Two Neglected Biologic Risk Factors in Bone Grafting and Implantology: High Low-Density Lipoprotein Cholesterol and Low Serum Vitamin D

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Following a failure of a bone graft or an implant placement, the hypothesis of a biological abnormality is rarely considered as a possible cause. A systematic search of peer-reviewed literature for dyslipidemia or vitamin D deficiency may explain this lack of consideration. Excess low-density lipoprotein cholesterol (dyslipidemia) is responsible for a slower bone metabolism or lower dental implant osseointegration. In addition, vitamin D is a key factor for linking innate and adaptive immunity. Both of these factors are compromised under the conditions of vitamin D deficiency. Therefore, vitamin D deficiency slows implant osseointegration and increases the risk of graft infection. Vitamin D is also involved in immune function and therefore allergic reactions.

Key Words: cholesterol, LDL cholesterol, vitamin D, failures, implants, bone grafts, infections, immune defense, osseointegration

INTRODUCTION

The search for a biological anomaly labeled as a risk factor before oral surgery is limited to disease states such as diabetes. However, it seems in recent years that cholesterol and vitamin D levels should be more systematically investigated. Good cholesterol (high-density lipoprotein [HDL]) and bad cholesterol (low-density lipoprotein [LDL]) need to be included in this investigation because both could have a negative effect on bone growth and osseointegration (high LDL or low HDL). Vitamin D is one the most important hormones involved in bone growth. In addition, vitamin D also plays a role in reducing the effects of inflammation and helps improve the body's natural immune reactions.

DYSLIPIDEMIA

LDL cholesterol and bone metabolism

Cholesterol is transported in the plasma predominantly as cholesteryl esters associated with lipopro-

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DOI: 10.1563/AAID-JOI-D-13-00062

teins. There are 2 types of lipoproteins: LDL (bad) and HDL (good).

In addition to cardiovascular diseases, there is evidence that high levels of cholesterol and triglycerides cause alterations in bone tissue. Krieger[1] demonstrated an increase in the number of osteoclasts, the inhibition of osteoblastic activity, and a decreased bone remodeling in hyperlipidemic rats. According to Luegmayr et al,[2] elevated levels of cholesterol may lead to an imbalance in the bone-remodeling process, a reduction of bone mass by increasing the activity, and a differentiation of osteoclasts. Furthermore, recent studies have pointed out possible links between periodontal infection and an increased risk for cardiovascular disease.[3,4]

An increase of circulating levels of oxidized LDL induces alveolar bone loss[5,6] and is associated with the severity of the local inflammatory response to bacteria as well as the susceptibility to periodontal disease in diabetic patients.[7]

Osteoblasts can bind, internalize, and then metabolize HDL3/LDL cholesterol and are capable of selectively taking up cholesteryl esters from these lipoproteins.[8] The bone releases enzymes that are involved in the oxidation of LDL. Therefore, it is possible that the oxidized LDL accumulated in the bone could induce subsequent deleterious cellular effects on bone density. Hyperlipidemia causes a reduction of bone density in vivo due to the inhibition of osteoblast differentiation by bioactive lipids.[9,10]

Indeed, the Demer group showed that oxidized LDL caused an inhibition of the alkaline phosphatase activity and also mineralization,[11] which are markers of osteoblast differentiation. In addition, it has recently been shown that oxidized LDL also induces cell death by apoptosis of osteoblastic cells.[12]

Hirasawa et al[8] confirmed that atherogenic conditions (high LDL levels) caused the death of osteoblasts.

What is the role of HDL? Various antioxidants carried by HDL may interrupt the cascade of events leading to the oxidation of LDL.[13] Another important property of HDL is its ability to inhibit cell death induced by oxidized LDL. In particular, it has been reported that HDL inhibits the apoptosis of monocytic cells by inducing cholesterol efflux and thus preventing the accumulation of cholesterol caused by the presence of oxidized LDL.[14] HDL should be considered as a bone cell protector.

Low vitamin D incidence on osseointegration and bone grafts

The most important related compound of vitamin D is vitamin D3 (cholecalciferol). Vitamin D is a steroid hormone that is acquired via diet or synthesized in the skin from cholesterol when sun (ultraviolet light) exposure is adequate. Cholesterol is converted to pre–vitamin D3 and then isomerized to vitamin D3. After binding to vitamin D–binding carrier protein, vitamin D3 is transported to the liver, where it is enzymatically hydroxylated by CYP27A1, generating 25-hydroxyvitamin D3 (calcidiol, or 25OHD3).[15]

In the bone, vitamin D stimulates the activity of osteoclasts and increases the production of extracellular matrix proteins by osteoblasts. Vitamin D also stimulates intestinal calcium absorption and inhibits the synthesis and secretion of parathyroid hormone.[16–19] Vitamin D deficiency can result from inadequate dietary intake together with the insufficient exposure to sunlight. Vitamin D deficiency in these patients is associated with a catabolic bone turnover and its main consequence, the occurrence of osteoporotic fractures.[20] Deficiency has also been linked to impaired fracture healing in clinical practice and in patients suffering a fracture.[21,22]

These results support the role of the steroid hormone in controlling bone regeneration. As osseointegration of dental implants also depends on bone regeneration, peri-implant bone formation was shown to be reduced in vitamin D–deficient rats.[23] Surprisingly, only limited preclinical data on the effect of vitamin D supplementation on bone regeneration are available.[24]

Overall, these studies suggest that vitamin D supplementation has beneficial effects on bone turnover in patients with vitamin D deficiency, which might also hold true for bone regeneration.

In a recent study, Dvorak et al[25] indicated that vitamin D deficiency has a negative impact on cortical peri-implant bone formation in ovariectomized rats, which can be compensated by a vitamin D–rich diet.

Vitamin D deficiency has been also implicated in various diseases such as diabetes, high blood pressure, cardiovascular diseases, and many cancers.[19] It has also been implicated in several allergic disorders and immune system dysregulation. Our

Table 1 Lipoprotein values*	
Cholesterol total	<2 g/L
Triglycerides	<2 g/L
LDL cholesterol	Men <1.6 g/L Women <1.5 g/L
HDL cholesterol	>0.35 g/L

*HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

understanding of vitamin D metabolism and biological effects has grown exponentially in recent years, and it has become clear that vitamin D has extensive immunomodulatory effects. It is now known that cells from the immune system contain all the characteristics needed to convert 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D during a bacterial infection.[26,27] Liu et al[28] showed that stimulation of TLR 2/1 engages a vitamin D–dependent intracellular circuit that results in the expression of antimicrobial peptides, such as defensins and cathelicidins, which enhances the microbicidal capability of the monocytes. These peptides have a broad range of actions against microorganisms, including bacteria, fungi, and viruses. It is interesting to observe that sera from African American individuals, who are known to have substantially lower serum vitamin D levels than whites, were inefficient in inducing genetic expression of cathelicidin.[27] This article published by Liu et al[28] triggered in recent years a very large scientific interest related to vitamin D, with more than 1500 articles published in 2012 and more than 2500 already in 2013. The nasal carriage in *Staphylococcus aureus* is a major risk for infections with the bacterium.[29] The vitamin D level is directly connected to this infection risk; Olsen suggests that vitamin D can improve the antibacterial immune response and thereby prevent *S aureus* colonization and carriage and subsequent disease.[30,31]

Flynn showed that vitamin D levels <20 ng/mL have a significant impact on length of stay, organ dysfunction, and infection rates.[32] Frieri and Valluri[33] showed that there was also a positive correlation with allergy subtypes and sinus infections with low vitamin D. In one of the early observational studies that pointed toward a connection between vitamin D and respiratory infections, Ginde et al[34] found an inverse relationship between serum 25(OH)D concentrations and the incidence of upper respiratory infections. Ginde et al[35] also found that vitamin D deficiency is associated with a high prevalence of severe infections in the hospital emergency department.

Vitamin D has since been studied in several clinical trials to characterize its role in respiratory infections.[36] In 2010, Sabetta et al[37] conducted a prospective cohort study showing that serum 25(OH)D concentrations of 38 ng/mL or greater were associated with a 2-fold decrease in the number of upper respiratory infections.

Serum levels

Serum level values are shown in Table 1 (lipoprotein) and Table 2 (vitamin D).

Discussion

Vitamin D also plays a predominant role in allergy. Insufficiency of vitamin D seems to be connected to the onset of atopy and food allergies.[38] The hypothesis is that vitamin D could have a central role in these pathological situations and that it may represent a novel preventive and/or therapeutic strategy. Numerous data are published on the relationship between vitamin D and asthma and allergies.[39,40] These results may indicate that the timing of the intervention of vitamin D levels may be a factor in subsequent allergic diseases. An alternative explanation is that different absolute amounts of vitamin D have alternate physiologic effects on allergic pathogenesis. Furthermore, although beyond the scope of this review, vitamin D may also affect the body's susceptibility and response to infectious organisms, a major trigger of wheezing at a young age.[39,40] In conclusion, the vitamin D serum level plays a predominant role in bone metabolism, sensibility to infections, and many allergy symptoms. We advance the hypothesis that allergic patients are often deficient in vitamin D.

The result of high LDL is a reduction of bone metabolism, inhibition of phosphatase alkaline, and

Table 2 Serum 25(OH) vitamin D levels	
Deficiency	<10 ng/mL
Insufficiency	10–30 ng/mL
Optimal	>30 ng/mL

an increase of the fat part in the bone. The result is a lower osseointegration and slower bone growth.

Branemark said in 1985, during an international meeting, "When I see a yellow bone, I cancel the transplant!" At that time, it was only a clinical observation. We now understand why. We have been focused on the high cholesterol risk in bone grafts for more than 10 years, and now we can explain why we had more failures in these cases.

Daily needs of vitamin D are 4000 IU, and the lack of sufficient vitamin D in one's diet is very common: An estimated 1 billion people worldwide are vitamin D deficient. Forty percent to 100% of US and European elderly men and women still living in the community (not in nursing homes) are deficient in vitamin D.[20] Stoker et al[41] found that about two-thirds of preoperative spinal fusion patients were vitamin D insufficient. About 50% of these insufficient patients were deficient (less than 15 ng/mL). In France, a review of patients in the Besançon hospital made by Malpica et al[42] revealed that 91% of patients were insufficient. In this insufficient population, 40% were deficient (less than 10 ng/mL). In the Suvimax French Study, the authors found 79% of patients insufficient (women patients, average 47 years old; range, 35–60 years). We can conclude that most of the population is insufficient. The medical consensus in 2012 is that "the population over the age of 65 years old has to be supplemented without any lab control."[43] Recently, Maier et al[44] asked: Is there an epidemic vitamin D deficiency in German orthopedic patients? Among preoperative orthopedic patients, Maier et al found that 85% were insufficient and 60% were deficient.

There is also clearly a close relationship between statins, cholesterol, and vitamin D. It is interesting to note that cholesterol and vitamin D have the same precursor, namely, 7-dehydrocholesterol.

We have a similarity to the clinical benefits of vitamin D in that it has been suggested that statins might somehow be analogues of vitamin D.[45] We know that statins have a beneficial effect in the reduction of infective or inflammatory episodes,[21] in a pattern similar to vitamin D. Statins increase the blood level of vitamin D as 25-hydroxyvitamin D and also the activated hormone 1,25-dihydroxyvitamin D.[46,47]

The supplementation of vitamin D in a daily diet also decreases the LDL cholesterol.[48] The link between osteoporosis and the metabolic syndrome could influence the therapeutic approach in both disorders and vitamin D. Supplementation may play an important role in prevention of these severe conditions.

Conclusion

We suggest exploring vitamin D serum level (prescription: 25OH vitamin D = D2 + D3) and LDL Cholesterol (prescription: cholesterol total + LDL + HDL cholesterol) systematically in patients who are diabetic, allergic, with hypertension, and previously in a difficult case of implants and/or bone grafting. This exploration is largely indicated in the case of a failure of bone graft or implant placement. Correcting these detected anomalies is obviously recommended. Further multicentric studies may be helpful for finding a correlation between implant facilities and vitamin D or/and cholesterol dosage.

Abbreviations

HDL: high-density lipoprotein
LDL: low-density lipoprotein
Vitamin D3: cholecalciferol

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