MODERN IMPLANT DENTISTRY

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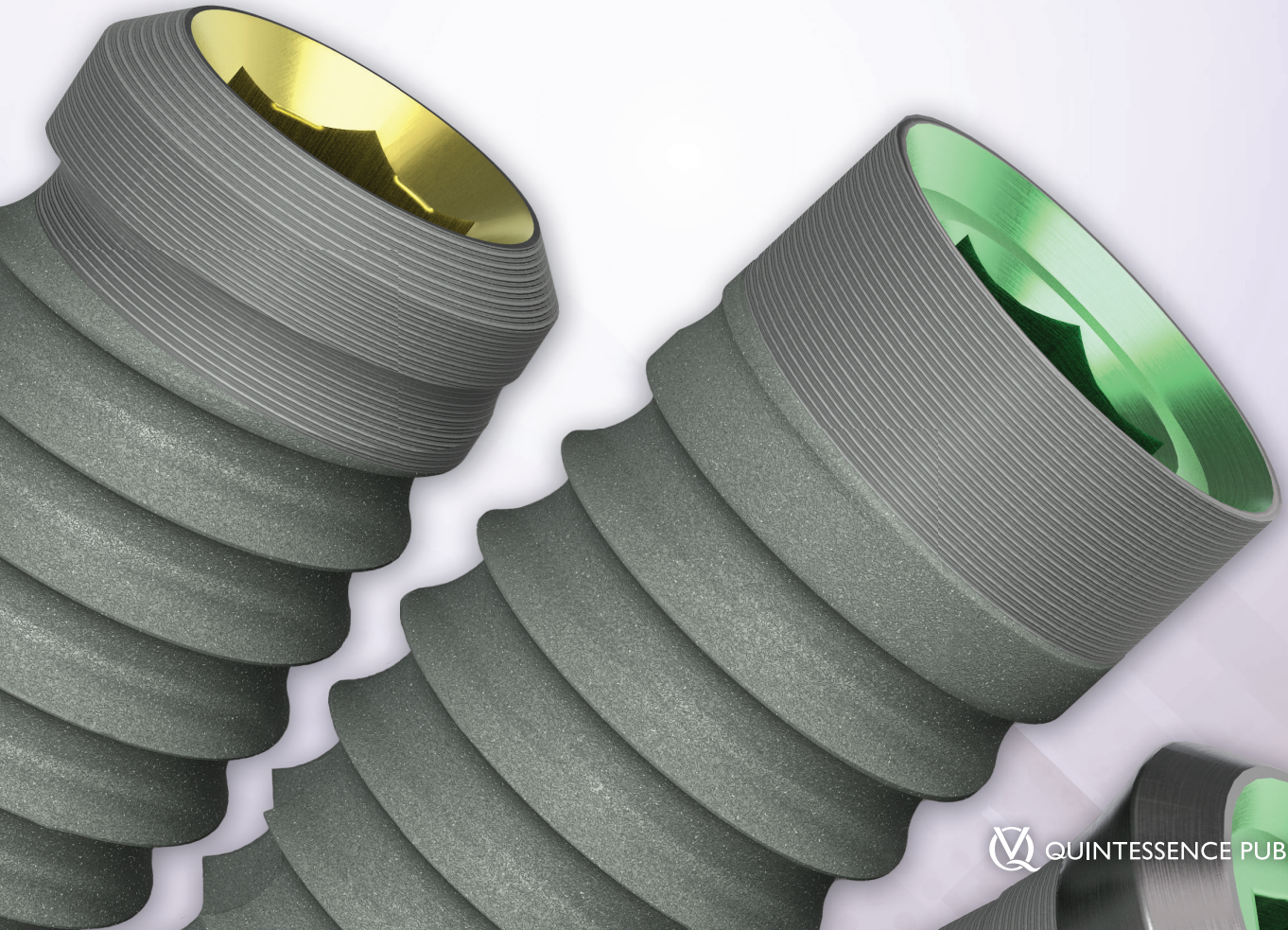

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PREFACE

The use of dental implants has become so widespread over the past few decades that scores of textbooks have been dedicated to this topic. As little as 50 years ago, the practice of dentistry did not include the modern implants, bone grafts, barrier membranes, or growth factors currently available in today's market. It wasn't until the late 1970s that Brånemark and his colleagues presented the two-stage threaded titanium implant procedure that we know today, following a decade of testing in various animal and human models. While the original Brånemark implant was a cylindrical fixture, over the years the shape has shifted to tapered, and many new implant types, body designs, and surface morphologies have been adopted. Entire companies have been formed with the goal of delivering faster, more predictable results to our patients. Today, the field has been trending, as rapidly as ever, into the world of digital implant dentistry. This book highlights all these groundbreaking discoveries, many of which are credited to the book's contributors—some of the most talented clinicians working in the profession today.

Over 50 authors from around the world have contributed to this textbook, all of them with different backgrounds and expertise in various subspecialties of implant dentistry. Chapters 1 to 4 focus on the biologic background for dental implants as well as medical considerations required prior to placing them, and chapters 5 and 6 are dedicated to documentation, including photography and CBCT imaging. Chapters 7 and 8 focus on treatment planning and digital workflow, and chapters 9 to 18 cover many surgical concepts, from single-tooth extraction to guided All-on-X treatment. Chapters 19 to 22 focus on the prosthetic options available to us in implant dentistry, while chapters 23 to 31 hit upon additional topics related to the field. These include soft tissue management, treatment of peri-implant disease, the socket shield technique, and marketing of dental implant therapy.

Preparing this textbook has been a massive undertaking. The editors wanted to bring you THE book on implant dentistry so every clinician, whether a beginner or a seasoned pro, can find what they need to practice implant dentistry well and continue to improve their skills and patient outcomes. To accomplish this goal, the book was written using only evidence-based approaches performed on a daily basis by experienced clinicians. As such, the techniques and advice given are based on real-world experiences in the clinic. As an added learning tool, over 60 surgical and clinical videos are included within the book (linked via QR codes) to SHOW you what these procedures and techniques and products look like in real life, not in photographs taken in ideal conditions.

We are very proud to present this book to you, and we hope to keep it updated over time as new developments, products, techniques, and research become available. The goal will always be to provide new and experienced clinicians with the most up-to-date and evidence-based textbook written in implant dentistry. As such, it is our hope that this book will benefit all implant surgeons by adding to their current knowledge base and improving their ability to make rational, evidence-based decisions in implant dentistry.

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BONE METABOLISM AROUND DENTAL IMPLANTS

RICHARD J. MIRON
ANGEL INSUA

SUMMARY

Despite the increasing number of studies in the field of implant dentistry investigating novel dental implant surfaces, biomaterials, and growth factors, comparatively very few have studied the biology and metabolism of bone healing and its implication in peri-implant tissue health. The aim of this chapter is to provide a thorough understanding of the biologic properties that impact bone formation and osseointegration, including the coupling mechanisms between immune cells and bone. This chapter focuses on the various bone cells in the body—osteocytes, bone lining cells (BLCs), osteoblasts, and osteoclasts—and their bone remodeling cycle. Furthermore, the importance of immune cells and their impact on biomaterial integration during bone formation and implant osseointegration is also discussed. Finally, the putative effects of cholesterol, hyperlipidemia, and vitamin D deficiency are addressed. Such factors should be monitored during patient care, and ultimately future research should focus on these avenues as well as meticulous maintenance programs to favor both early and long-term maintenance and stability of dental implants.

OBJECTIVES

- Understand how overall patient health directly affects dental implant osseointegration
- Understand the key cells involved in bone formation, maturation, and maintenance
- Understand the direct role of immune cells on biomaterial and dental implant integration
- Understand the essential role of optimizing the immune system prior to dental implant placement
- Investigate the relationship between vitamin D deficiency and early implant failure and how to avoid such pitfalls

Bone regeneration requires bone grafting materials that possess excellent biocompatibility and osteoinductivity without eliciting an antigenic effect. While companies that manufacture replacement biomaterials intended to mimic autogenous bone grafts often report on their osteoconductive, osteoinductive, or osteogenic potential, autogenous bone still favors the greatest bone regeneration compared to allografts, xenografts, and synthetic alternatives because it combines all three of these properties. Thus, despite the increasing number of

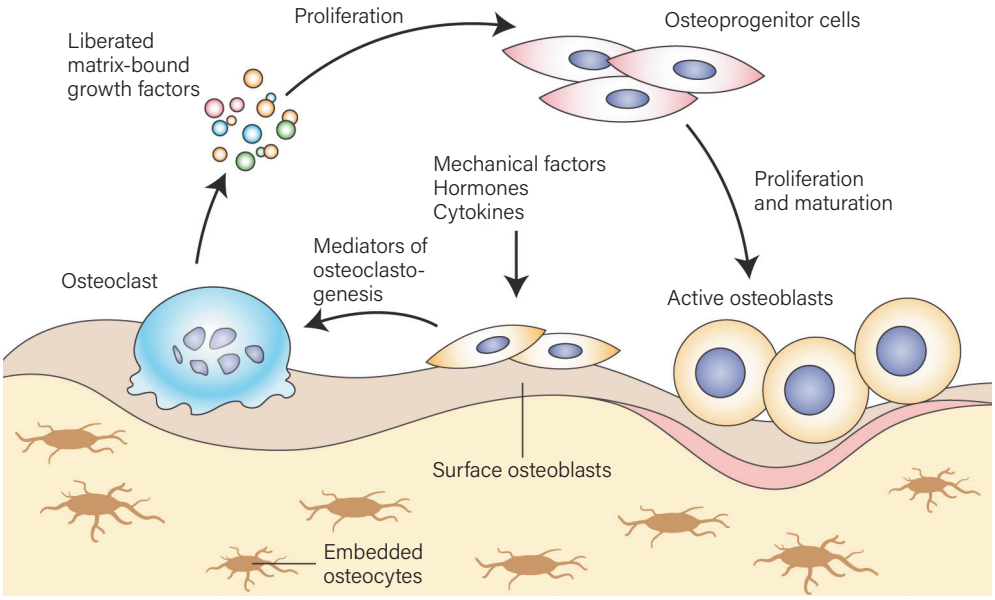

FIG 1-1 The bone remodeling cycle. Osteoclasts—cells that destroy and resorb bone—are present on the bone matrix surface and liberate growth factors and cytokines to the local microenvironment. These growth factors act on mesenchymal stem cells/progenitor cells to rapidly stimulate their proliferation and differentiation toward bone-forming osteoblasts. Osteoblasts lay new bone matrix and, once embedded within the bone matrix, become osteocytes.

new bone grafting materials brought to market as substitute replacement grafts, to date there is no true replacement for autogenous bone grafts.[1] Autografts carry no risk of immunologic reaction or disease transmission and provide optimal conditions for the penetration of new blood vessels and migration of osteoprogenitor cells. In contrast, many bone grafting substitutes are osteoconductive but have limited osteoinductive potential.[2]

For bone regeneration to take place, especially with foreign-body biomaterials such as allografts and xenografts or dental implants, there is a great need to better understand the regulatory properties and integration process of these biomaterials. After all, no matter the biomaterial placed, bone formation relies on immune-related factors working at the cellular level. The aim of this chapter is therefore to provide the biologic background on the cells involved in graft consolidation and give a brief overview of fracture healing. This chapter focuses on the bone cells involved in bone formation and dental implant osseointegration, including osteocytes, BLCs, osteoblasts, and osteoclasts, and their bone remodeling cycle. The chapter also addresses the importance of immune cells and their impact on biomaterial integration, as well as the putative effects of cholesterol, hyperlipidemia, and low vitamin D levels.

Bone Cells: Osteoclasts, Osteoblasts, and Osteocytes

There are three main cell types in bone tissue involved in the bone remodeling cycle: osteoclasts, osteoblasts, and osteocytes[3] (Fig 1-1). Osteoclasts are the bone-resorbing cells that degrade bone tissues. They are derived from hematopoietic stem cells following their differentiation from monocytes in response to two key factors: receptor activator of nuclear factor kappa-B ligand (RANKL)[4] and macrophage colony-stimulating factor (M-CSF).[5] Osteoclasts can be characterized histologically based on their multinucleated morphology and expression of tartrate-resistant acid phosphatase (TRAP), cathepsin k (CatK), and the calcitonin receptor (CTR). Their formation, activity, and survival are also regulated by various hormones (such as calcitonin and estrogen) that regulate several downstream cytokines and cellular pathways.[6] Activated osteoclasts form distinct and unique membrane domains, including the sealing zone, the ruffled border, and the functional secretory domain, which facilitate resorption of bone or bone graft particles.[7] Rearrangement of their F-actin fibers from the cytoskeleton forms a ring shape consisting of a dense continuous zone of highly dynamic podosomes.[8] These podosomes allow for mineralized bone to be gradually resorbed, creating grooves and tunnels on the bone surface. This process is also quite important for bone remodeling because the resorbed bone liberates calcium phosphates and growth factors contained within the bone matrix that attract bone-forming osteoblasts to the local environment.[9]

Osteoblasts perform the opposite role of osteoclasts and are responsible for bone formation (see Fig 1-1). They are derived from cells of the mesenchymal lineage, and their formation and development are controlled locally and systemically by several growth factors, including bone

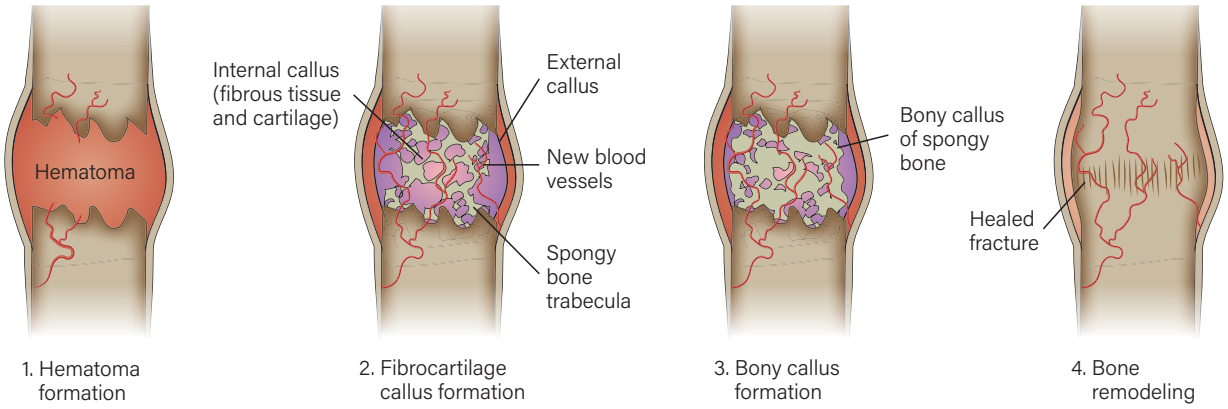

FIG 1-2 The fracture healing process is divided into four phases: *(1)* hematoma formation, *(2)* fibrocartilage callus formation, *(3)* bony callus formation, and *(4)* bone remodeling.

morphogenetic proteins (BMPs).[10,11] Osteoblasts secrete a range of molecules including growth factors, cell adhesion proteins, and other extracellular matrix molecules that support new bone formation.[6] While osteoblasts are forming bone, they become embedded within bone tissues and transform into osteocytes.

Contrary to the short lifespan of osteoblasts and osteoclasts, osteocytes can live for decades within the bone matrix. They no longer produce new bone and instead undergo morphologic changes, losing cytoplasm organelles and acquiring a stellar shape morphology with numerous extensions that connect to other osteocytes through the canalicular network.[12] Osteocytes can then transmit signals through this network similar to neuron communication; this communication has a profound impact on neighboring osteoblasts, osteoclasts, and osteocytes. While it was initially believed that osteocytes served only a mechanical transduction function,[13] more recently their role has been deemed one of the most important within the bone tissues because they release numerous paracrine signals to their environment, thereby influencing both osteoblasts and osteoclasts.[12,14,15]

Fracture Healing and Graft Consolidation

Fracture healing is an important process that involves various cell types and a variety of signaling pathways.[3,16,17] Unlike other tissues in the body, bone tends to regenerate and repair itself quite rapidly. Natural fracture healing is a four-stage process (Fig 1-2). The first step is hematoma formation. Following injury, a blood clot forms, creating a fibrin matrix with an abundance of infiltrating inflammatory and immune cells that take place with an activation of platelets.[16,18] These cells secrete an array of growth factors that initiate the second and third phases of fracture repair.[16,18] At the terminal end of the first phase, osteoclast formation occurs from precursor monocytes, and these osteoclasts invade the bone surface, commencing bone resorption.[16]

The second phase of fracture healing is the repair phase. During this phase, a bone callus is formed. Initially, blood vessels begin to form with infiltration of mesenchymal progenitor cells; this process is responsible for creating a fibrocartilagenous tissue that matures into bone. This woven bone is gradually replaced with dense lamellar bone to form a dense bony callus in phase 3.[19]

The final phase is the remodeling phase, during which the callus is gradually resorbed. In this stage, the bone is replaced by native bone lacking scar tissue.[20] It has been shown that during this phase, resident macrophages play a predominant role in orchestrating host cells.[21,22] While these four phases are not described in great detail within the present chapter, it is important to note that graft consolidation is tightly regulated by secretion of growth factors and cytokines (also secreted from autogenous bone particles and blocks). This is all tightly regulated in very distinct cell-to-cell communication events that take place during bone regeneration.[3]

Role of Osteocytes and Bone Lining Cells in Bone Remodeling

Osteocytes

Osteocytes are the pivotal cells in the regulation of bone mass and structure, along with osteoblasts and osteoclasts.[23] Osteoblasts are derived from mesenchymal stem cells and

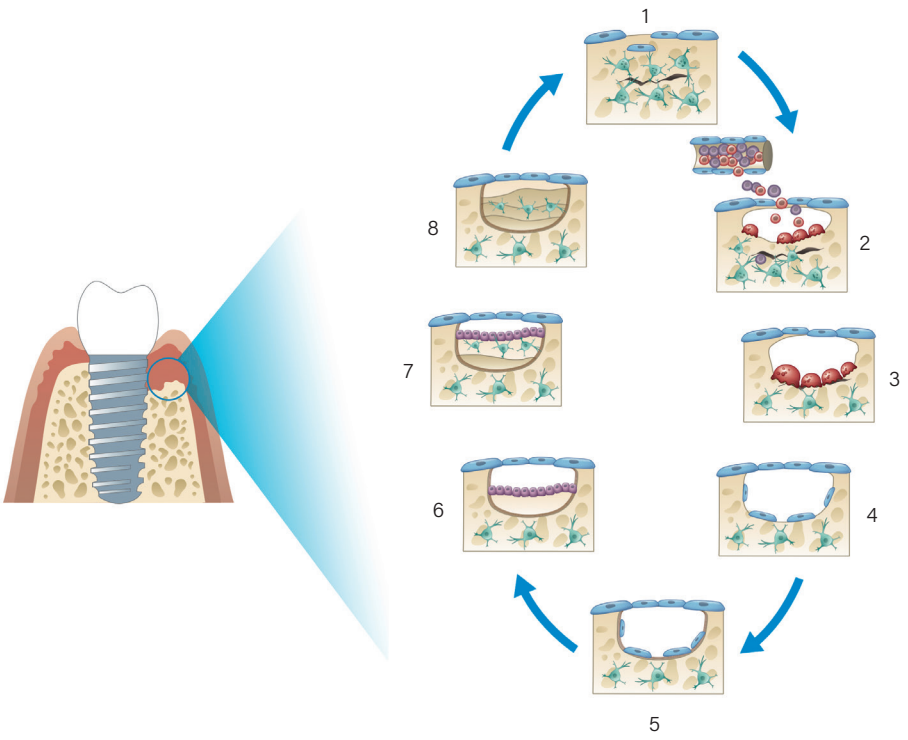

FIG 1-3 Bone remodeling after excessive implant torque. *(1)* Excessive torque promotes bone damage, including the osteocyte network. *(2)* Osteoblasts and osteoclasts are recruited from the blood, from the marrow, or from BLCs to populate the bone remodeling compartment. *(3)* Osteoclasts remove the damaged bone. *(4)* BLCs clean the debris after osteoclast resorption. *(5)* BLCs secrete fibrillar collagen. *(6)* This collagen layer allows osteoblasts to attach. *(7)* Osteoblasts deposit osteoid to fill the compartment. *(8)* Osteoblasts trapped in the osteoid become osteocytes or BLCs, after which most undergo apoptosis. (Reprinted with permission from Seeman.[34])

synthesize new bone matrix.[24] Osteoclasts are terminally differentiated multinucleated cells from the monocyte-macrophage lineage; beyond their resorbing bone function, these cells are also a source of cytokines that play an important role in bone homeostasis.[25] Osteocytes are terminally differentiated osteoblasts, and their primary function is to support bone structure and mechanosensation.[24] Osteocytes may act as regulators of bone remodeling by modulating osteoclast and osteoblast activities.[25] These stellate-shaped cells are located within lacunae surrounded by mineralized bone matrix and present with connections through cytoplasmic prolongations with surface BLCs but also with bone marrow.[15,25]

Bone lining cells

BLCs are cells involved in bone formation much like preosteoblasts, osteoblasts, and osteocytes.[26] They are characterized by a flat-shaped architecture along bony surfaces[25] and may be considered latent osteoblasts.[27] In human cancellous bone, around 65% of osteoblasts undergo apoptosis, with approximately 30% differentiating into osteocytes[28]; the reduced remnants become BLCs and chondroid-like cells.[26,28] BLCs maintain their proliferative capability and often differentiate into other osteogenic cells.[29,30] Various studies have shown that some factors can induce their proliferation prior to bone formation,[31] while mature osteoblasts are unable to divide.[26] Osteoblasts may also undergo a quiescent stage when there is no bone resorption or remodeling,[29] but the function of BLCs might be more complex than a simple latent state,[32] including catabolic and anabolic bone processes[31] and rapid bone formation under osteogenic signaling.[32]

In the complex process of bone remodeling,[33,34] external factors such as mechanical loading, irradiation, parathyroid hormone (PTH), fibroblast growth factor-2 (FGF2), sclerostin inhibition, or inflammation may lead BLCs to exit the quiescent stage and enter into an active function phase by re-forming their cuboidal appearance and their secretory capability.[25,31,35] The presence of BLCs observed histologically indicates a strong sign of osteogenic potential[29] and is often regarded as a major source of osteoblasts and proliferating preosteoblasts in the adult population.[31] This prominent role in new bone formation was previously highlighted[28,32] when rapid bone formation was observed after mechanical loading without previous bone resorption. Early peak bone formation after 3 days was only possible if BLCs underwent reactivation and reaquired their secretory capacities.[28,32]

Moreover, BLCs exert a prominent function during bone resorption,[36] demonstrated by their ability to express key ostoclastogenesis markers including M-CSF receptor (M-CSFR), and after the modulation of bone resorption, BLCs play another important role in the early stages of bone formation by entering the resorption lacunae to remove collagen fibers and debris left by osteoclasts (Fig 1-3). Subsequent to this cleaning function, BLCs secrete a layer of fibrillar collagen, allowing osteoblasts to attach and deposit new osteoid.[36]

Role of Macrophages in Bone Regeneration, Implant Osseointegration, and Breakdown

Macrophages play a prominent and central role in bone homeostasis and bone/biomaterial integration around dental implants.[37] Specifically in bone tissues, a special subset of macrophages, termed *osteal macrophages* (or *OsteoMacs*), have recently been highlighted as playing a pivotal role in the fate of implant osseointegration.[37] The general role of OsteoMacs in bone is to act as immune surveillance cells within their microenvironment.[38,39] When a foreign-body biomaterial such as a dental implant is inserted transmucosally into alveolar bone, a rapid accumulation of macrophages is typically found at the implant surface.[40] Chehroudi et al clearly showed that bone formation on titanium dental implant surfaces was routinely preceded by macrophage accumulation (prior to bone deposition).[40] Despite this prominent finding, over 90% of research to date has focused on osteoblast and fibroblast behavior toward material surfaces, with only a small percentage (10%) dedicated to immune cell interactions including monocytes, macrophages, osteoclasts, leukocytes, and multinucleated giant cells (MNGCs).[41] This major discrepancy is difficult to understand given the fact that macrophages and immune cells in general dictate how biomaterials will eventually be integrated into host tissues.

A series of key studies on OsteoMacs has shown that their removal during bone development is consistently associated with a reduction in bone modeling, bone remodeling, and bone repair.[42–45] Furthermore, in primary osteoblast cultures (containing macrophages), the simple removal of macrophages from these in vitro systems leads to a 23-fold decrease in the mineralization potential of bone cells.[44,46] Therefore, while basic studies have clearly pointed to their vast and substantial role in bone biology, much less information is available concerning the response of macrophages to implanted biomaterials such as bone grafts and dental implants. It is therefore crucial that we gain a better understanding of how immune cells and macrophages behave in relation to dental implant osseointegration and maintenance.

Macrophage polarization: M1 and M2 phenotypes

Macrophages are some of the most plastic cell types found in the human body. They polarize completely from the classical M1 macrophages (involved in tissue proinflammation) toward M2 (tissue regeneration) macrophages (Fig 1-4). They may also fuse into osteoclasts and resorb bone or fuse into MNGCs, where their role remains poorly defined.[47,48]

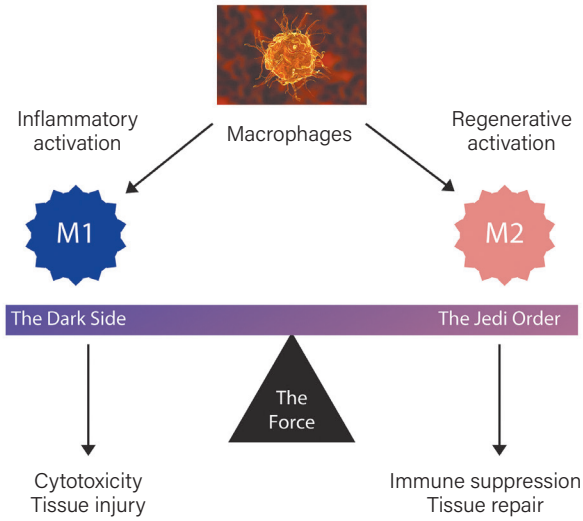

FIG 1-4 Macrophage polarization of both M1 and M2 phenotypes. M1 macrophages typically represent tissue inflammation and destruction. M2 macrophages are responsible for healing and tissue resolution.

The primary difference between M1 and M2 macrophages is that M1 macrophages have their arginine metabolism shifted to nitric oxide (NO) and citrulline, whereas M2 macrophages are shifted toward ornithine and polyamines.[49] M1 macrophages produce NO as a main effector molecule capable of inhibiting cell proliferation,[50] while M2 macrophages generate ornithine, increasing cell proliferation and repair through polyamine and collagen synthesis.[51]

During dental implant osseointegration, classical M1 macrophages secrete a wide array of proinflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), IL-6, IL-12, MMP-2, and MMP-9, typically induced by interferon gamma (IFN-γ) and lipopolysaccharide (LPS) or TNF-α (in vitro).[50,52] In contrast, M2 macrophages are produced in response to IL-4 or IL-13 and also secrete a wide variety of proregenerative cytokines including platelet-derived growth factor BB (PDGF-BB), transforming growth factor beta 1 (TGF-β1), vascular endothelial growth factor (VEGF), IL-4, IL-10, and chemokine ligand 18 (CCL18). As can be expected, their polarization around implant surfaces is highly relevant for implant integration and long-term stability. Their role, especially as it relates to peri-implant infection, is extremely vital for the long-term maintenance of dental implants.

Macrophages, immune cells, and the foreign body reaction

It has been reported that implant osseointegration is a long-term equilibrium between host immune cells and bone biomaterials.[53–55] The literature has showed that

MNGC accumulation on implant surfaces leads to biomaterial breakdown and possible implant failure/rejection.[53–55] These papers demonstrate that implant osseointegration and eventual peri-implant bone loss is likely a direct result of an M1-M2 shift in macrophage polarization. Interestingly, invading periodontal pathogens are known to secrete LPS, a known and direct molecule influencing proinflammatory M1 macrophage polarization.[56] Hence, it is important to examine foreign body reaction, equilibrium between M1 and M2 macrophages, and MNGC polarization. Furthermore, these studies stressed heavily the material rejection with MNGC accumulation, further implicating the role of immune cells. As such, clinicians should always consider the dramatic importance and role of immune cells and general immune cell health during dental implant placement (see later section on vitamin D deficiency and chapter 2).

Bone Remodeling Around Dental Implants

After dental implants are anchored, a sequence of immune-inflammatory responses followed by angiogenesis and eventually osteogenesis take place to achieve osseointegration. Initial protein adsorption is based on implant surface topography and hydrophilicity. Accordingly, thrombin and fibrinogen adhere to the implant surface. Later, neutrophils populate the implant recipient site before the monocytes and macrophages infiltrate the area. Cytokines and growth factors are then released and stimulate collagen matrix deposition around the titanium oxide layer, leading to newly formed woven bone (usually 5 days later). In a matter of 8 to 12 weeks, lamellar bone initiates biologic stability, or osseointegration.[33]

Just like the natural dentition, implants are subjected to soft and hard tissue remodeling after restoration delivery. The biologic width around dental implants has recently been shown to be about 3.5 mm, which is far greater than that around natural teeth.[57] This physiologic bone remodeling mechanism to a foreign-body biomaterial is led by RANKL, which promotes macrophage activation into osteoclasts. It has been suggested that the microgap in two-piece implants might be associated with the presence of inflammatory cell infiltrate, which can lead to crestal bone loss by affecting both soft and hard tissues.[58] A pumping effect of the liquid contained in the implant cavities may move into the peri-implant compartment due to the cyclical loading of the implant-abutment interface and facilitate the colonization of the gap and inner walls of the implant by gram-positive and gram-negative bacteria.[58] These organic fluids with bacterial byproducts and endotoxins could upregulate the expression of proinflammatory cytokines in peri-implant tissues and stimulate the chemotaxis of active osteoclasts.[58] Over time, leakage associated with micromovements can lead to a persistent inflammatory reaction and eventual bone loss around the implant neck as well as peri-implantitis.[59] Research has hinted that internal implant connections provide a better seal than external ones, but either can provide a complete seal.[60,61] Ongoing developments in implant and abutment design aim to limit this risk and reduce future crestal bone loss associated with microgap inflammation.

Effect of Excess Implant Torque on Bone Healing

Bone biology under implant insertion

Adequate implant insertion torque (IT) values (25–45 Ncm) have been suggested to prevent micromovements that could lead to fibrous encapsulation. On the flip side, high IT has also been associated with an increase in critical pressure, triggering microfractures and bone necrosis.[62] It has been shown in animal models that high IT elicits a complex process of microdamage, which stimulated targeted bone remodeling.[63] This was supported by a radiographic, histomorphometric, and histologic investigation that clearly demonstrated greater peri-implant bone loss in the early stages of healing for implants placed with a high IT (> 50 Ncm) compared with those more passively placed.[64] High IT has been shown to lead to osteocyte apoptosis and consequently may promote higher levels of RANKL secretion to the surrounding environment to remove apoptotic cells.[65,66] These findings highlight the importance of minimizing microfractures as a consequence of high IT to predictably preserve the peri-implant bone level. While a lack of primary stability may potentially jeopardize osseointegration, high IT might not favor the preservation of the peri-implant tissue level, so a reasonable level of torque must be achieved.

Alveolar bone density further influences primary stability. The maxillary ridge has been classified into four major types[67]; accordingly, denser bone is located in the anterior mandibular region, whereas more porous trabecular bone is detected in the posterior maxillary area. Recent findings seem to point to the influence of bone atrophy on bone density.[68] Notwithstanding, the overlying cortex is mainly responsible for the mechanical stability of implants. Even when cortical bone has a higher elastic modulus[69] and compressive strength than cancellous bone,[70] the restrained vascularity of compact bone (ie, minimal to no migration of differentiating osteogenic cells) may result in peri-implant bone loss. Therefore, because of limited blood supply and lack of bone marrow, the number of osteoblasts in the bone

remodeling area may be limited, which can prevent the area from reaching the critical osteoblastic cell density required for bone formation to occur.[71,72]

Crestal bone levels under high and low IT

For immediate implant placement with or without immediate loading, primary stability is necessary (> 32 Ncm).[73,74] For delayed implant placement, on the other hand, an understanding of the resorption process of the bundle bone and the bone macroarchitecture and density might dictate the drilling sequence and IT applied. As such, implant placement performed with high IT (≥ 50 Ncm) has been shown to be prone to marginal bone loss and recession, notably in the presence of a thin buccal bone.[75] Marginal bone loss was found to be substantially higher when higher IT thresholds (> 70 Ncm) were studied.[76] This association was statistically significant when including all IT values (up to 176 Ncm).

Because of this risk of marginal bone loss, novel approaches for implant placement are being investigated. Simplified drilling methods are one proffered solution, and they do not seem to jeopardize the process of osseointegration.[75,76] Wider implants installed under higher IT have shown adequate secondary stability and high bone-to-implant contact (BIC), although healing delay was reported due to necrosis of the existing bone.[77] Findings from another group indicated that submerged implants inserted at 0 Ncm IT displayed similar outcomes at 4 months compared to those inserted at 30 or 70 Ncm.[78] Clinical outcomes echo the uncertain impact of high IT on peri-implant bone loss compared to low IT. Future research is currently investigating alternative strategies including the application of osseodensification protocols,[79] lasers,[80,81] or ultrasound tools[82–85] to enhance osseointegration.

Factors Affecting Bone Metabolism

Cholesterol and fatty acids

Within the last three decades, high-fat and high-cholesterol diets have become increasingly more prevalent in industrialized societies,[86] and as a consequence, the morbidity and mortality of obesity-related diseases such as cardiovascular disease and hyper-inflamed conditions have also increased.[87,88] Obesity is also associated with an enhanced risk of periodontal disease.[89,90]

Obesity and high levels of cholesterol production have been linked for years, but the relation between obesity and serum levels is low.[91–93] Similarly, the relationship between bone and body fat is complex and not totally understood.[94] Bone marrow fat (BMF) is the accumulation of fat cells inside the bone marrow tissue.[95] An inverse correlation between bone mass and BMF has been reported.[94–97] Higher adipogenesis in bone marrow may result in lower osteoblastogenesis, and these adipocytes can secrete saturated fatty acids that may impair osteoblast viability by inducing apoptosis and autophagy.[95,96] Adipocytes can also release proinflammatory and osteoclastogenic cytokines (eg, TNF-α and IL-6) and adipokines and express RANKL.[94,95,97–99]

In other words, fatty acids[96] and high levels of cholesterol[100] may disturb the bone formation–bone resorption equilibrium by downregulating the Wnt signaling pathway.[101] This is probably due to the effects of higher levels of TNF-α and sclerostin.[102] The Wnt pathway balances the differentiation of mesenchymal stem cells by inhibiting adipogenesis and promoting osteoblast proliferation, maturation, and differentiation.[96] Animal studies have shown more bone resorption, less bone formation and bone mass, and higher levels of bone turnover markers in subjects with high-cholesterol diets.[96,100,103–105]

In addition, obesity induces a systemic inflammation condition with high levels of circulating cytokines and increased production of monocytes, neutrophils,[106,107] and adipose tissue macrophages.[108,109] These cytokines and the accumulation of cholesterol in macrophages can alter the ratio of M1-M2 macrophages, promoting an M1 proinflammatory environment and thereby increasing the numbers of monocytes/macrophages in circulation.[108,110]

The influence of obesity and increased levels of cholesterol and triglycerides have been extensively described in the medical field, but the effect of hyperlipidemia on dental implant osseointegration has not yet been fully elucidated.[111] Significantly more peri-implant bone loss, reduced bone formation, and lower strength in the bone-implant interface has previously been reported in mice after a 12-week high-fat diet.[111] On the other hand, Dündar et al reported that there was no difference in BIC 12 weeks after implant placement between rabbits following a 3-month high-fat diet versus normal diet.[112] Because hyperlipidemia might impair bone quantity and density, negative effects on implant osseointegration might be speculated, but no conclusive evidence to date has been found.

Vitamin D

The link between vitamin D deficiency and early implant failure has recently gained attention, with data demonstrating higher failure rates compared to even smoking and generalized periodontitis.[113] Vitamin D is a fat-soluble hormone that regulates calcium phosphate homeostasis and mineral bone metabolism.[114] It is transformed into the active form (1,25-dyhydroxyvitamin D3) by hydroxylation, first in the liver and then in the kidney.[115] This vitamin can stimulate

osteoblast bone matrix production, coupling bone resorption to formation and optimizing bone remodeling.[116] It increases calcium absorption in the intestine, leading to a reduction in PTH secretion and lower systemic bone resorption[115,117,118] with a possible inhibition of osteoclastogenesis.[119] 1,25-dyhydroxyvitamin D3 can stimulate bone resorption by binding to osteoblast vitamin D receptors (VDRs) and by altering the balance between RANKL and osteoprotogerin (OPG).[120–123]

Vitamin D is a common substance in the prevention and treatment of osteoporosis, but research investigating its direct effects on dental implant osseointegration has just begun.[118] Kelly et al studied the effects of vitamin D deficiency on the osseointegration process in rats and reported up to 66% lower BIC values and mechanical bone strength 2 weeks after implant placement.[124] Noteworthy is that the authors suggest that implant failure might be confounded by the rising deficiency of vitamin D prevalence in various patient populations.[124] On the other hand, Zhou et al reported a significant increase in peri-implant bone density, BIC (1.5 times higher), and peri-implant trabecular microarchitecture following implant placement in rats who had undergone an 8-week regimen of oral vitamin D supplementation.[118] Similar results were reported in mice with chronic kidney disease (CKD), suggesting that vitamin D treatment may be an effective approach for implant placement in patients with CKD.[125] Recently, the effect of topical application of vitamin D (10%)[126] and melatonin (5%)[127] solutions on the surface of immediate implants placed in dogs was evaluated. Both topical applications significantly improved new bone formation around implants and reduced crestal bone loss at 12 weeks following surgery,[127] demonstrating the positive correlation between vitamin D and early stages of osseointegration. In combination, these results suggest that vitamin D has a protective effect on bone healing after implant insertion. Chapter 2 further describes this link and the importance of vitamin D levels in implant patients.

Hyperglycemia

The number of adults with diabetes worldwide increased from 108 million in 1980 to 422 million in 2014.[128] Type 1 diabetes (previously known as *insulin-dependent*, *juvenile*, or *childhood-onset*) is characterized by deficient insulin production and requires daily administration of insulin. Type 2 diabetes (formerly called *non-insulin-dependent* or *adult-onset*) results from the body's ineffective use of insulin. Type 2 diabetes comprises the majority of people with diabetes around the world and is largely the result of excess body weight and physical inactivity.[129] It is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.

Diabetes mellitus has been related to a deficient metabolism of the skeletal tissue due to a suppression in osteoblast function and lower bone formation potential, independent of the type of bone, the location, and mechanical loading.[130] A higher risk of implant failure has been related to uncontrolled diabetes,[131] and undiagnosed diabetes might be a possible reason for failed implants.[132]

Ajami et al reported delayed bone formation and remodeling in animals with hyperglycemia.[132] Early bone mineralization might be affected due to a compromised intrafibrillar collagen mineralization, whereas interfibrillar and cement line mineralization remained normal.[133] Diabetes also promotes a hypercoagulative state and a delay in fibrin clot resolution due to an increase in thrombin formation, platelet activation, and fibrin resistance.[134] These events hinder platelet cytokines and growth factor release and cause limited pericyte and endothelial migration into the implant surface and thereby reduced angiogenesis.[135]

Other factors

Metabolic issues are not the only factors influencing bone remodeling. Medication, for example, might induce changes in bone cells and bone turnover and lead to bone loss around dental implants.[136] Higher bone turnover seems to expose more implant surface, particularly in the mandible.[136] Serotonin reuptake inhibitors have been related to an increase in bone loss and higher implant failure,[137] so updated and thorough medical records are essential to avoid complications.

Hypersensitivity to titanium particles or ions released from the implant surface may also affect implant survival.[136] Corrosion of the implant surface or degradation of the titanium dioxide layer can liberate wear particles that induce inflammatory reactions in the peri-implant tissues.[138] In orthopedics, aseptic loosening is the main reason for long-term failures of hip and knee implants.[139]According to this model, wear particles are recognized as foreign-body substances and phagocytosed by macrophages.[138] Later, M1 cells release inflammatory cytokines that promote osteoclastogenesis and osteolysis.[138]

Furthermore, it is important to note that certain antiseptic solutions commonly used in implant dentistry, such as chlorhexidine (CHX), have been shown to cause inflammation and/or fibroblast apoptosis, leading to M1 macrophage polarization. In cases following surgery, it is advised to avoid CHX because it may delay healing. Recent studies have shown nearly a 2,000-fold increase in release of inflammatory markers such as TNF-α when gingival fibroblasts were exposed to CHX.[140]

One novel replacement option that has shown promising results both before and after surgery is StellaLife's recovery kit, a homeopathic wound healing rinse (Fig 1-5). It favors better wound healing of the defect site as well as improved pain management with microbial resistance.[141] A split-mouth study revealed that the StellaLife VEGA Oral Care Recovery Kit performed better than many frequently utilized materials including Peridex, plasma rich in growth factors (PRGF), platelet-rich plasma (PRP), Emdogain, and PerioSciences products. The following conclusions were reported in the StellaLife test group[141]:

- The product achieved anesthetic pain relief.
- Healing was faster than with the control products.
- At 1 week, the sites treated with StellaLife resembled the other sites at 1 month (those treated with Peridex, PRGF, PerioSciences, PRP, or Emdogain).
- Less pain was associated with the sites treated with StellaLife.
- Fewer problems were reported for the sites treated with StellaLife.
- The pain level (rated as 5 or less the first day followed by less than 3 the consecutive days) was lower than anticipated (7 on a scale of 1 to 10).

StellaLife was initially developed to limit the need for narcotic drugs during healing and thereby battle the growing problem of narcotic dependence and addiction in the United States. In a study of 150 patients, all patients unanimously reported having fewer problems and recovering more quickly while utilizing StellaLife's VEGA system compared to other products and therefore required fewer narcotic pain medications.

Conclusion

While implants have been highly researched over the years, it remains equally important to better understand how loading and implant bed preparation affect BLCs and osteocyte viability and signaling both at early and late time points. Furthermore, the effects of systemic levels of cholesterol, fatty acids, and vitamin D are important factors that may affect implant survival. In addition, the prominent role of immune cells (eg, OsteoMacs and MNGCs) on bone formation, bone remodeling, and implant osseointegration and maintenance must be researched further to discover how immune cells can be controlled to favor long-term stability and prevent peri-implant disease. Future research investigating these various topics is ongoing.

FIG 1-5 StellaLife Recovery Kit used both before and after implant surgery.

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2

VITAMIN D DEFICIENCY AND EARLY IMPLANT FAILURE

RICHARD J. MIRON

SUMMARY

Dental implants are generally considered a very safe and highly predictable surgical procedure, yet each year a number of implants placed into adequate bone volume are lost within the first 8 weeks of healing. This chapter describes how nutritional deficiencies, namely that of vitamin D, are partly to blame. Vitamin D deficiency is one of the most prominent and known deficiencies in modern industrialized societies. Vitamin D is a fat-soluble vitamin critical for proper immune function as well as bone homeostasis. Recent dental implant studies have demonstrated that while smoking and generalized periodontitis are associated with a 50% to 200% increase in dental implant failure, vitamin D deficiency is associated with up to a 300% increase in early implant failure. These shocking findings further highlight the fact that systemic health, including adequate vitamin and mineral intake, play a critical role in biomaterial/dental implant integration.

This chapter briefly presents recent research on the prominent links between vitamin deficiencies (particularly vitamin D) and early implant failure. Thereafter, a quick and easy in-office testing kit for vitamin D is presented that uses a simple finger prick, similar to glucose testing. Finally, supplementation guidelines and recommendations from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) are presented for deficient patients with the aim of minimizing early implant failure potentially caused by vitamin/mineral deficiencies.

OBJECTIVES

- Understand the important epidemiologic studies linking higher immune-related disorders among the US population and dental implant failure rates
- Learn how a lack of general health and increased use of medications may alter proper immune cell health
- Discover how vitamin D deficiency in the US population affects bone metabolism
- Understand the links between vitamin D deficiency and early implant failure
- Learn how to test vitamin D levels in the office in 15 minutes
- Understand proper supplementation guidelines for before and after implant placement

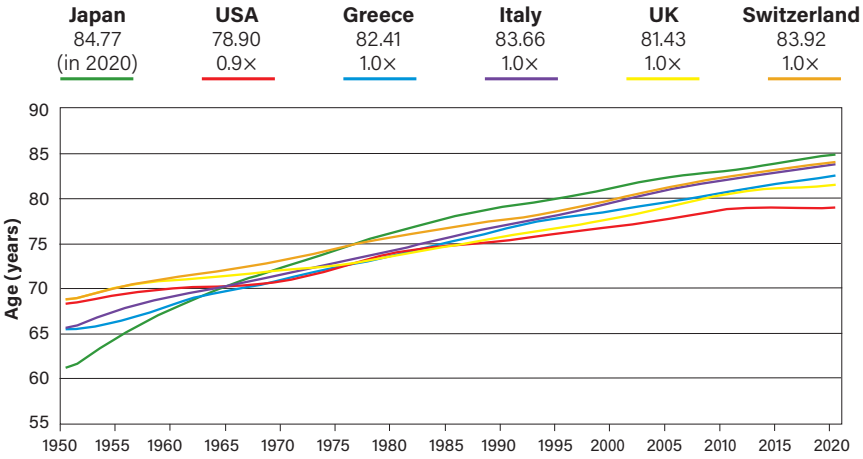

FIG 2-1 Life expectancy in the United States versus other industrialized countries. Since 2014, life expectancy has leveled in the United States and even seen a slight dip, whereas it has continued to trend upward in almost all other comparable countries.

Vitamin D deficiency is a worldwide public health problem that spans all age groups from children to adults. As we age, our ability to absorb vitamin D naturally decreases, and very few foods naturally contain sufficient doses. Of course we have a wonderful source of vitamin D available to us—the sun—but with most of the population working indoors, the majority of people in industrialized nations do not receive enough sunlight daily to maintain sufficient levels of vitamin D. As a result, epidemiologic studies report that roughly 70% of society worldwide is deficient.[1]

Vitamin D deficiency is most known for its association with osteoporotic and postmenopausal women. Few realize, however, its drastic and substantial role in various other diseases. These include depression, dementia, Alzheimer's disease, asthma, cancer, cardiovascular disease, and diabetes, among others highlighted throughout this book. Vitamin D is essential for gastrointestinal calcium absorption, mineralization of osteoid tissue, and maintenance of serum ionized calcium level. It is also important for other physiologic functions, such as muscle strength, neuromuscular coordination, and hormone release.[2] More recently, vitamin D deficiency has also been associated with up to a 300% increase in dental implant failure, and more associations with other dental-related complications are being discovered as well.[3–12] Optimizing levels prior to surgery therefore becomes fundamental for maximizing wound healing. This chapter discusses the association between vitamin D deficiency and dental implant–related failures and bone grafting complications.

Understanding Foreign Body Reactions and Health

Importance of the immune system

Many years ago, scientists believed that it was bone cells (osteoblasts and osteoclasts) that would interact with a dental implant and, following an integration period, lay down new bone matrix for a happy coexistence of the implant within the body. However, modern research has shown that it is not bone cells that interact with this newly introduced biomaterial but in fact immune cells that gather around it. It is the immune system that dictates whether the biomaterial will be accepted and integrate within the body or be rejected altogether. It is the immune system that is ultimately responsible for the integration of any foreign substance.[13] Therefore, when an individual has problems relating to the immune system, dental implant complications (ie, failure to integrate) may occur. That is why it is so vital that a healthy immune system is maintained.

Poor health in the United States

Despite boasting some of the best medical institutions, hospitals, and universities in the world, the United States has one of the sickest populations in the world. Americans take the most medication per capita, and their average life expectancy is much lower than the populations of comparable industrialized nations (Fig 2-1). Over the past 70 years, life expectancy has consistently risen globally in industrialized

countries, as health care and our understanding of science and medicine has improved. However, in 2014, the life expectancy for the United States population leveled and even dipped slightly, and it has not recovered or increased since, while all other comparable countries continued their upward trend. Evidence shows that this decline in US life expectancy is directly linked to the declining nutrition we eat and the unhealthy lifestyle we live here in the United States, both of which impact our immune systems and their ability to fight disease. Even US children have seen an alarming rise in immune-related disorders; child allergies have increased over tenfold in the last 50 years.[14,15]

This reality of poor immune health in the United States is important to consider because practicing dentists are placing biomaterials into more and more patients with compromised immune systems, which means greater risk of early implant failure and biomaterial-related complications.

Vitamin D deficiency is one of the most concerning issues in terms of immune health. Vitamin D is a powerful immunomodulator, and without it the immune system does not function as efficiently, thus making patients more susceptible to immune-related problems including allergies and compromised biomaterial integration. With adults and children spending more time than ever before indoors, the rate of vitamin D deficiency among the global population has almost doubled in the past decade alone.[16] This means that clinicians are placing implants into less healthy patients, and, despite recent improvements in biomaterial compatibility, osseointegration outcomes will be affected, thereby affecting implant failure rates as well.

Understanding Vitamin D and Its Optimal Levels

A reliable marker of vitamin D status is serum 25-hydroxy vitamin D (25-OHD), and a level below 20 ng/mL defines deficiency. Levels above 30 ng/mL are required to maximize the bone health and nonskeletal benefits of vitamin D (Table 2-1). For individuals undergoing any type of dental-related procedures, levels between 40 and 60 ng/mL are generally recommended, because levels may decrease significantly following a period of physical stress (eg, a dental surgical intervention).

Unfortunately, foods do not contain sufficient concentrations of vitamin D to maintain appropriate levels for immune health. Even the foods with the most vitamin D—cod liver oil (400–1,000 IU/teaspoon), fresh caught salmon (600–1,000 IU/3.5 oz vitamin D3), tuna (236 IU/3.5 oz vitamin D3), egg yolk (20 IU/yolk vitamin D3 or D2), and fortified milk, cheese, or yogurt (100 IU/3 oz, usually vitamin D3)—contain relatively low concentrations of vitamin D, considering

TABLE 2-1 Vitamin D concentrations in humans from deficient to toxic

Status	Serum 25-OHD	Vitamin D concentration
Severe deficiency	< 10 ng/mL	< 25 nmol/L
Deficiency	< 20 ng/mL	< 50 nmol/L
Insufficiency	21–29 ng/mL	50–74 nmol/L
Sufficiency	30–100 ng/mL	75–250 nmol/L
Optimal	30–60 ng/mL	75–150 nmol/L
Presurgery	40–60 ng/mL	100–150 nmol/L
Toxic	> 150 ng/mL	> 375 nmol/L

deficiency should be treated with 5,000 to 10,000 IU/day for a 4- to 12-week period to restore vitamin D sufficiency.

According to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) guidelines, it is recommended that supplementation maintain levels above 30 ng/mL.[17] The Endocrine Society in the USA recommends achieving a concentration of more than 30 ng/mL (> 75 nmol/L) of 25-OHD. The Endocrine Society also advocates an intake of 1,500 to 2,000 IU/day (37.5–50 µg) in all adults, and obese patients (BMI > 30) should take as much as three times that.[17]

Dental-Related Complications Associated with Vitamin D Deficiency

In addition to supporting the immune system and biomaterial integration, vitamin D decreases general oxidative stress and minimizes additional inflammation caused by surgery. Therefore, vitamin D deficiency can lead to various complications in the dental field.

In 2009, a study investigated the role of vitamin D on dental implant osseointegration in rats.[9] In this study, implants were placed in both normal control and vitamin D–deficient animals and subjected to push-out tests as well as histologic analysis. The push-out tests revealed an approximate 66% decrease in value in the vitamin D–deficient group as well as significantly lower bone-to-implant contact (BIC) in the vitamin D–deficient group as early as 14 days after implant placement. It was concluded that the effect of vitamin D deficiency is actually quite profound. Future clinical research was recommended to benefit patient care by further evaluating the link between vitamin D deficiency and the potential for early or late implant failure.

TABLE 2-2 Number of patients, early failures, and failure rates within groups

	Number of patients	Number of early failures	Failure rate (%)
Overall	885	35	3.9
Sex			
Males	455	18	3.9
Females	430	17	3.9
Age at surgery			
< 40 years	100	5	5.0
40–60 years	412	15	3.6
> 60 years	373	15	4.0
Smoking habit			
Heavy smokers (> 15 cigarettes/day)	98	6	6.1
Light smokers (1–15 cigarettes/day)	184	8	4.3
Nonsmokers	603	21	3.4
History of periodontal disease			
Generalized periodontitis	97	6	6.1
Localized periodontitis	218	10	4.5
No periodontitis	570	19	3.3
Vitamin D serum levels			
< 10 ng/mL	27	3	11.1
10–30 ng/mL	448	20	4.4
> 30 ng/mL	410	12	2.9

Following years of preclinical studies demonstrating the marked impact of vitamin D deficiency on osseointegration, clinical studies began linking vitamin D deficiency with implant failure in 2014, beginning with case reports. Bryce and MacBeth reported that vitamin D deficiency was suspected as a causative factor in the failure of immediate implants and advised assessment of vitamin D levels prior to implant surgery, especially in patients having undergone either long-term hospital care or a recent traumatic injury/event.[4] Choukroun et al also noted that vitamin D deficiency was associated as a risk factor in bone grafting procedures.[5]

In 2016, Fretwurst et al reported that a number of implants required removal or were lost for unexplained reasons in a dental university clinic.[6] These patients were then sent for various blood analyses to investigate a potential cause. It was found in each case report that extremely low serum vitamin D levels (< 20 µg/L) were reported in all cases. This study group described that after a 6-month period of healing and adequate vitamin D supplementation (> 46 µg/L), implants were successfully osseointegrated in all cases.[6] It was recommended that future randomized clinical trials be conducted to investigate the relationship between vitamin D deficiency and implant failure, osteoimmunology, and early implant complications.[6]

In 2017, Insua et al wrote an extensive review article on the concept of peri-implant disease being driven by osteoimmunology, osteal macrophages, and their related breakdown and maintenance.[8] An entire section was dedicated to vitamin D deficiency and its correlation with lower BIC and potential complications and peri-implant bone loss over time. Furthermore, the immune system was also discussed during homeostasis of peri-implant tissue/osseointegration.[8]

In 2018, Mangano et al published a retrospective study investigating over 1,700 implants in 885 patients.[7] The results are shown in Table 2-2. To date, this represents the largest study on the association between vitamin D deficiency and dental implant failure; in it, known complications such as smoking and generalized periodontitis were compared with vitamin D deficiency in terms of their implant failure rates. It was reported that both heavy smoking (defined as 15 cigarettes per day) and generalized periodontitis were associated with approximately a 50% increase in early implant failure compared to controls. Severe vitamin D deficiency (defined as serum levels < 10 ng/mL), on the other hand, was reported to be associated with nearly a 300% increase in overall implant failure compared to controls.[7] The conclusions from this study demonstrate the need for adequate testing, prevention, and supplementation both prior to dental implant placement and for maintenance.[7]

Testing Vitamin D Levels

Standard vitamin D tests are routinely performed by measuring serum vitamin D levels in whole blood serum; this provides an adequate analysis of blood vitamin D levels. However, an issue arises in the dental practice, where patients and dentists seek convenient and fast screening methods. To address this need, NanoSpeed developed a novel vitamin D test kit (Test4D) that is based on a simple finger prick test and only takes 10 minutes to get results (Fig 2-2). The technology utilizes the principle of a competitive immunoassay. The assay is based on the competition for 25-OHD present in the blood/serum sample and vitamin D present on the test line for a fixed number of antibody-gold conjugate. Depending on the concentration

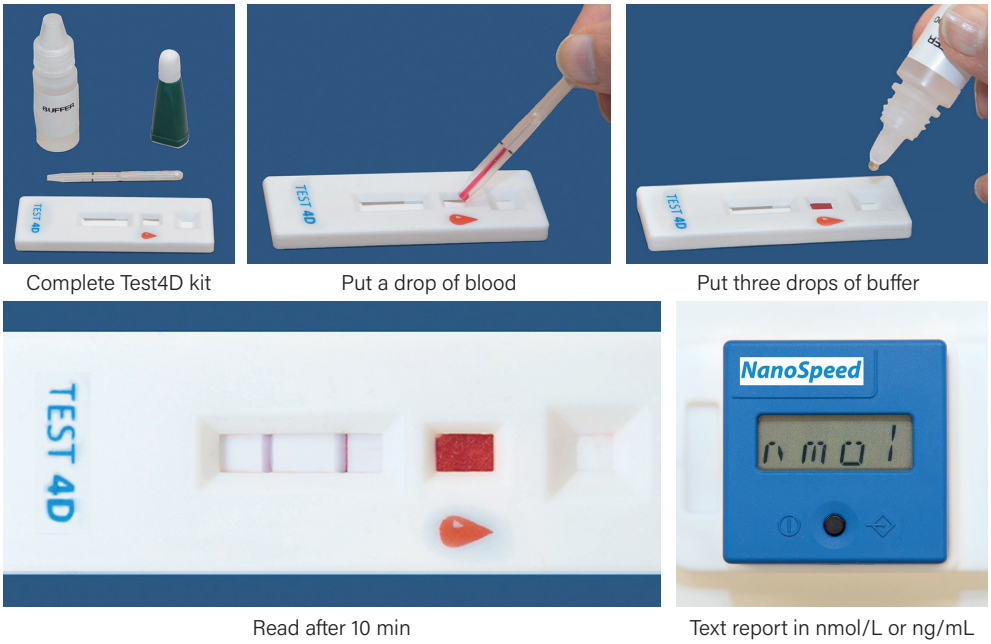

FIG 2-2 Step-by-step instructions for utilizing the 10-minute vitamin D detection system (Test4D) for in-office use.

of vitamin D in the blood/serum, there will be a varying number of free antibody-gold conjugate molecules that will bind to the vitamin D on the test strip, showing a colored line in the test line zone.

During the specimen preparation, a blood sample (10 µL) is collected from a finger prick and placed on the assay (*red mark* in Fig 2-2). Three full drops of the chase buffer are added into the square buffer well of the cassette, and within 10 minutes, the vitamin D measurement may be obtained.

With this easy-to-use and convenient technology, it becomes possible to assess vitamin D levels prior to dental implant placement or bone grafting surgery to determine whether supplementation is needed to minimize implant/graft failure. When patients are deficient, supplementation is recommended as highlighted in the next section.

Supplemental Recovery Program: The Science Behind Dental Healing

Ideally, all patients should achieve optimal levels of vitamin D and important co-factors prior to dental surgery. Bone-related support includes vitamin K, magnesium, calcium, manganese, and boron, among others. To support this goal, DentaMedica has formulated a 6-week supplementation program specifically designed to boost levels (10,000 IU/day) for the 4 weeks prior to surgery and 2 weeks of maintenance postsurgery (Fig 2-3). For patients over 65 years of age, patients with diabetes, patients who smoke, patients with reported immunocompromise, or patients taking corticosteroids, a 12-week program is recommended (8 weeks prior to surgery and 4 weeks postsurgery). The DentaMedica supplements are taken both in the morning and in the evening, and patients stop all other forms of supplementation during their use.

FIG 2-3 DentaMedica's 6-week recovery program is aimed at optimizing vitamin D and antioxidant levels prior to implant placement.

Antioxidants and Their Role in Wound Healing

Antioxidants in the diet have some remarkable benefits and valuable properties that play an irreplaceable role in the maintenance of periodontal health, bone physiology, and soft tissue wound healing. Antioxidants are molecules that

BOX 2-1 Overall vitamin deficiency in the US population

Vitamin A = 34% deficient	Vitamin E = 60% deficient
Vitamin C = 25% deficient	Calcium = 38% deficient
Vitamin D = 70% deficient	Magnesium = 45% deficient

help to prevent tissue damage caused by reactive oxygen species (ROS). Growing evidence suggests that ROS are crucial regulators of several phases of wound healing. In recent years, ROS have gained attention because of their central role in the progression of many inflammatory diseases.[18] Excessive production of ROS or impaired ROS detoxification causes oxidative damage, which has been shown to be a main cause of nonhealing chronic wounds and tissue degeneration.[19,20]

In simple terms, ROS are oxygen-free radicals and other nonradical oxygen derivatives involved in tissue degradation.[21] They are produced during normal cellular metabolism by cells in most tissues. To combat oxidative stress, all cells in the body are equipped with an intrinsic store of antioxidants, which prevent tissue damage.[22] However, when this balance is shifted and there are not enough antioxidants to match the high levels and activity of ROS, DNA damage, protein damage, and lipid peroxidation can occur. This in turn leads to impaired wound healing and long-term chronic degenerative disease as well as whole body tissue inflammation, all of which have been linked with common diseases such as dementia and various cancers.

The problem is that much of the US population has insufficient antioxidant levels. In fact, epidemiologic studies from the United States have demonstrated that vitamin deficiencies range dramatically among the population (Box 2-1). Absorption of vitamins and minerals is negatively affected by poor diet, aging, immunosuppressive drugs, chemotherapy or radiotherapy, and diseases like diabetes. Furthermore, alcohol consumption,[23] smoking,[24] and hypertension[25] are all associated with higher rates of vitamin deficiencies and/or oxidative stress as well as oral health diseases like periodontitis. As such, supplementation with low–molecular weight antioxidants and ROS-detoxifying enzymes has become vital for many individuals with deficiencies.[26]

There are two categories of antioxidants: (*1*) enzymatic antioxidants such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase/reductase, DNA repair enzymes, and various metal ion sequestrators; and (*2*) scavenging antioxidants or chain-breaking antioxidants such as ascorbic acid (vitamin C), carotenoids (including retinol-vitamin A), uric acid, α-tocopherol (vitamin E), coenzyme Q, and polyphenols (flavonoids). All are potent antioxidants commonly associated with improved wound healing.

In an effort toward the maintenance of optimal levels of the aforementioned antioxidants (as well as the overall desire for patients to improve general health), additional supplementation with vitamins and minerals to treat nutritional deficiencies have become routine in modern culture. Nevertheless, prior to implant placement, the treating clinician should factor into account that a large percentage of the population remains deficient in many important vitamins and minerals and that all patients would benefit from high-quality dosing prior to implant placement with vitamins made under GMP standards (good medical practice).

Necessary Vitamins and Minerals for Healing and Recovery

Vitamin D

Vitamin D is an extremely important vitamin for bone metabolism and is well known for its role in calcium homeostasis. It also acts as a powerful antioxidant with anti-inflammatory activity because it acts directly on immune cell cytokine expression.[27] As explained throughout this chapter, vitamin D deficiency is by far the most prevalent and severe deficiency in the modern population, and supplementation is always required.

Vitamin C

Vitamin C plays a significant role in periodontal health and maintenance. Vitamin C is a potent antioxidant; its primary function is as a radical scavenger, and it is required for the synthesis of collagen hydroxylation in humans.[28] It also contributes to immune defense by supporting various cellular functions of both the innate and adaptive immune system. Vitamin C supports epithelial barrier function against pathogens and promotes the oxidant scavenging activity of the soft tissues, thereby potentially protecting against environmental oxidative stress by ultimately killing the microbia. Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. Furthermore, infections significantly impact vitamin C levels due to enhanced inflammation and metabolic requirements.[29]

Vitamin C is rapidly depleted and oxidized within the extracellular fluids during oxidative stress.[30] It is especially important for bone-forming osteoblasts to lay new bone matrix. Sources of vitamin C include natural fruits and vegetables such as gooseberry, broccoli, kiwi, grapefruits, citrus fruits, cauliflower, strawberries, pineapple, cherries, and potatoes. It is recommended to eat high levels prior to dental surgery.

Flavonoids

Flavonoids are polyphenolic compounds found in plants known to contain potent antioxidant, anti-inflammatory, anti-allergic, antiplatelet, and antitumor activities.[31] They also have a positive effect against diverse diseases such as cancer, neurodegenerative diseases, and cardiovascular disease.[32] A potent synergistic relationship exists between flavonoids and vitamin C; together they make a powerful antioxidant combination.[33] Flavonoids also help to protect blood vessels from rupture or leakage. A popular source of flavonoids is green tea. Other sources include parsley, onions, blueberries and other berries, bananas, citrus fruits, Ginkgo biloba, red wine, sea buckthorns, and dark chocolate (with a cocoa content of > 70%).

B vitamins

Vitamin B1 (also called *thiamin*) and vitamin B2 (also called *riboflavin*) are both vitamins that help convert food into energy. Vitamin B1 is a hydrosoluble vitamin that plays a role in several biologic processes, particularly glucose metabolism.[34] Vitamin B2 helps maintain eyesight.

Vitamin B12 helps regulate the nervous system and plays a role in growth and red blood cell formation. It is found primarily in meat and dairy products. Vitamin B6 (also called *pyridoxine*) helps the body fight infections. It is primarily found in chickpeas, tuna, salmon, whole grains and cereals, beef liver, ground beef, and chicken breast.

Biotin is a water-soluble vitamin that's a part of the vitamin B family that also helps convert certain nutrients into energy. It plays an important role in the health of your hair, skin, and nails.

Carotenoids

Carotenoids are a set of naturally colored pigments. Vitamin A is one of the major carotenoids. Carotenoids are antioxidant in nature and have protective effects on vitamins C and E. They also show synergistic effects by scavenging reactive nitrogen species. Beta-carotene is the main source of vitamin A in the diet. Carotenoids have a significant influence on other antioxidants, and hence they are considered vital in antioxidant defense mechanisms. Sources include tomatoes, apricots, guavas, watermelons, papayas, and pink grapefruits.

Magnesium

Magnesium is a cofactor in more than 300 enzyme systems that regulate diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation.[35,36] Magnesium is also required for energy production, oxidative phosphorylation, and glycolysis. It contributes to the structural development of bone and is required for the synthesis of DNA, RNA, and the antioxidant glutathione. Magnesium also plays a role in the active transport of calcium and potassium ions across cell membranes. It is mostly consumed in nuts, almonds, cashews, peanuts, and spinach.[36]

Zinc

Zinc is an essential trace element (micronutrient) that plays important roles in human physiology. Zinc is a cofactor for many metalloenzymes required for cell membrane repair, cell proliferation, growth, and immune system function. The pathologic effects of zinc deficiency include the occurrence of skin lesions, growth retardation, impaired immune function, and compromised would healing.[37]

Manganese

Manganese is predominantly stored in the bones, liver, kidney, and pancreas and provides a role in the formation of connective tissue, bones, blood-clotting factors, and sex hormones. It assists in fat and carbohydrate metabolism, calcium absorption, and blood sugar regulation.

Selenium

Selenium is yet another powerful antioxidant that fights oxidative stress and helps defend the body from chronic diseases.

In addition to the aforementioned antioxidants, there are a number of other micronutrients and macronutrients that may play a significant role in periodontal health and disease prevention. All recovery programs should provide antioxidants as their major beneficial component in the prevention of disease and implemented wound healing.

Case Report of Implant Failure as a Suspected Result of Vitamin D Deficiency

Dental implants are routinely placed with long-term success rates above 90% to 95%.[38–41] Yet a small percentage of implants are lost each year with unexplained findings. This section presents such a case where vitamin D deficiency was the suspected culprit for the failure.

A 73-year-old man presented with sufficient alveolar ridge width for implant placement in the posterior mandible (Fig 2-4a). The patient was not on any medication and was considered healthy. Following midcrestal flap elevation, a bone reduction was performed to allow adequate

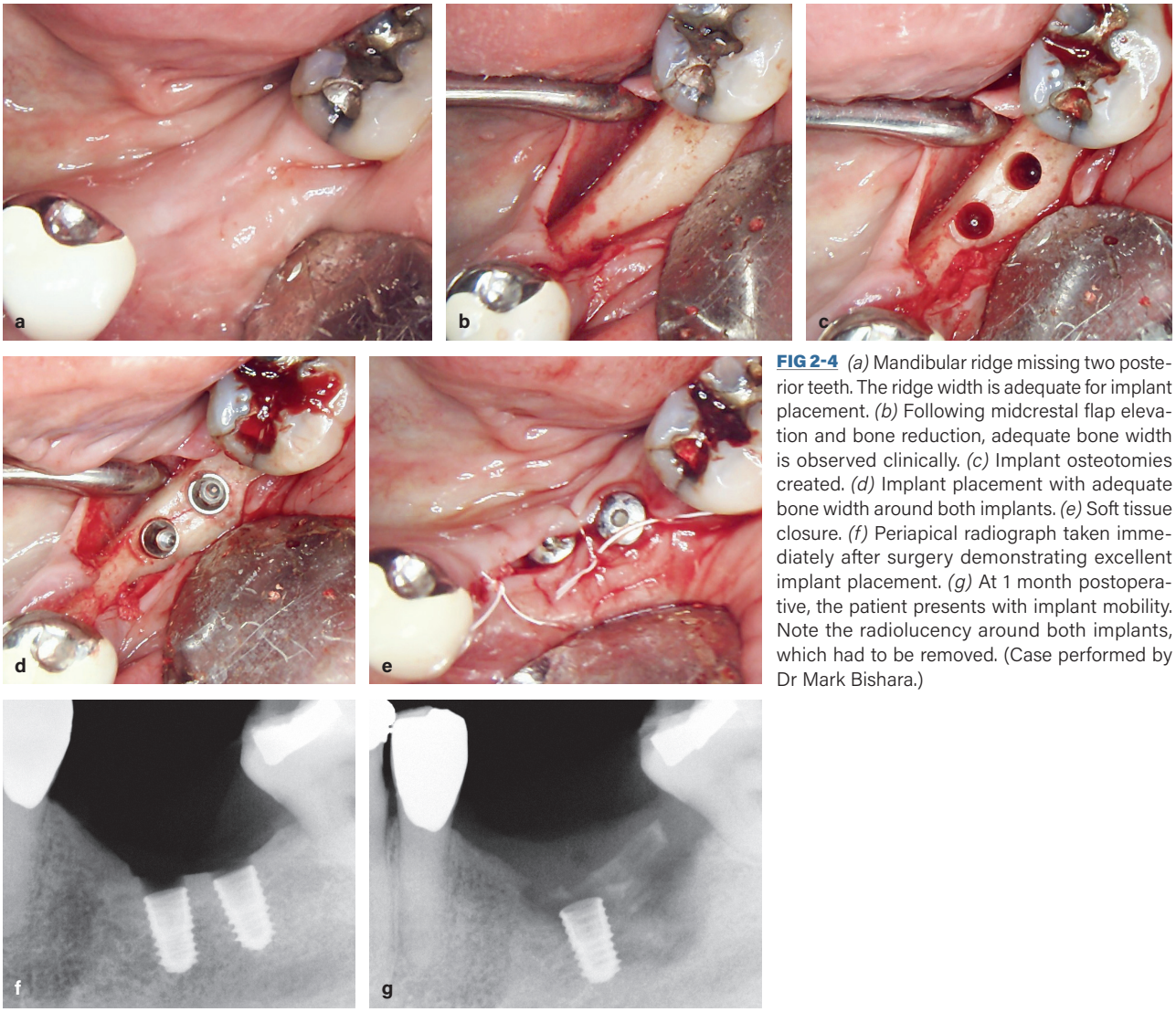

FIG 2-4 *(a)* Mandibular ridge missing two posterior teeth. The ridge width is adequate for implant placement. *(b)* Following midcrestal flap elevation and bone reduction, adequate bone width is observed clinically. *(c)* Implant osteotomies created. *(d)* Implant placement with adequate bone width around both implants. *(e)* Soft tissue closure. *(f)* Periapical radiograph taken immediately after surgery demonstrating excellent implant placement. *(g)* At 1 month postoperative, the patient presents with implant mobility. Note the radiolucency around both implants, which had to be removed. (Case performed by Dr Mark Bishara.)

width for implant placement with 1 to 2 mm of remaining width on the buccal and lingual (Fig 2-4b). Note the excellent ridge width. Figure 2-4c demonstrates the implant osteotomies leaving adequate bone width on either side. Following implant placement at torque values of 40 Ncm (Fig 2-4d), soft tissue closure was obtained (Fig 2-4e), and the patient was advised to maintain hygiene and perform saltwater rinses after meals. A periapical radiograph was taken immediately after implant placement and demonstrates adequate bone levels (Fig 2-4f).

At the 2-week recall, suture removal was performed, and the patient was advised to be seen 1 month later. At the 1-month postoperative recall, clinical mobility of the implants was observed, and periapical radiography revealed severe bone loss around the implants (Fig 2-4g). The implants had to be removed.

The patient was sent for medical analysis to determine why the implants failed. Upon testing of a full blood workup, the main finding was the patient's low vitamin D levels in the deficient range. The patient was then supplemented with a 12-week recovery program with DentaMedica, and subsequent implant placement was successful.

This case represents a typical scenario whereby simple osseointegration is expected in a relatively straightforward case yet unexplained early failure occurs. Once the vitamin levels are recovered and optimized to promote local healing, however, implant placement is successful.

Patient Testing and Supplementation

As explained earlier in this chapter, vitamin D testing is recommended prior to any bone grafting or implant placement procedures. This has been made easy with the NanoSpeed Test4D, which uses a simple finger prick to get the blood necessary for testing (see Fig 2-2). Upon discovery of low vitamin D levels, patients can be supplemented with the DentaMedica recovery program to achieve adequate levels prior to surgery. After the initial regimen, patients may elect to remain on DentaMedica, taking half doses throughout the remaining course of their implant therapy and maintenance programs.

In a 2021 study by Paz et al, the effects of DentaMedica were investigated in a case series from routine dental practice.[42] The aim of the study was twofold: (*1*) to assess three different methods of evaluating vitamin D, including two finger prick tests and standard routine blood labs; and (*2*) to evaluate the effects of a 6-week course of DentaMedica supplementation on vitamin D levels.

The first important finding was that 65% of the population had an initial vitamin D deficiency (below 30 ng/mL). Secondly, no differences in vitamin D levels (±5 ng/mL) were found between either of the finger prick tests (Rapid D, Vit4D) when compared to standard blood tests, confirming the accuracy of the in-office devices. And finally, after supplementation with DentaMedica, vitamin D levels increased from an average of 24.76 ng/mL to 50.11 ng/mL. Every participant enrolled in the study achieved significantly higher vitamin D scores within a 6-week period, reaching sufficient levels for implant placement. And every implant placed in the study after supplementation osseointegrated successfully. Larger clinical trials are needed in the future to further evaluate the long-term success of implants in patients with and without optimized vitamin D levels.

Conclusion

Vitamin D deficiency remains one of the most prevalent vitamin deficiencies in modern populations, and a direct link has been reported between vitamin D levels and bone tissue homeostasis and remodeling in the literature. Vitamin D is one of the body's most powerful immunomodulators as well, and as such it directly affects the body's ability to accept or reject foreign biomaterials. Recent studies have demonstrated an early implant failure rate nearly 300% higher for implants placed in patients with vitamin D deficiency compared to patients with adequate levels of vitamin D, which is why testing and supplementation are recommended prior to any surgical intervention.

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