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VITAMIN D DEFICIENCY AND EARLY IMPLANT FAILURE

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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 American 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

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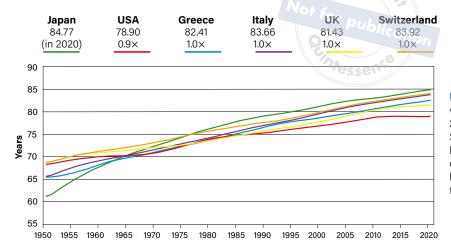


FIG 2-1 Life expectancy in the United States versus other industrialized countries. Since 2014, life expectancy has leveled in the United States and even seen a slight dip, whereas it has continued to trend upward in almost all other comparable countries. In some countries like Japan, life expectancy is 10 years higher than in the United States.

itamin 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 is deficient. [AU: Is this worldwide or only among industrialized nations?]

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. 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. In Japan, the life expectancy is almost 10 years higher! 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 population [AU: US or worlding has almost doubled in the past decade alone. The eans that clinicians are placing implants into less healthy patients and, despite recent improvements in biomaterial compatibility, osseointegration outcomes will be affected and more implant failures should be expected. [AU: Edits ok?]

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

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

Status	Serum 25 OH	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	

low concentrations of vitamin D, considering 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 three times that.¹⁷[AU: Correct?]

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. 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 (BIC) contact 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.

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

<u> </u>				
	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. These patients were then sent for various blood analysis to investigate a potential cause. It was found in each case report that extremely low serum vitamin D levels (< 20 μ g/L) were reported in all cases. This study group described that after a 6-month period of healing and adequate vitamin D supplementation (> 46 μ g/L), implants were successfully osseointegrated in all cases. 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.

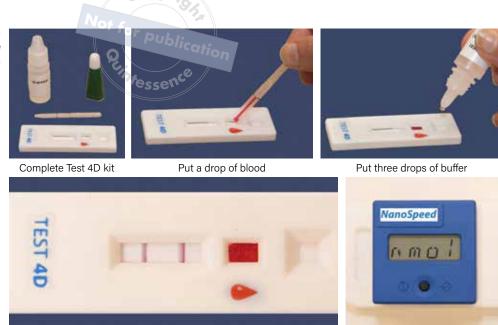
In 2017, Insua et al wrote an extensive review article on the concept of peri-implant disease being driven by osteo-immunology, osteal macrophages, and their related breakdown and maintenance.⁸ An entire section was dedicated to vitamin D deficiency and its correlation with lower BIC and potential complications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

In 2019, Mangano et al published a retrospective study investigating over 1700 implants in 885 patients. 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. 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 (Test 4D) 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 (Test 4D) for in-office use.



Read after 10 min

Text report in nmol/L or ng/mL

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 $\mu L)$ 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 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/

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



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.

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 general US population

Vitamin A = 34% deficient Vitamin C = 25% deficient Vitamin D = 70% deficient Vitamin E = 60% deficient Calcium = 38% 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. 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. 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. 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. [AU: Ok as edited? Original was confusing.]

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. [AU: All or just the scavenging antiquidants?]

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.

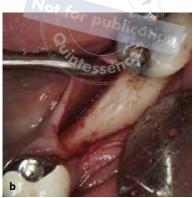
Case Report of Implant Failure as a Suspected Result of Vitamin D Deficiency

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.

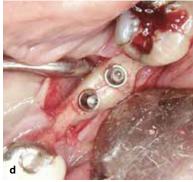
A 73-year-old man presented with sufficient alveolar ridge width for implant placement in the posterior mandible (Fig 2-4a). The patient was not on any medication and was considered healthy. Following midcrestal flap elevation, a bone reduction was performed to allow adequate width



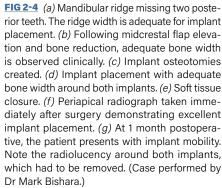


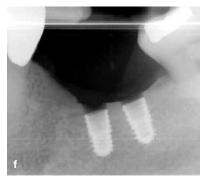














for implant placement with 1 to 2 mm of remaining width on the buccal and lingual (Fig 2-4b). Note the excellent ridge width. Figure 2-4c demonstrates the implant osteotomies leaving adequate bone width on either side. Following implant placement at torque values of 40 Ncm (Fig 2-4d), soft tissue closure 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 References

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 Test 4D, 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 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.

Woo YS, Kim S, Jeong JH, Jung YE, Kim MD, Bahk WM. Vitamin D deficiency/insufficiency among inpatients with depressive symptoms. Clin Psychopharmacol Neurosci 2019;17:121–124.

- Wimalawansa SJ, Razzaque MS, Al-Daghri NM. Calcium and vitamin D in human health: Hype or real? J Steroid Biochem Mol Biol 2018:180:4–14.
- Akhavan A, Noroozi Z, Shafiei AA, Haghighat A, Jahanshahi GR, Mousavi SB. The effect of vitamin D supplementation on bone formation around titanium implants in diabetic rats. Dent Res J (Isfahan) 2012;9:582–587.
- Bryce G, MacBeth N. Vitamin D deficiency as a suspected causative factor in the failure of an immediately placed dental implant: A case report. J R Nav Med Serv 2014;100:328–332.
- Choukroun J, Khoury G, Khoury F, et al. Two neglected biologic risk factors in bone grafting and implantology: High low-density lipoprotein cholesterol and low serum vitamin D. J Oral Implantol 2014;40:110–114.
- Fretwurst T, Grunert S, Woelber JP, Nelson K, Semper-Hogg W. Vitamin D deficiency in early implant failure: Two case reports. Int J Implant Dent 2016;2:24.
- Mangano GF, Oskouei SG, Paz A, Mangano N, Mangano C. Low serum vitamin D and early dental implant failure: Is there a connection?
 A retrospective clinical study on 1740 implants placed in 885 patients.
 J Dent Res Dent Clin Dent Prospects 2018;12:174–182.
- Insua A, Monje A, Wang HL, Miron RJ. Basis of bone metabolism around dental implants during osseointegration and peri-implant bone loss. J Biomed Mater Res A 2017;105:2075–2089.
- Kelly J, Lin A, Wang CJ, Park S, Nishimura I. Vitamin D and bone physiology: Demonstration of vitamin D deficiency in an implant osseointegration rat model. J Prosthodont 2009;18:473–478.
- Liu W, Zhang S, Zhao D, et al. Vitamin D supplementation enhances the fixation of titanium implants in chronic kidney disease mice. PLoS One 2014;9:e95689.
- Mangano F, Mortellaro C, Mangano N, Mangano C. Is low serum vitamin D associated with early dental implant failure? A retrospective evaluation on 1625 implants placed in 822 patients. Mediators Inflamm 2016;2016:5319718.
- Xiong Y, Zhang Y, Guo Y, et al. 1α,25-Dihydroxyvitamin D₃ increases implant osseointegration in diabetic mice partly through FoxO1 inactivation in osteoblasts. Biochem Biophys Res Commun 2017; 494:626–633.
- Miron RJ, Bosshardt DD. OsteoMacs: Key players around bone biomaterials. Biomaterials 2016;82:1–19.
- Warren CM, Jiang J, Gupta RS. Epidemiology and burden of food allergy. Curr Allergy Asthma Rep 2020;20:1–9.
- Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011;128:e9–e17.
- Mirzakhani H, Al-Garawi A, Weiss ST, Litonjua AA. Vitamin D and the development of allergic disease: How important is it? Clin Exp Allergy 2015;45:114–125
- Pludowski P, Holick MF, Grant WB, et al. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol 2018;175:125–135.
- Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal 2014;20:1126–1167.
- Cano Sanchez M, Lancel S, Boulanger E, Neviere R. Targeting oxidative stress and mitochondrial dysfunction in the treatment of impaired wound healing: A systematic review. Antioxidants (Basel) 2018;7.
- Wei W, Liu Q, Tan Y, Liu L, Li X, Cai L. Oxidative stress, diabetes, and diabetic complications. Hemoglobin 2009;33:370–377.
- 21. Lushchak VI. Free radicals, reactive oxygen species, oxidative stress and its classification. Chem Biol Interact 2014;224:164–175.
- Sies H. Oxidative stress: Oxidants and antioxidants. Exp Physiol 1997;82:291–295.
- Park JB, Han K, Park YG, Ko Y. Association between alcohol consumption and periodontal disease: The 2008 to 2010 Korea National Health and Nutrition Examination Survey. J Periodontol 2014;85:1521–1528.



- Jang AY, Lee JK, Shin JY, Lee HY. Association between smoking and periodontal disease in Korean adults: The fifth Korea National Health and Nutrition Examination survey (2010 and 2012). Korean J Fam Med 2016;37:117–122.
- Ahn YB, Shin MS, Byun JS, Kim HD. The association of hypertension with periodontitis is highlighted in female adults: Results from the Fourth Korea National Health and Nutrition Examination Survey. J Clin Periodontol 2015;42:998–1005.
- Schafer M, Werner S. Oxidative stress in normal and impaired wound repair. Pharmacol Res 2008;58:165–171.
- Anand N, Chandrasekaran SC, Rajput NS. Vitamin D and periodontal health: Current concepts. J Indian Soc Periodontol 2013;17:302–308.
- Wilson JX. Regulation of vitamin C transport. Annu Rev Nutr 2005;25:105–125.
- 29. Carr AC, Maggini S. Vitamin C and immune function. Nutrients 2017;9.
- Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. Proc Natl Acad Sci U S A 1989;86:6377–6381.
- Vinson JA, Jang J. In vitro and in vivo lipoprotein antioxidant effect of a citrus extract and ascorbic acid on normal and hypercholesterolemic human subjects. J Med Food 2001;4:187–192.
- Faggio C, Sureda A, Morabito S, et al. Flavonoids and platelet aggreqation: A brief review. Eur J Pharmacol 2017;807:91–101.
- Tapas AR, Sakarkar DM, Kakde RB. Flavonoids as nutraceuticals: A review. Trop J Pharm Res 2008;7:1089–1099.
- 34. Polegato BF, Pereira AG, Azevedo PS, et al. Role of thiamin in health and disease. Nutr Clin Pract 2019;34:558–564.

35. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press, 1997.

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- Coates PM, Paul MC, Blackman M, et al. Encyclopedia of Dietary Supplements (Online). Boca Raton, FL: CRC Press, 2004.
- Lin PH, Sermersheim M, Li H, Lee PHU, Steinberg SM, Ma J. Zinc in Wound Healing Modulation. Nutrients 2017;10:16.
- Moraschini V, da C Poubel LA, Ferreira VF, dos SP Barboza E.
 Evaluation of survival and success rates of dental implants reported in longitudinal studies with a follow-up period of at least 10 years: A systematic review. Int J Oral Maxillofac Surg 2015;44:377–388.
- Chrcanovic BR, Albrektsson T, Wennerberg A. Smoking and dental implants: A systematic review and meta-analysis. J Dent 2015;43:487–498.
- 40. Del Fabbro M, Wallace SS, Testori T. Long-term implant survival in the grafted maxillary sinus: A systematic review. Int J Periodontics Restorative Dent 2013;33:773–783.
- Slagter KW, den Hartog L, Bakker NA, Vissink A, Meijer HJA, Raghoebar GM. Immediate placement of dental implants in the esthetic zone: A systematic review and pooled analysis. J Periodontol 2014;85:e241–e250.
- Paz A, Stanley M, Mangano FG, Miron RJ. Vitamin D deficiency and early implant failure: Outcomes from a pre-surgical supplementation program on vitamin D levels and antioxidant scores. Oral Health Prev Dent 2021;19:495–502.