the past two decades that new products are rapidly being brought to market year after year, each with various claims in their regenerative potential. Therefore, it is critical that treating clinicians optimize their regenerative outcomes with a better understanding of the biologic properties of each of these classes of biomaterials. The most common classification of bone grafting materials involves *(1)* autogenous bone coming from the same individual, *(2)* allografts coming from human cadaver bone, *(3)* xenografts coming from another animal source, and *(4)* synthetically fabricated alloplasts. This chapter presents an overview of the specific regenerative properties of each of these classes of bone grafting materials, including their osteogenic, osteoinductive, and osteoconductive properties. Thereafter, a direct comparison is made between each of the bone grafts, particularly relating to their uses in dentistry.

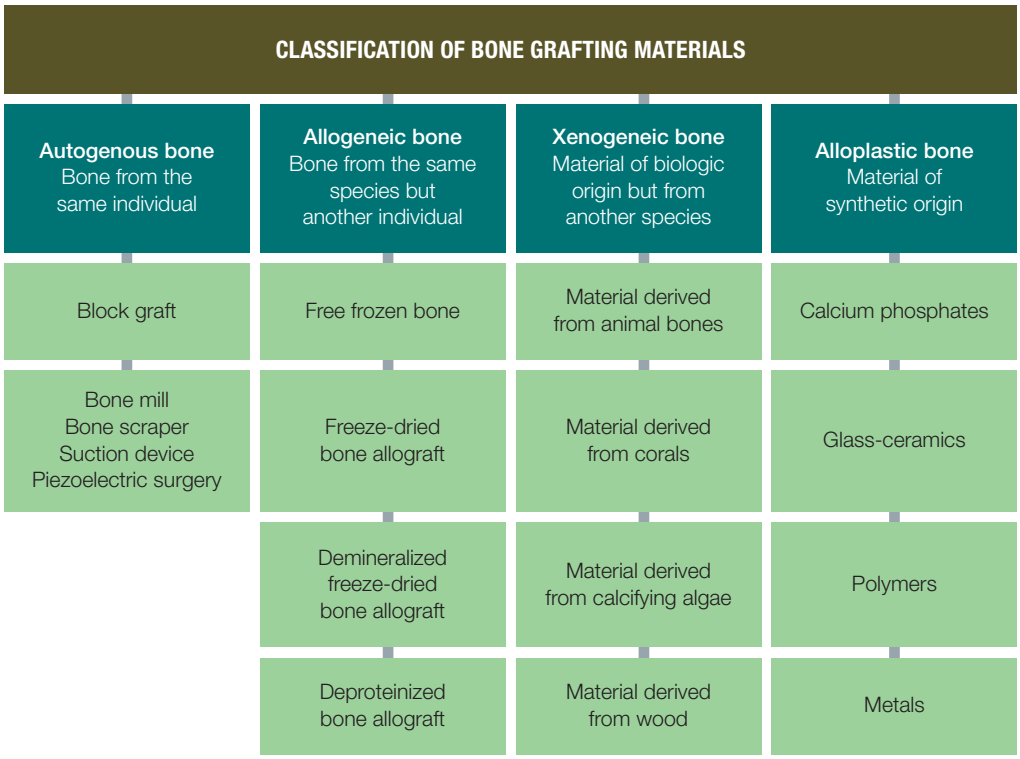

FIG 1-1 Classification of bone grafting materials including autografts, allografts, xenografts, and alloplasts.

Originally bone grafting materials were developed to serve as a passive, structural supporting network with their main criteria being biocompatibility.[1,2] Nevertheless, advancements in tissue engineering and regenerative medicine have allowed for a large array of bone grafts to be brought to market, each possessing their various advantages and disadvantages (Fig 1-1). Today many bone grafting materials have been designed with specific surface topographies at both the microscale and nanoscale aimed to further guide new bone formation once implanted in situ. The growing number of bone grafts currently available have an estimated global market value now surpassing $2.5 billion annually, with over 2.2 million procedures performed.[3] As such, the need for better "smart" biomaterials becomes vital, owing to the aging population and the increased number of bone grafting procedures performed yearly for diseases such as osteoporosis, arthritis, tumors, and trauma.[4]

Bone grafting materials have been extensively studied in the field of dentistry (as well as in orthopedic medicine) to fill bone defects caused in large part by periodontal disease. The clinical indications for using bone grafting materials range from single sites to extensive full-arch cases. Some grafts need to be highly osteoinductive to facilitate the regrowth of vertical or horizontal bone (such as autografts), whereas others must be nonresorbable to prevent future resorption (bovine-derived xenografts). Considering the wide range of uses for bone grafting materials, no single material can fulfill each of these tasks. Furthermore, it is often necessary to combine two or more classes of bone grafts to obtain a successful and predictable result. While each of the grafting materials needs to fulfill several properties related to their use, including optimal biocompatibility, safety, ideal surface characteristics, proper geometry and handling, as well as good mechanical properties, bone grafts are routinely characterized based on their osteogenic, osteoinductive, and osteoconductive properties (Table 1-1). The ideal grafting material should therefore *(1)* contain osteogenic progenitor cells within the bone grafting scaffold capable of depositing new bone matrix, *(2)* demonstrate osteoinductive potential by recruiting and inducing mesenchymal stem cells (MSCs) to differentiate into mature bone-forming osteoblasts, and *(3)* provide a scaffold that facilitates 3D tissue ingrowth.

Consequently, the gold standard for bone grafting is autogenous bone, harvested either as a bone block or bone particles, as presented in chapter 2. These grafts display an excellent combination of the three important biologic properties of bone grafts: osteoconduction, osteoinduction, and osteogenesis.[5] Despite their potent ability to improve new bone formation, the

TABLE 1-1 **Classification of bone grafting materials used for the regeneration of periodontal intrabony defects**

Material characteristic	Ideal	Autograft	Allograft	Xenograft	Alloplast
Biocompatibility	+	+	+	+	+
Safety	+	+	+	+	+
Surface characteristics	+	+	+	+	+
Geometry	+	+	+	+	+
Handling	+	+	+/–	+	+
Mechanical characteristics	+	+	+/–	+	–
Osteogenic	+	+	–	–	–
Osteoinductivity	+	+	+/–	–	–
Osteoconductivity	+	+	+	+	+

limitations, including extra surgical time and cost as well as limited supply and additional patient morbidity, have necessitated alternatives. These include bone allografts (from fresh-frozen or freeze-dried bone allograft [FDBA], demineralized freeze-dried bone allograft [DFDBA], and deproteinized bone allograft), xenografts (derived from animals, corals, calcifying algae, or wood), and an array of synthetic alloplasts (hydroxyapatite [HA], β-tricalcium phosphates [β-TCPs], biphasic calcium phosphates [BCPs], polymers, glass-ceramics, and bioactive glasses).[6–10] Although these materials are osteoconductive by definition, only a limited number of osteoinductive materials are available.[2]

Bone Regeneration

Predictable bone regeneration in the oral cavity is one of the most difficult surgical procedures faced by the treating dentist. An understanding of a number of key factors is nevertheless necessary to better optimize regenerative outcomes. The field of tissue engineering proposed that three main factors are necessary for bone and tissue regeneration (Fig 1-2). First, a scaffold (bone grafting material or fibrin clot) is required to facilitate cell repopulation and tissue regrowth in the defect area. Second, signaling molecules are required to stimulate new tissue regeneration and to recruit future progenitor cells to the defect site. Third, osteogenic cells are required to deposit new bone matrix. While these three properties optimize tissue engineering, it remains equally as essential to understand that both time as well as an optimal environment (stability, loading stimulation, perfusion of oxygen, pH of bone tissues, viability of surrounding bone walls, etc) are necessary to further optimize new bone formation (see Fig 1-2). A variety of bone grafting materials, barrier membranes, and signaling molecules (bone morphogenetic protein 2 [BMP-2], platelet-derived growth factor [PDGF]) have been brought to market to fulfill this task (Fig 1-3).

While all grafting materials are osteoconductive based on their ability to promote new bone formation and support 3D tissue ingrowth, little additional bone-inducing potential is provided by this property alone. In contrast, autogenous bone is osteogenic due to its incorporation of living progenitor cells that may further stimulate new bone formation, and it is also osteoinductive based on its ability to secrete growth factors to the local microenvironment. All other bone grafts are completely devoid of living cells and are therefore not considered osteogenic (see Table 1-1). The majority of research to date on bone grafting

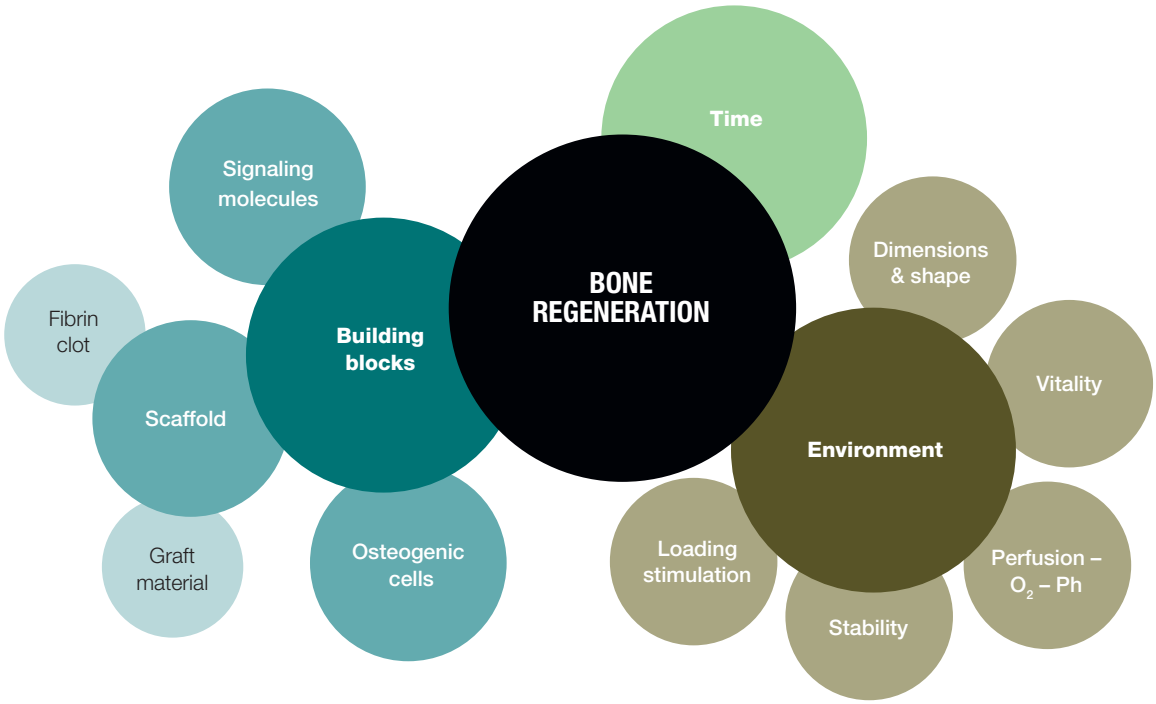

FIG 1-2 Factors responsible for bone formation. While a scaffold, signaling molecules, and osteogenic cells are the building blocks of tissue engineering, other factors including adequate time and appropriate environmental factors are crucial for optimal bone regeneration.

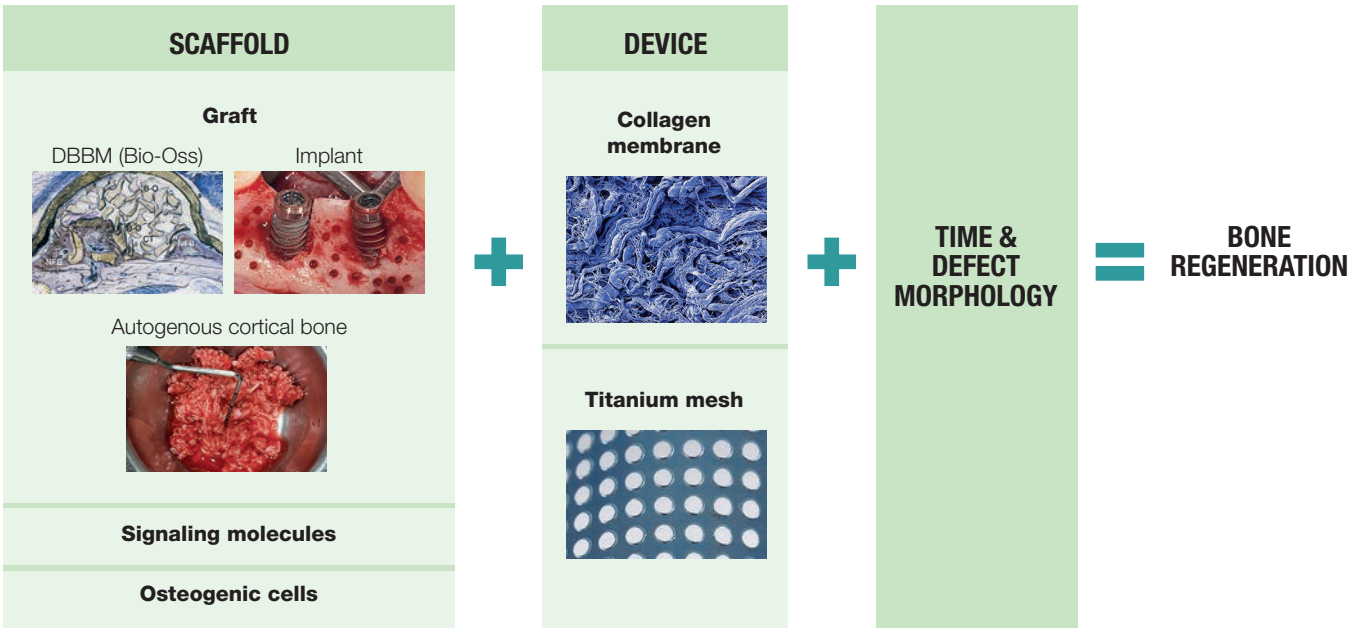

FIG 1-3 Examples of grafts/scaffolds (deproteinized bovine bone mineral [DBBM], Bio-Oss [Geistlich]; autogenous bone; implant) and devices (barrier membranes fabricated out of collagen or titanium) that may facilitate new bone formation. (Courtesy of Dr Ferdinando D'Avenia.)

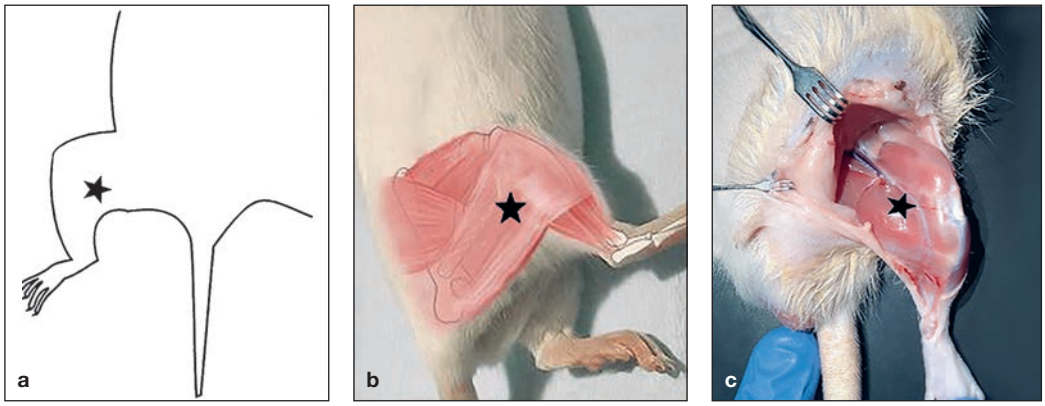

FIG 1-4 *(a to c)* Ectopic bone formation model. The femur is dissected, and either a bone grafting material or growth factor is placed in the muscle away from the bone.

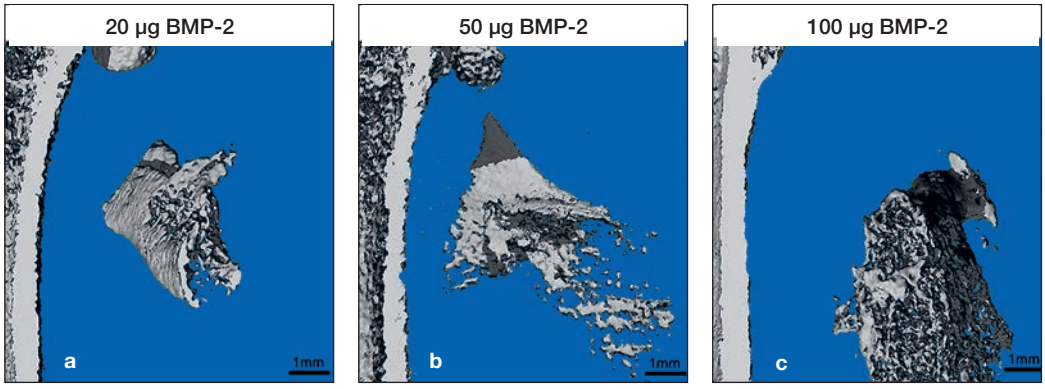

FIG 1-5 *(a to c)* Example of a dose-dependent increase in ectopic bone formation with increasing concentrations of recombinant human BMP-2 (rhBMP-2) from 20 to 100 µg. (Reprinted with permission from Zhang et al.[11])

materials has been focused on optimizing their osteoinductive potential. Simply put, an *osteoinductive biomaterial* (as defined by Dr Marshall Urist, an orthopedic surgeon, in the 1960s) is a biomaterial that is capable of inducing extraskeletal (ectopic) bone formation—that is, bone formation in areas where bone should not be formed, such as in muscle, epithelial tissue, or soft tissue. Originally, osteoinductive materials were characterized by investigating methods in which demineralized bone matrix could induce ectopic bone formation in the gastrocnemius muscle (in the lower leg) of rats and mice. Figure 1-4 illustrates a typical model utilized to confirm the presence of osteoinductivity. Figure 1-5 demonstrates the ability of BMP-2 at increasing doses to promote ectopic bone formation in a dose-dependent manner.[11]

With the advancements made in medical technology, our ability to accurately characterize biologic events has been drastically improved. As such, it was recently proposed that the osteoinduction phenomenon be divided into three principles[2] (Fig 1-6). These included the ability of an osteoinductive material to *(1)* recruit mesenchymal osteoprogenitor cells (MSCs), *(2)* induce an undifferentiated MSC into a mature bone-forming osteoblast, and *(3)* induce ectopic bone formation when implanted in extraskeletal locations. The combination of these three principles maximizes the bone graft's osteoinductive potential and ability to contribute to new bone formation.[2] The following sections introduce the four classes of bone grafting materials and briefly discuss their advantages and limitations.

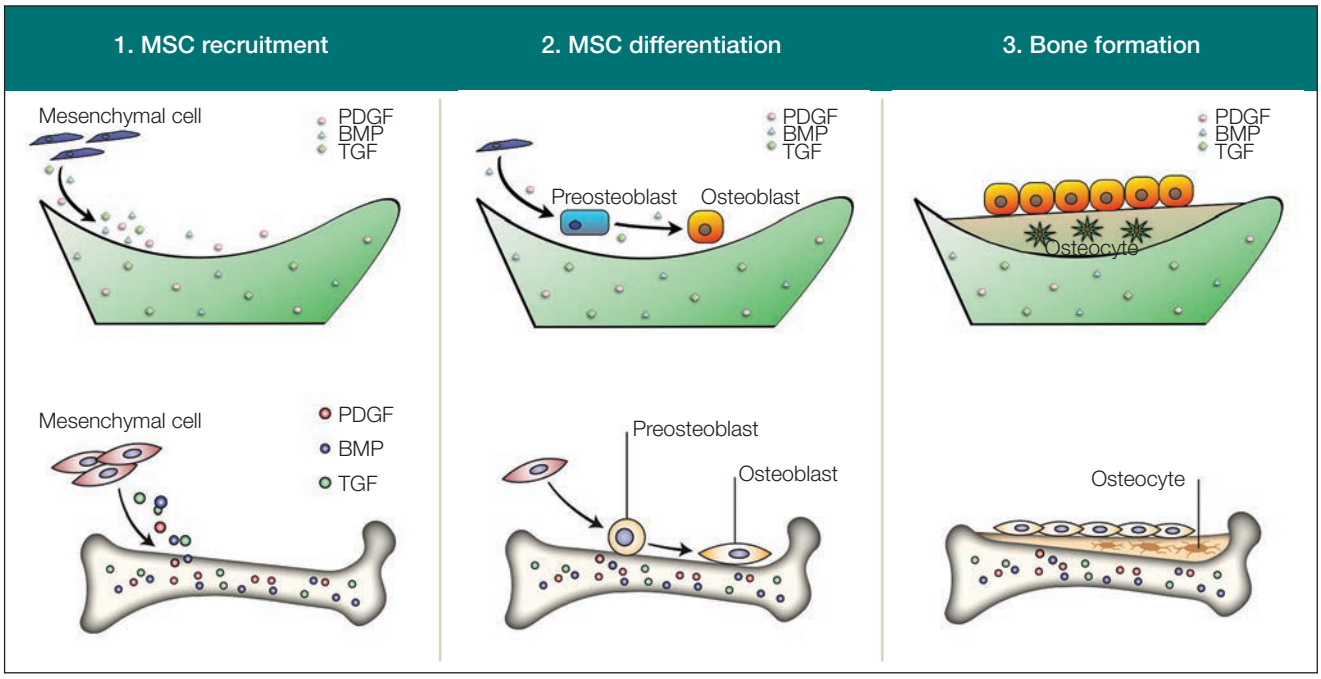

FIG 1-6 Principles of osteoinductive materials: *(1)* Osteoinductive materials should be capable of recruiting MSCs to bone graft surfaces through growth factor release. *(2)* The material should promote MSC differentiation into osteoblasts. *(3)* Osteoblasts must be capable of forming ectopic bone in vivo. TGF, transforming growth factor. (Reprinted with permission from Miron and Zhang.[2])

Autografts

Autogenous bone grafting involves the harvesting of bone obtained from the same patient. Typical sites in the oral cavity include the mandibular symphysis (chin area) or anterior mandibular ramus (the coronoid process). Interestingly, it has been demonstrated in various studies that harvesting technique has a significant influence on the viability of cells within the scaffold as well as future integration within bone[5,12–14] (see chapter 2). The main advantage of autogenous bone is that it incorporates all three of the primary ideal characteristics of bone grafts (ie, osteoconduction, osteoinduction, and osteogenesis). Primarily composed of bone matrix and osteocytes, these grafts are known to release a wide variety of growth factors, including BMPs, PDGF, transforming growth factor β (TGF-β), and vascular endothelial growth factor (VEGF), and to regulate bone formation/resorption via the RANKL/OPG (receptor activator of nuclear factor κB ligand/osteoprotegerin) pathway.[14] A number of studies using autogenous bone alone have been documented with respect to defect healing.[15–18] Autografts remain the gold standard in bone grafting, and complicated bone defects often require at least partial incorporation of autografts in order to improve graft consolidation (see chapter 2).

Allografts

Bone allografts involve the harvesting of bone obtained from a human cadaver that has been safely processed and decontaminated. They are typically categorized into two groups: *(1)* fresh-frozen bone or *(2)* FDBA and DFDBA. While allografts have been the most widely utilized replacement grafting material in North America, a number of European and Asian countries do not permit their use due to their safety concerns. One of the main advantages of allografts over other commercially available bone grafts is that they possess osteoinductive potential, mainly found in the demineralized grafts. Many studies have demonstrated their effectiveness in promoting new bone formation across a wide array of defect types[19–22] (see chapter 3). Allografts remain the ideal replacement material for a number of common procedures in dentistry, including extraction socket healing, sinus elevation procedures, guided bone regeneration (GBR) procedures, and in conjunction with implant dentistry.

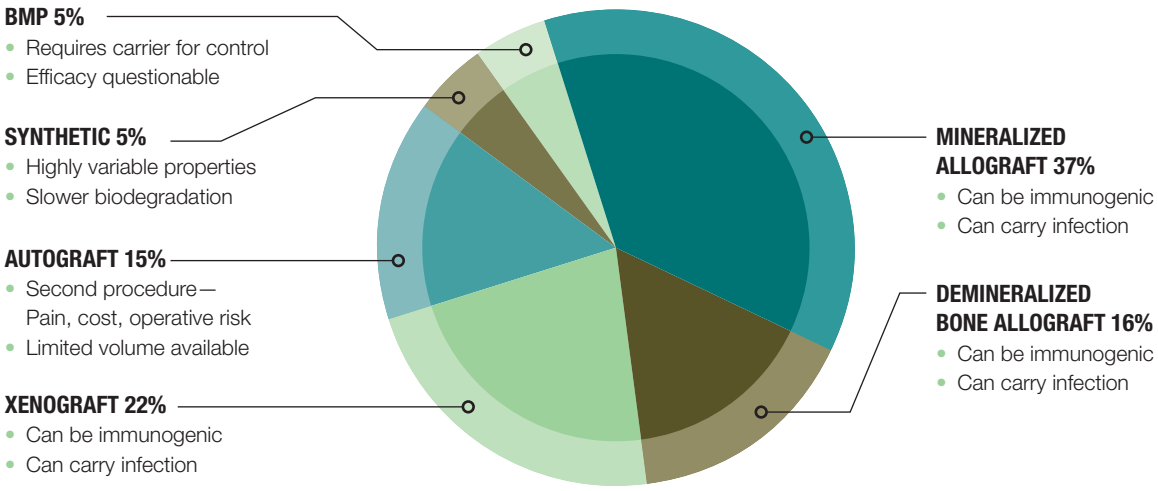

FIG 1-7 Proportional use of bone grafting materials in North America. The largest percentage (slightly over 50%) is dedicated to allografts, while 15% are autografts, 22% are xenografts, 5% are synthetic materials, and 5% are rhBMP-2.

Xenografts

While allografts have primarily been utilized in North America, xenografts derived from animal donors have principally been utilized in Europe and Asia due to their extensive history of documented clinical evidence. One well-documented xenograft is deproteinized bovine bone mineral (DBBM), which is a highly purified anorganic bone matrix mineral ranging in size from 0.25 to 1.0 mm under the trademark name Bio-Oss (Geistlich). The advantages of utilizing DBBM as a bone graft include its documented safety, its mineral content comparable to that of human bone, and its nonresorbable characteristics. While xenografts do not possess any form of osteogenic or osteoinductive potential due to their complete deproteinization process, their nonresorbable features make them attractive bone grafts under a variety of clinical settings.[23–27] Their clinical use is presented in detail in chapter 4.

Alloplasts

Alloplasts are synthetically developed bone grafts fabricated in a laboratory derived from different combinations of HA, β-TCP, polymers, and/or bioactive glasses.[28–31] Although they possess an osteoconductive surface that allows cell attachment and proliferation and 3D bone growth, compared to the other classes of bone grafts, they have generally demonstrated inferior bone-forming ability in a number of comparative studies. Nevertheless, a number of alloplasts have been fabricated with the incorporation of various recombinant growth factors able to facilitate bone or periodontal regeneration.[2] The use of alloplasts is covered in detail in chapter 6.

Proportional Use of Bone Grafting Materials

Figure 1-7 demonstrates the proportional use of each grafting material in North America. The largest proportion of bone augmentation procedures performed in the United States are conducted with mineralized allografts (37%), with another 16% of the market using demineralized bone allografts. Therefore, a total of 53% of grafting procedures performed in the dental field are routinely augmented with allografts. Interestingly, 22% of all bone grafting procedures are performed with xenografts, the great majority of these utilizing Bio-Oss. Only approximately 15% of dental bone augmentation procedures are performed with autografts, despite their being the gold standard. These are generally performed by trained surgeons and require additional surgical skill sets and lengthier surgical procedures. Interestingly, 5% of bone augmentation procedures are performed with re-

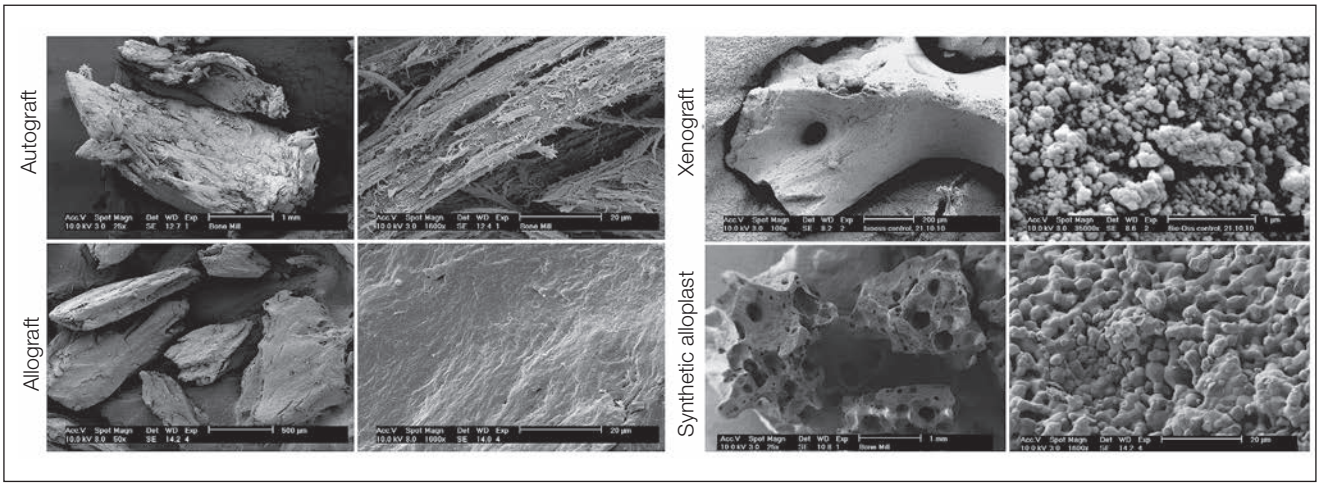

FIG 1-8 Scanning electron microscopy of four commonly utilized bone grafting materials in dentistry, including autogenous bone harvested with a bone mill, DFDBA, DBBM, and a synthetically fabricated BCP. (Reprinted with permission from Miron et al.[32])

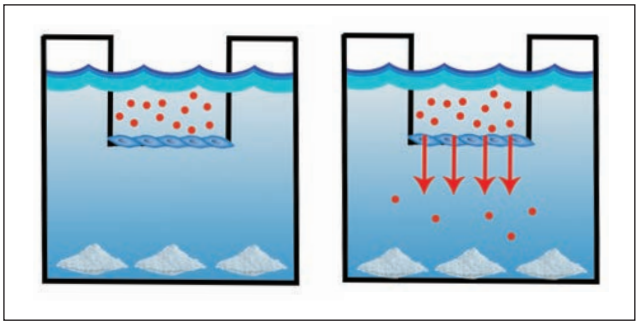

FIG 1-9 Transwell assay investigating the ability of MSCs to migrate toward a bone grafting material. MSCs are placed in the upper compartment with small pores, and shortly thereafter a bone grafting material/growth factor is placed in the lower compartment. After 24 hours, cells that have passed through the pores are counted and quantified to determine the ability of each material to be recruited toward the introduced biomaterial.

combinant human BMP-2 (Infuse Bone Graft, Medtronic), and another 5% are conducted with synthetic alloplasts, primarily limited to "holistic" clinics or patients requesting the use of non–human/animal-derived products (see Fig 1-7).

Regenerative Properties of Autografts, Allografts, Xenografts, and Synthetic Alloplasts

As part of a series of experiments performed from 2009 to 2016, the authors' research group was interested in the regenerative potential of various bone grafting materials and more specifically how each class of bone graft compared with one another. Figure 1-8 illustrates the typical morphology of each of these bone grafting materials.[32] One common trait between all grafts is their roughened surface topographies, especially the synthetically fabricated alloplast materials (see Fig 1-8). Cells of the bone-forming lineage (osteoblasts) act much more favorably on roughened surfaces when compared to smooth surfaces. Thereafter, cell migration was assessed using a transwell assay (Fig 1-9). In this test, MSCs are placed into an upper compartment with small pores, and either a bone grafting material or growth factor is then introduced into the lower chamber. Cells that are attracted to the material then pass through the pores and may thereafter be counted to investigate the potential for each of the biomaterials to recruit cells. This experiment showed that only autografts and allografts are capable of recruiting cells (Fig 1-10), likely as a result of their incorporation of chemotactic growth factors including BMP-2 and PDGF. In a second experiment, cell proliferation (ability for cells to multiply) was investigated when cells were seeded onto each of the bone grafting materials. While all bone grafts were able to induce cell proliferation, autografts showed superiority when compared to all other groups (Fig 1-11).

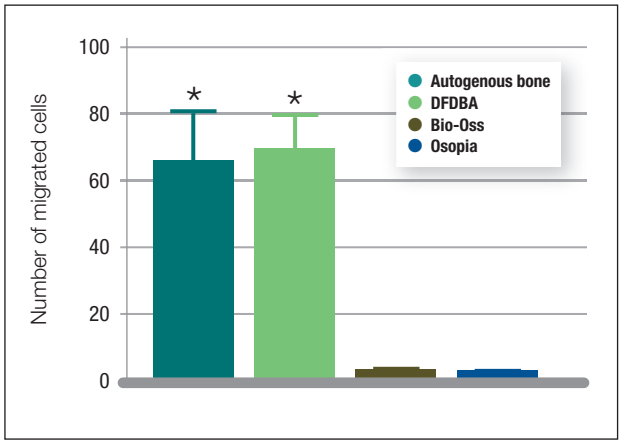

FIG 1-10 Migration assay using a Boyden chamber of bone marrow stromal cells (BMSCs) seeded in the presence of autogenous bone harvested with a bone mill, DFDBA, DBBM (Bio-Oss), and a synthetically fabricated BCP (Osopia, Regedent). Results from this study demonstrated that only autogenous bone and the allograft were able to recruit cells due to their incorporation of growth factors including BMPs and PDGF. The *asterisk* (*) denotes a significant difference. (Data from Miron et al.[32])

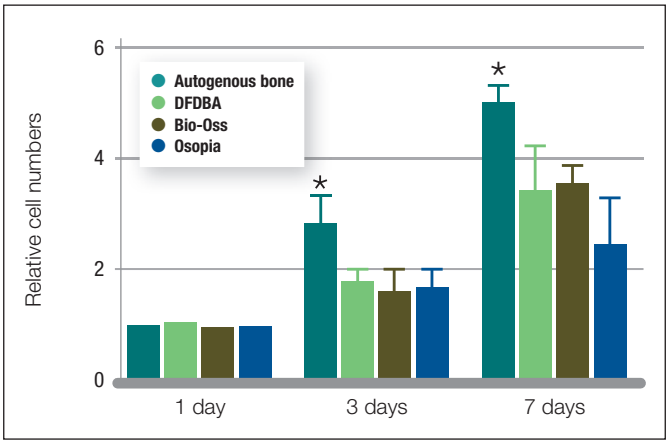

FIG 1-11 Proliferation assay of BMSCs seeded on each bone grafting material and quantified for cell number 1, 3, and 7 days post-seeding. It was observed that autografts performed significantly better than all other groups at 3 and 5 days. The *asterisk* denotes a significant difference. (Data from Miron et al.[32])

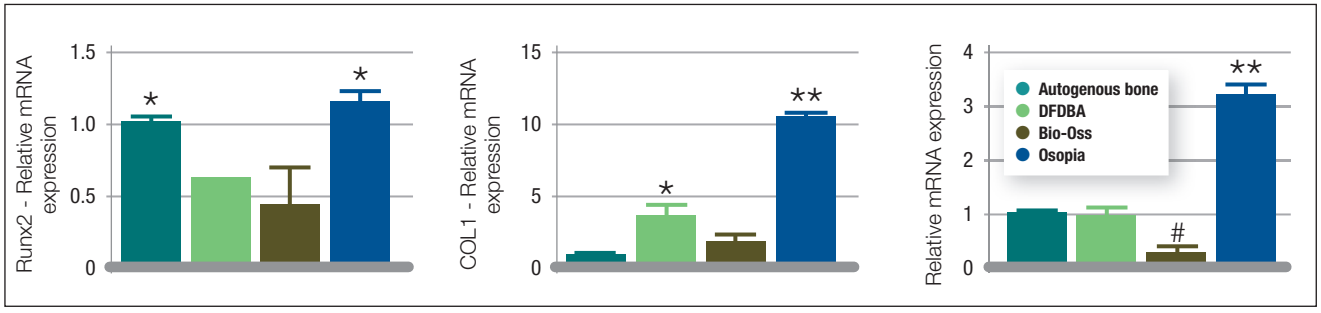

FIG 1-12 Relative mRNA levels of Runx2, collagen-1 (COL1), alkaline phosphatase (ALP), and osteocalcin (OC) to investigate osteoblast differentiation of BMSCs seeded on autogenous bone harvested with a bone mill, DFDBA, DBBM (Bio-Oss), and a synthetically fabricated BCP (Osopia) at 3 days post-seeding. It was found that both autogenous bone and the novel synthetically fabricated osteoinductive bone grafts were able to promote rapid differentiation of stem cells toward bone-forming osteoblasts. The *asterisk* denotes a significant difference, the *double asterisk* (**) denotes a value significantly higher than all other groups ($P < .05$), and the *number sign* (#) denotes a value significantly lower than all other groups. (Data from Miron et al.[32])

Lastly, the differentiation of MSCs toward the osteoblast lineage was then investigated. It was found that autogenous bone chips induced osteoblast differentiation with the greatest potential, while a novel synthetic osteoinductive material (Osopia, Regedent; see chapter 7) also showed an ability to transform MSCs toward osteoblasts (Fig 1-12). It must be noted that, routinely, synthetic alloplasts do not perform well in such studies and that the commercialization of this particular synthetic bone graft shows much additional potential when compared to previous synthetic bone grafts, as highlighted in chapter 7. Figure 1-13 demonstrates the ability of DFDBA, Bio-Oss, and Osopia (alloplast) to induce ectopic bone formation. Notice that Bio-Oss was unable to induce any form of ectopic bone formation. Furthermore, Fig 1-14 shows ectopic bone formation in the calf muscle of beagle dogs resulting from use of Osopia. Routinely, however, alloplasts are not able to induce ectopic bone formation.

In summary, Table 1-2 depicts the regenerative potential of each of these classes of bone grafting materials. Not surprisingly, autogenous bone performed significantly better than all other classes of bone grafts and remains the gold standard replacement material. The ability for allografts to participate in osteoinduction corresponds well with data from North America that demonstrates that allografts are the most heavily utilized replacement biomaterial for bone grafting (see Fig 1-7). Interestingly, the xenografts had no ideal properties for bone

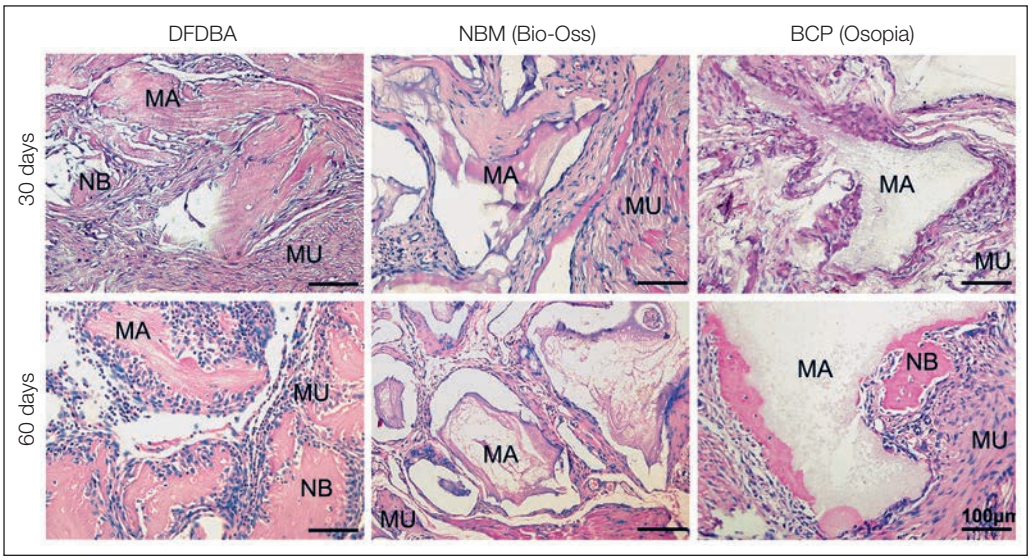

FIG 1-13 Hematoxylin-eosin (h&e) staining of representative samples of DFDBA, natural bone mineral (NBM; Bio-Oss), and a synthetic BCP (Osopia) implanted into the calf muscles of beagle dogs at 30 and 60 days to analyze ectopic bone formation in vivo. MA, material; MU, muscle; NB, new bone. Bar = 100 μm. Both DFDBA and BCP were able to promote ectopic bone formation, confirming their osteoinductive potential. (Reprinted with permission from Miron et al.[32])

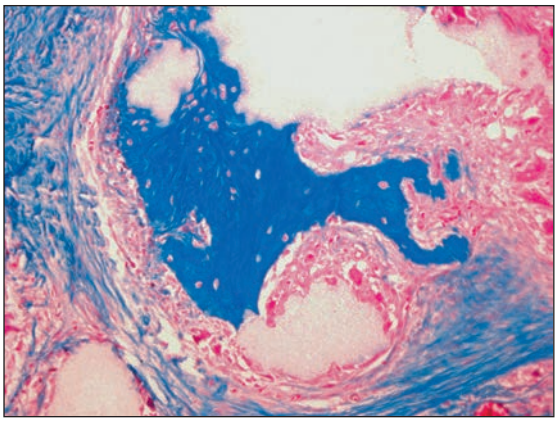

FIG 1-14 Mason staining demonstrating ectopic bone formation for BCP (Osopia) scaffolds when implanted in the muscle of beagle dogs at 60 days. (Reprinted with permission from Miron et al.[32])

TABLE 1-2 **Bone-inducing potential of the four classes of bone grafting materials**

	Autograft	Allograft (DFDBA)	Xenograft	Alloplast (BCP)
Cell recruitment	×	×		
Cell proliferation	×			
Cell differentiation	×			×
Ectopic bone formation	×	×		×

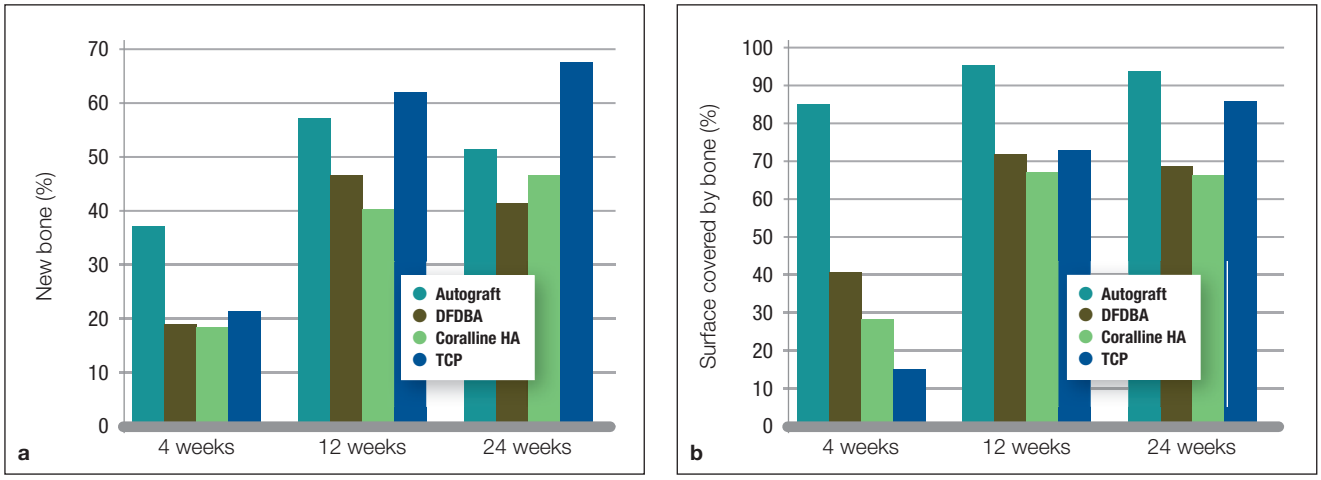

FIG 1-15 *(a)* Percentage of new bone in standardized bone defects in the mandibles of minipigs grafted with particulated autograft, DFDBA, xenogeneic coral-derived HA (coralline HA), or alloplastic β-TCP. *(b)* Percentage of grafting material surface covered with bone as an indicator of the osteoconductive potential of the particulated graft. (Data from Buser et al.[33])

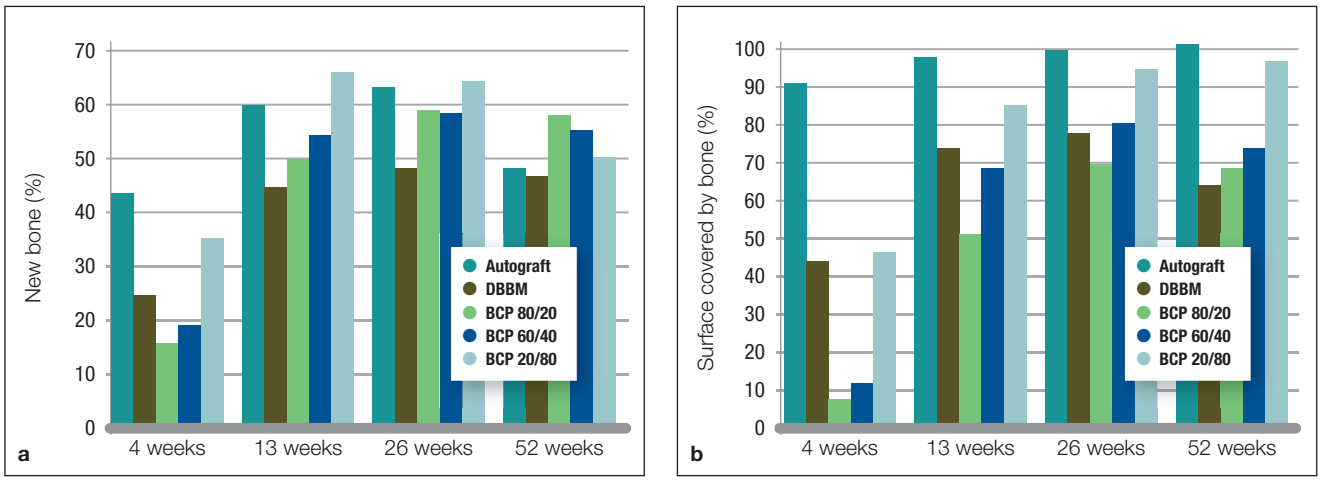

FIG 1-16 *(a)* Percentage of new bone formation in standardized bone defects in the mandibles of minipigs grafted with particulated autograft, DBBM, or BCP with three different ratios of HA and β-TCP. In the early healing phases, more new bone formation is seen in defects grafted with BCPs with high β-TCP content. *(b)* Percentage of grafting material surface covered with bone in standardized bone defects in the mandibles of minipigs. (Data from Jensen et al.[7])

regeneration, yet they still routinely dominate more than 20% of all grafting procedures. Xenografts were unable to promote cell recruitment or cell proliferation, and furthermore they were the only group that did not induce spontaneous osteoblast differentiation of MSCs, nor did they have any ability to produce ectopic bone formation. Chapter 4 fully characterizes the importance of xenografts in dentistry, mainly due to their nonresorbable properties, and discusses their relevance and necessity for various indications in regenerative dentistry. Lastly, it must be noted that typically synthetic bone grafting materials have shown no capability of enhancing bone formation. Nevertheless, the promising and novel BCP Osopia demonstrates osteoinductive potential based on its ability to produce ectopic bone formation and rapidly transform stem cells into bone-forming osteoblasts. This new class of bone grafts is highlighted in chapter 7.

Importantly, a series of in vivo studies performed at the University of Bern have routinely shown that autogenous bone induces faster new bone formation when compared to other bone substitute materials, including xenografts, allografts, and synthetically fabricated alloplasts[33] (Figs 1-15 and 1-16). Therefore, without question autogenous bone remains the gold standard for bone regeneration.

Conclusion

Autografts are known to contain growth factors within their matrix[34,35] that support the recruitment and proliferation of stem cells and induces their differentiation toward bone-forming osteoblasts. The authors' previous studies have clearly demonstrated that autografts are able to release a wide array of growth factors over time, including BMPs, TGFs, insulin-like growth factors (IGFs), and VEGFs.[35] Interestingly, the harvesting technique utilized to collect bone particles has been shown to have a tremendous impact on the final prepared autograft (highlighted in detail in chapter 2).

Allografts, on the other hand, have been shown to be the replacement grafting material of choice for a variety of reasons. This is highlighted by their extensive use in the countries that permit and support their use. Allografts are widely used in North America, whereas local regulations in Europe have restricted their practice, which in general has limited their popularity in certain countries. The advantages of allografts are presented in detail in chapter 3.

Xenografts, in contrast, have a very low bone-forming ability. Nevertheless, they are the second most utilized class of biomaterials due to their nonresorbable properties, which makes them advantageous under various clinical indications (see chapter 4).

Lastly, laboratory-fabricated synthetic materials have not been utilized frequently due to their lower bone-forming properties and often fast degradation rates. Alloplasts are primarily limited in use to "holistic" clinics and for various research endeavors. Nevertheless, years of research in the Netherlands has pioneered the development of the first mineralized, synthetically fabricated osteoinductive bone graft without the use of growth factors (ie, Osopia).[36,37] These novel grafts are presented in chapter 7.

In summary, each bone graft category has various regenerative advantages and disadvantages. As a result, each also has specific clinical indications. Most importantly, the clinician should understand that no single bone grafting material can be utilized for all clinical indications, therefore necessitating a better understanding of each of their individual regenerative properties and clinical indications. The final chapter of this textbook discusses how to optimize the use of each of these classes of bone grafts for various regenerative protocols to take full advantage of their regenerative properties while minimizing their potential disadvantages.

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02

Autogenous Bone: The Gold Standard for Bone Regeneration

Richard J. Miron / Homayoun H. Zadeh / Tobias Fretwurst / Kathia Nelson / Yufeng Zhang / Reinhard Gruber / Michael A. Pikos / Ferdinando D'Avenia

Summary

For bone regeneration, there is a great clinical need for bone grafting materials that possess excellent biocompatibility and osteoinductivity without eliciting an antigenic effect. Replacement biomaterials have attempted to mimic autogenous bone grafts, with manufacturers commonly reporting on their osteoconductive, osteoinductive, or osteogenic potential. Of all grafting materials presently available on the market, however, only autogenous bone simultaneously takes advantage of these three properties by totally immunocompatible means. Autografts release a wide array of growth factors and cytokines that regulate the behavior of bone-forming osteoblasts and bone-resorbing osteoclasts. Several factors remain essential to optimize autogenous bone harvesting. Over the past decade, studies have revealed the impact of bone harvesting techniques on the consolidation of autografts. It is now known that certain harvesting techniques improve the viability of cells contained within autografts and further release higher levels of growth factors. This chapter provides the biologic background on bone cells derived from autografts involved in graft consolidation and discusses how harvesting technique is tightly regulated to bone cell viability and subsequent growth factor release. Thereafter, the clinical indications for autogenous bone (either in block or particle form) are presented with various case presentations to support their use. Lastly, a new concept termed *bone conditioned media* is presented as part of future research geared toward collecting autogenous bone-inducing growth factors derived from autogenous bone particles.