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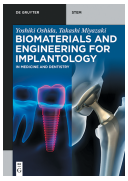

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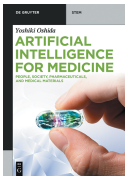

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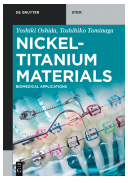

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Bone-Grafting Biomaterials

Autografts, Hydroxyapatite, Calcium-Phosphates, and Biocomposites

DE GRUYTER

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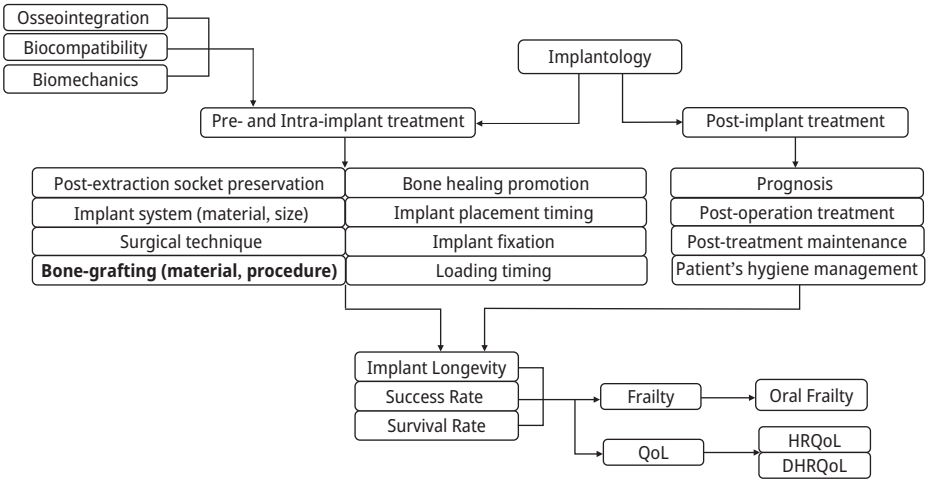
Preface

Once a patient is evaluated as a candidate for implant recipient (free from all risky contraindications for implant treatments), the patient will face various stages of treatment, including pre-, intra-, and post-treatments, as well as operational procedures. Referring to attached figure, once the placed implant(s) is biologically fused to receiving hard/soft tissues (i.e., establishment of osseointegration), the patient is allowed to use implant(s) under normal occlusal function or ordinary daily activities. Thus the successfully functioning implant(s) is expected to exhibit a quite long-term service (aka, longevity) to which success rate and survival rate are contributed. The long-term servicing implant(s) would, in general, enhance patient's health-related quality of living (HRQoL) or dental health related quality of living (DHRQoL). Of course, to this end, a great corporation and responsibility should be demanded from patients, which should include daily hygiene management and well-organized maintenance checkup schedule.



While QoL concept has been considered as a sort of a subjective evaluation from each implant recipient in either orthopedic treatment or dental treatment, the longevity, success rate, and survival rate should be evaluated in terms of direct or indirect objective, based on scientific examinations and/or observations, as well as clinical case data. Demographically, the term "longevity" is a synonym for the life expectancy; in the same way, longevity is normally used in medical and dental fields. Especially, the longevity of placed orthopedic joint replacement implants and dental implants are principally subjected to be discussed. The longevity is controlled by several crucial factors, which should include pre-operation procedures (e.g., appropriate implant system selection, post-extraction treatment for dental implant, etc.), intra-operation procedures (e.g., surgical skill and infection management, etc.), and post-operation issues

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(e.g., poor hygiene and uncontrollable diabetes or an increased body-mass index or missing of preventive cares from both physicians and patient, etc.).

As seen in the figure, bone-grafting (with materials and procedures) is positioned in the pre-implantation and/or intra-implantation stages. The subsequent occurring success rate and survival rate are strongly relied on appropriate selection of bone-grafting materials as well as proper choice of grafting technique.

In this book, we will be discussing types and procedures of bone-grafting, anatomy, and physiochemistry of natural bone tissue, type of bone-grafting materials, supportive devices for bone-grafting procedures, and technical sensitivity of bone-grafting methods.

Contents

List of nomenclatures

AAAA	autolyzed antigen-extracted allogeneic
ABBM	anorganic bovine bone mineral
ABG	autogenous block graft
ACP	amorphous calcium phosphate
ADSCs	adipose-derived stem cells
ALP	alkaline phosphatase
AM	additive manufacturing
ARST	alveolar ridge split technique
BAG	bioactive glasses
BBA	bone bank allografts
BCC	body-centered cubic
BCP	biphasic calcium phosphates
BCT	biomechanical computed tomography
BHA	bovine-derived hydroxyapatite
BJ	binder jetting
BMD	bone mineral density
BMI	body-mass index
BMP	bone morphogenetic protein
BRS	bioresorbable scaffolds
BRU	bone remodeling units
CAP	cold atmosphere plasma
CBCT	cone-beam-computed tomography
CCP	cubic close packed
CDHA	calcium-deficient hydroxyapatite
CGF	concentrated growth factor
CMC	carboxymethylcellulose
CPBS	chitosan-poly(butylene succinate)
CPC	calcium phosphate cements
cpTi	commercially pure titanium
CS	chitosan
CSTi	cancellous structured titanium
μCT	micro-computer tomography
DBBM	deproteinized bovine bone mineral
DBM	demineralized bone matrix
DCPA	dicalcium phosphate anhydrous
DCPD	dicalcium phosphate dihydrate
DEXA	dual energy X-ray absorptiometry
DF	fractal dimension
DFDBA	Demineralized FDBA
DMLS	direct metal laser sintering
DHRQoL	dental health-related quality of living
EBM	electron beam melting
EBSS	Earle's balanced salt solution
ECM	extracellular matrix
EDL	electrical double layer
EGF	epidermal growth factor
EPC	endothelial progenitor cells

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FBR	foreign body reaction
FCC	face-centered cubic
FDA	US Food and Drug Administration
FDBA	freeze-dried bone allograft
FDM	fused deposition modeling
FFI	full-length femur imaging
FGF	fibroblast growth factor
FTIR	Fourier transform infrared
GAG	glycosaminoglycan
GBR	guided bone regeneration
GFs	growth factors
GTR	guided tissue regeneration
HA	hydroxyapatite
HAS	hip structural analysis
HCP	hexagonal closed packed or hexahedron
HEPES	(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)
hFOB	human fetal osteoblastic
HIV	human immunodeficiency virus
hMSC	human mesenchymal stem cells
HR-pQCT	high-resolution peripheral quantitative computed tomography
HRQoL	health-related quality of living
HV	hydroxy-valerate
IAN	inferior alveolar nerve
IGFs	insulin-like growth factors
ISQ	implant stability quotient
L-PBF	laser powder bed fusion
MCPA	monocalcium phosphate anhydrous
MCPM	monocalcium phosphate monohydrate
mCT	micro-computed tomography
MDCT	multidetector computed tomography
MIS	minimally invasive surgery
MNGCs	multinucleated giant cells
MSCs	mesenchymal stem cells
NBCM	native bilayer collagen membrane
NIH	National Institutes of Health
OC	osteocalcin
OCP	octacalcium phosphate
OCT	octahedron
OHRQoL	oral health-related quality of living
OPF	osteoperiosteal flap
OPG	osteoprotegerin
P3HB	poly(3-hydroxybutyrate)
PASS	primary closure, angiogenesis, space maintenance, stability of wound (principle)
PCL	polycaprolactone
PDA	polydopamine
PDGF	platelet-derived growth factor
PE	polyethylene
PEEK	poly ether ketone
PEG	polyethylene glycol

PET	poly(ethylene terephthalate)
PGA	poly(glutamic acid)
PHB	poly hydroxyl butyrate
PHEMA	polyhydroxyethyl methacrylate
PLA	polylactide or polylactic acid
PLGA	polylactideglycolide copolymer or copoly(lactic-glycolic acid
PLLA	poly(L-lactic acid)
PMMA	polymethylmethacrylate
PMN	polymorphonuclear
PP	polypropylene
PPE	polyphosphoester
PPF	poly(propylene fumarate)
PPF	periosteal pocket flap (technique)
PRF	plasma-rich in fibrin
i-PRF	injectable form of PRF
L-PRF	leukocyte PRF
PRP	platelet-rich plasma
PSU	poly sulfone
PTFE	polytetrafluoroethylene
d-PTFE	high-density PTFE
e-PTFE	expanded PTFE
PTH	parathyroid hormone
PTMC	polytrimethylene carbonate
PU	polyurethanes
PVA	poly(vinyl alcohol)
PVC	polyvinyl chloride
QCT	quantitative computed tomography
REMS	radiofrequency echographia multi-spectrometry
RGD	Arg-Gly-Asp amino acid
SBF	simulated body fluid
SEM	scanning electron microscopy
SF	silk fibroin
SLM	selective laser melting
SLS	selective laser sintering
TBS	trabecular bone score
TCP	tricalcium phosphate
TE	tissue engineering
TEA	triethanolamine
TGF	transforming growth factor
THA	total hip arthroplasty
TKA	total knee arthroplasty
TSA	total shoulder arthroplasty
TTCP	tetra-calcium phosphate
UHMWPE	ultra-high molecular weight polyethylene
VEGF	vascular endothelial growth factor
VFA	vertebral fracture assessment

1 Introduction

In this chapter, we will discuss the interrelationship of bone-grafting materials and their applications in both medicine and dentistry implantology. As seen in Figure 1.1, bone-grafting materials are categorized in a global term of the biomaterials and further classified into, generally, natural bone-grafting materials, synthetic bone-grafting materials, and supporting membrane structures. In an area of application, traumatized bone healing is the most important process in both orthopedic implants and dental implants via osteointegration.

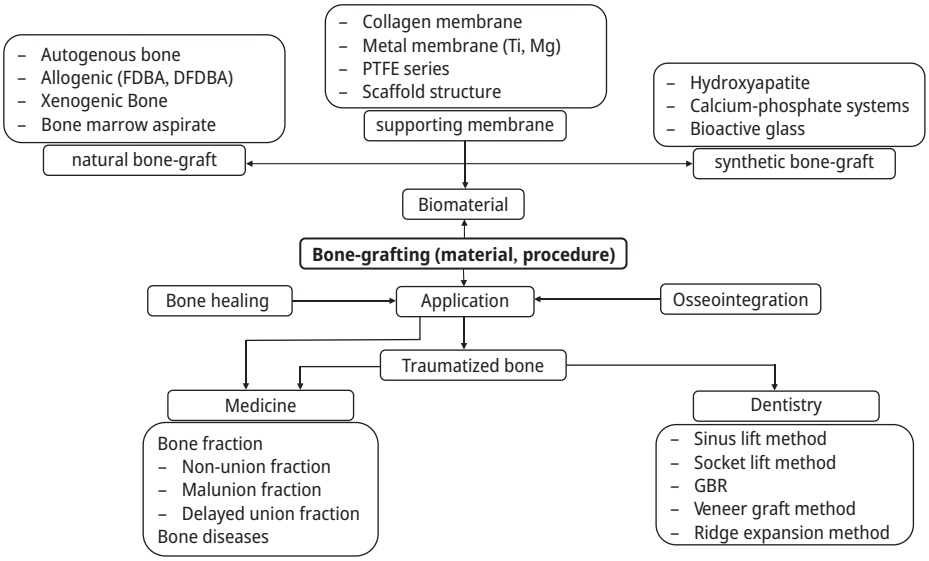

Figure 1.1: Interrelationship of bone-grafting materials with applications in both medical and dental fields. (FDBA: freeze-dried bone allograft; DFDBA: demineralized FDBA; PTFE: poly-tetra-fluoroethylene; GBR: guided bone regeneration).

1.1 Success rate and survival rate

The most common of these replacement joints are artificial knees and hips, which constitute almost 90% of the worldwide demand for joint implants. As a result of various technological breakthroughs, other extremity joint implants for ankles, shoulders, elbows, hands, feet, and jaws are increasingly more common as well [1, 2]. It is reported that more than 7 million Americans are living with a knee or hip implant and the number is increasing rapidly every year [3]. It was also reported that (i) in 2011, orthopedic surgeons performed 306,000 total hip replacements in the US alone and (ii) also in 2011, doctors also performed an additional 50,600 revision procedures to

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replace previously implanted artificial hips [3]. Even in these circumstances, the expected longevity of placed orthopedic implants is more than 20 years [2, 4] or between 15 and 20 years [5].

The placed implants are constantly subjected to hostile environments including biomechanics, biotribology, and biotriocorrosion [6]. In the case of joint implants, tribological action in biological environment would produce the wear debris, which might be harmful to surrounding soft/hard vital tissues. These are challenges to material scientists as well as surface engineers. Actually, several remarkable R&D outcomes have been recognized to prolong lifespan expectation of placed implants. Shot peening or laser peening onto orthopedic implant surfaces has been carried out to develop beneficial surface-negative residual stresses [2, 7–12]. Recently structural integrity of materials has been manipulated to facilitate osseointegration. Such new methods can include: (i) controlled porosity of implant surface skin by the ion-assisted polymerization process to create bio-functional 3D-printed Ti implants or by selective laser melting to create porous titanium implants with enhanced bone-mimicking mechanical properties [13] or additive manufacturing technology [14] and (ii) functional gradation from core to skin of the implants [6, 10, 15], in which there is a descending gradation of mechanical strength from core to skin; reversely, a descending slope of biological characteristics from skin to core.

It was reported that around 120 million people in the United States alone are missing at least one of their natural teeth and an incredible 36 million or more people have no teeth at all (namely, edentulous) [16]. Normally, dental implant treatment includes three components that technically make up a single dental implant; these different components must all be considered when determining how long an implant-supported restoration will last. They are an implant main body (most of which is immersed into bone or augmented bone), abutment, and prosthesis. Most sources put the average lifespan of a dental implant at around 25 years or more; however there are also some sources that say implant posts can be permanent [17]. There are also reports confirming the 25-year longevity [18, 19]. The implant-supported restoration, in general, may need to be replaced approximately every 10–15 years since the constant forces of chewing and biting will eventually wear down the exterior surface thereof [17, 20].

Implants are often evaluated in terms of either success rate or survival rate, as described before. There is a definitive difference between these two terms [1]. The term “success” is used if a particular implant meets the success criteria it is being evaluated with, while the term survival simply implies that the implant exists in the body or mouth and appears not to include evaluated biofunction. However, the survival rate has been treated as a longevity indicator. Singh et al. [21], examining patients with total shoulder arthroplasty (TSA), reported that (i) 2,207 patients underwent 2,588 TSAs, with 63% of patients with underlying diagnosis, (ii) 212 TSAs were revised during the follow-up, and (iii) at 5-, 10- and 20-year implant survival rates were 94.2%, 90.2%, and 81.4%, respectively. It was reported that THA (total hip arthroplasty) achieves excellent technical outcomes with 10-year survival exceeding 95%, 25-year implant survival greater

than 80%, and significant benefits for pain, mobility, and physical function [22, 23]. Bae et al. [24] performed 224 revision TKAs (total knee arthroplasty) in 194 patients from September 1990 to June 2009 and reported that (i) the 5-, 8-, and 10-year survival rates were 97.2%, 91.6%, and 86.1%, respectively, (ii) re-revision TKAs were performed on 20 knees because of infection (seven knees), loosening (six knees), polyethylene wear (six knees), and periprosthetic fractures (one knee), and (iii) the long-term survival rate of revision TKA was satisfactory, but careful attention is necessary to detect the late failure.

Historically, we had three important international conferences on acceptable criteria for dental implants [25, 26]. During the NIH Harvard Conference (1978), the following five criteria were set forth as acceptable success rate: (1) less than 1 mm of movement in each direction is allowed, (2) X-ray observed transmission images cannot serve as a reference standard, (3) bone resorption of less than 1/3 of the vertical height of the implant is acceptable, (4) no untreatable gingivitis, no inflammation, nor infection, no damage to adjacent teeth, no paresthesia or hypoesthesia, and (5) should function for 5 years in more than 75% cases. In 1986, the conference organized by Albrektsson had reached a consensus for acceptable criteria: (1) upon examination, individual unconnected implant should not move, (2) no X-ray penetration image around the placed implant, (3) vertical interim bone-sorption over time after 1 year after implant placement should be less than 0.2 mm, and (4) no persistent or irreversible signs or symptoms due to the implant (pain, infection, nerve paralysis, paresthesia, mandible injury, etc.), and (5) under the above conditions, a 5-year success rate of 85% shall be the lowest success criterion. At the latest conference (at Toronto, 1988), the followings were determined as acceptable success criteria: (1) the implant supports a functional and aesthetic superstructure that satisfies both the patient and the implantologist, (2) no pain, discomfort, sensory changes, or signs of infection caused by the implant, (3) when clinically examined, (4) the average annual vertical absorption after the start of the function should be less than 0.2 mm. During the Toronto Osseointegration Conference, the “more than 85% survival rate for 5 years, more than 80% after 10 years” was also determined, leading to further material development including commercially pure titanium (cpTi) as well as surface modification technologies.

The term “survival” is defined as the condition in which the implant remains in the mouth. If you have peri-implantitis but the implant is not removed, the placed implant can be considered alive (survive). On the other hand, the term “success” is recognized as a condition in which there are no subjective symptoms and no findings of peri-implantitis and there are four major factors influencing the success rates of placed implants. They include: (1) correct indication and favorable anatomic conditions (bone and mucosa), (2) good operative technique, (3) patient cooperation (oral hygiene), and (4) adequate superstructure design and fabrication [6].

Referring to Figure 1.2, Nishinaka [27] tries to differentiate survival rate and success rate, comparing two distinctive outcomes two years after implant surgery, in which (A) represents a development of peri-implantitis while (B) exhibits an excellent prognosis.

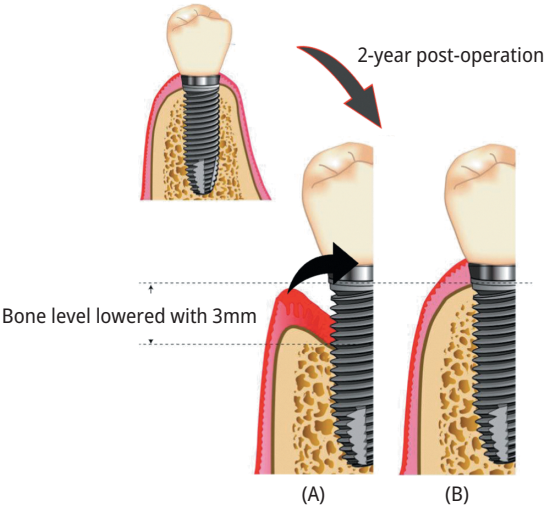

Figure 1.2: Two outcomes after two years after implant surgery: (A) developed peri-implantitis and (B) excellent prognosis [27, with kind permission of Dr. Nishinaka, Japan].

In either case, there was no movement in the placed implant, and the patient was able to eat without any problems with only a slight discomfort in the gingiva of the implant as a subjective symptom. It was observed that as for the objective findings of (A), the gums were inflamed due to infection, bleeding and pus were observed, and the bone level was about 3 mm lower than when it first functioned due to the spread of inflammation. In light of the criteria for success established at the Toronto Conference, although the implant was not movable and there was no functional problem, infection originating from the implant was observed, and vertical bone resorption was also 3 mm (if no abnormality is found, about 0.4 mm is the Toronto Conference standard if 2 years have passed), so it was evaluated as a failure on the basis of the Toronto standard. In the case of (B), it functioned in the mouth without falling out during the 2-year functional period, so the survival rate (2 years) can be evaluated to be 100%. Of course, regarding case (B), since it meets the success criteria established at the conference, it can be said that the success rate in the second year is 100%. Thus, there is a qualitative difference between the success rate and survival rate of implant treatment. In other words, survival is an indicator that does not reflect the health status of the implant [27].

As the living standard of the population improves, dental restoration has become the definitive therapy for most dental defects. Implants have been recognized as the "third set of teeth," since they are beautiful, comfortable, and have good chewing efficiency, making them feel like natural teeth [28]. Large-scale studies have reported that the long-term survival rates of implants are between 93.3% and 98% [29, 30], indicating that dental implants are an effective treatment for edentulousness. Busenlech-

lar bone, most often identified in the posterior maxilla. Four bone types are shown in Figure 3.6. Shemtov-Yona [77] mentioned that, despite the wide use of the abovementioned bone classifications, these classifications can be useful during pre-operative or operative stages, particularly during drilling the implant osteotomy [84, 85].

Figure 3.6: Misch bone quality classification [modified after 79].

Since bone quality and quantity are important factors with regard to the survival rate of dental implants, Goiato et al. [86] conducted a systematic review of dental implants inserted in low-density bone to determine the survival rate of dental implants with surface treatments over time, covering the period July 1975 to March 2013. A total of 3,937 patients, who had received a total of 12,465 dental implants, were analyzed. It was reported that (i) the survival rates of dental implants according to the bone density were: type I, 97.6%; type II, 96.2%; type III, 96.5%; and type IV, 88.8%, (ii) the survival rate of treated surface implants inserted in low-density bone was higher (97.1%) than that of machined surface implants (91.6%), and (iii) surface-treated dental implants inserted in low-density bone have a high survival rate and may be indicated for oral rehabilitation.

3.4.2 Bone mineral density

To measure bone mass and density, the dual-energy X-ray absorptiometry (DXA) technique has been widely employed to obtain bone mineral content (BMC in gr) as well as areal bone mineral density (aBMD in gr/cm^2) [12]. DXA results explain a substantial portion of the effects of bone size, shape, and material properties and are strongly correlated with bone mechanical performance and fracture risk [87–90]. DXA method is used to diagnose osteoporosis earlier as a risk for bone fracture and monitor the effectiveness of osteoporosis treatments. The output of a DXA test is a number called a T-score, as seen in Figure 3.2. Normal is zero (0). The more negative the number, the weaker the bones and the more likely they are prone to break. If T-score is −2.5 or below (such as −3.0), then there is a risk for development of osteoporosis, assuming there is no other reason to have such a low T-score [90, 91].

4.2 Types of natural bone-grafting materials

Basically, there are two types of bone-grafting materials: i.e., they are natural bone materials and synthetic bone substitutes. Figure 4.1 illustrates all these bone-grafting materials. Referring to Figure 4.1 [3], a patient possesses variety of bone sources from own body (autograft), from a human donor (allograft), or from an animal model (xenograft), or various types of synthetic and biologically based, tissue-engineered biomaterials and combinations of these substitutes [11]. Besides the above three natural bone-grafting materials (autografts, allografts, and xenografts), there are still phytogenic materials such as algae-based or coral-based materials [5, 6, 12, 13]. All grafting materials have one or more of these three mechanisms of action (osteogenesis, osteoinduction, and oesteoconduction). The mechanisms by which the grafts act are normally determined by their origin and composition. An autogenous bone harvested from the patient forms a new bone by osteogenesis, osteoinduction, and osteoconduction. Allografts harvested from cadavers have osteoconductive and possibly osteoinductive properties, but they are not osteogenic. Xenografts and alloplasts are typically only osteoconductive [7]. In this section, natural bone-grafting materials are discussed.

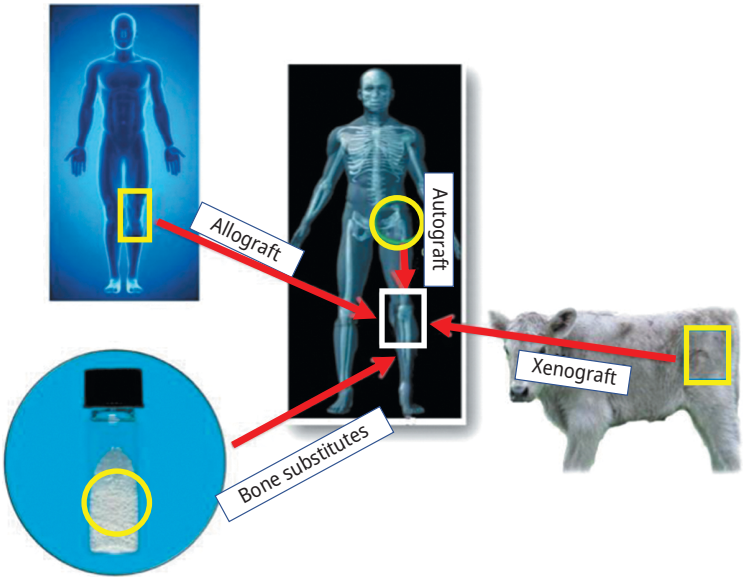

Figure 4.1: Types of bone-grafting materials and their recipient [3].

ters that need to be addressed in the successful implementation of porous scaffolds in vivo. Numerous studies have been performed to hasten osseointegration in porous Ti scaffolds and to improve their mechanical properties under occlusal and masticatory forces by altering the surface chemistry, introducing new biocompatible alloys, designs, and pore characteristics, or impregnating surface coatings with bone growth factors such as BMPs. It is thus envisaged that the breakthroughs and developments in manufacturing methods, micro- and nanoengineering, metallurgy, and biology will lay the foundations for more advanced and functional Ti foam scaffolds for dental applications [41].

Figure 9.1 shows the trabecular metallic dental implant with a structure and elasticity similar to cancellous bone – consisting of a titanium cervical and internal core section (upper section) covered by a trabecular metal sleeve (middle section) and joined by a titanium apical section (lower section).

Figure 9.1: Trabecular metal dental implant with a structure and elasticity similar to cancellous bone [modified after 41].

Magnesium has been suggested as a revolutionary biodegradable metal for use as an orthopedic material. As a biocompatible and degradable metal, it has several advantages over the permanent metallic materials currently in use, including eliminating the effects of stress shielding, improving biocompatibility concerns in vivo, and improving degradation properties, removing the requirement of a second surgery for implant removal. The rapid degradation of magnesium, however, is a double-edged sword as it is necessary to control the corrosion rates of the materials to match the rates of bone healing. In response, calcium phosphate coatings have been suggested as a means to control these corrosion rates. The potential calcium phosphate phases

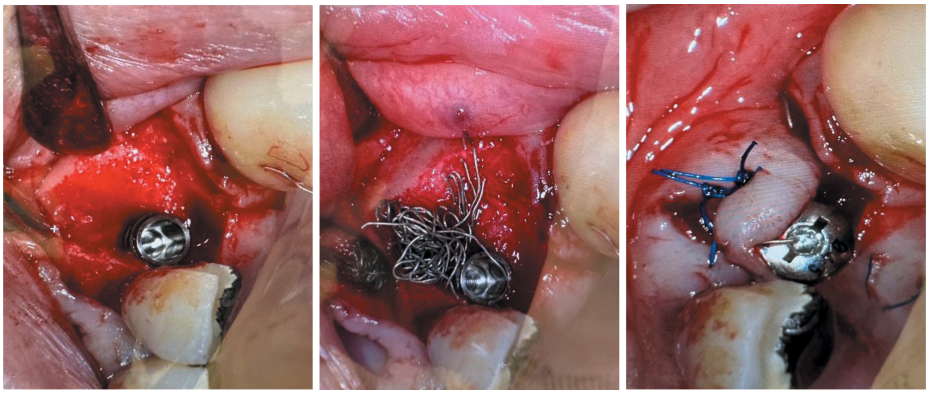

Figure 1: Placement implant and bioresorbable pure magnesium wire network.

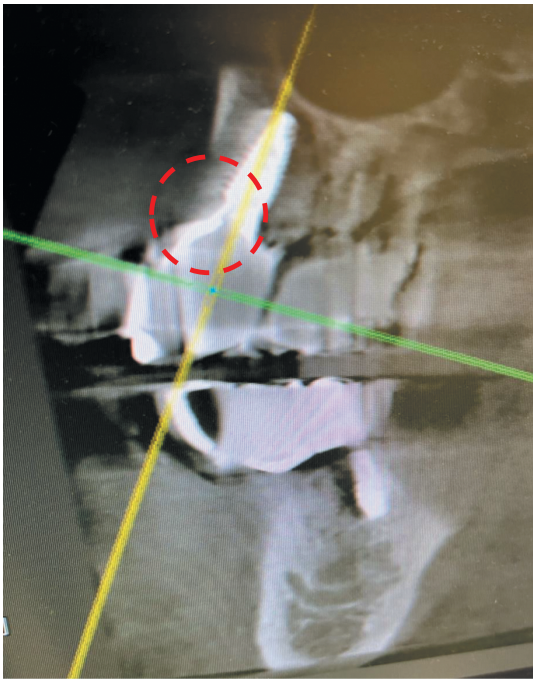

Figure 2: X-ray image, taken two months after Mg wire placement, where broken red circle indicates the area where Mg wire network was placed.

an important and effective role in maintaining sufficient space, and as a result, new bony structure can be generated and grown in a relatively short period of healing time.

In implant dentistry, the implant stability quotient (ISQ) value is considered as an important parameter to judge the success of placed implant. The ISQ is the value on a