Hyperlipidemia Associated Oxidative Stress and Its Impact on Bone Regeneration and Dental Implant Osseointegration

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ABSTRACT

Hyperlipidemia is recently recognised as a factor that could impair bone regeneration and dental implant osseointegration. High fat diets raise oxidised lipid levels in blood, which accumulate in bone and suppress osteoblast function, tipping the balance toward bone resorption. Excess lipids also induce oxidative stress and inflammatory cytokine production in bone, further inhibiting bone formation. These changes may affect implant osseointegration. At the cellular level, high lipid levels cause overproduction of reactive oxygen species and inhibit Wnt/β-catenin signalling in osteoblasts. Health promotion strategies should address these mechanisms. Lipid lowering drugs such as statins may improve bone healing ability both by reducing blood lipids and by directly stimulating bone formation. Antioxidant nutrients or drugs may counteract lipid driven ROS and inflammation. Emerging approaches include epigenetic interventions to boost osteoblast gene expression and dampen inflammatory pathways. Improving lipid control alongside these future targeted therapies may help preserve bone health and implant success in patients with hyperlipidemia associated oxidative stress. While very exploratory, incorporating molecular level approaches into continuing clinical protocols could represent a path towards future therapies. Maximizing postoperative management is essential in order to limit the effects of hyperlipidemia induced negative microenvironment at implant sites. This could include controlling laboratory levels of lipids prior to surgery.

KEYWORDS

hyperlipidemia; oxidative stress; bone regeneration; dental implant osseointegration; osteoblast function; reactive oxygen species; inflammation

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INTRODUCTION

Hyperlipidemia is the condition where cholesterol and triglycerides elevated in circulation. Hyperlipidemia is a known risk factor for cardiovascular disease and increasing evidence suggests hyperlipidemia has important implications for skeletal biology and oral health (1). Hyperlipidemia can become dysregulated in such a way that alters lipid metabolism very quickly within the human body to the extent that it causes issues with normal bone remodeling and repair (2). The process of bone regeneration is a balance of forces between the formation of osteoblasts, and osteoclast resorption, that is mediated through a series complex mediators, including Wnt/β-catenin signalling, transcription factors Runx2 and Osterix that regulate osteoblast activity, and cytokines that control the activity of both osteoblasts, and osteoclasts (3–5). Hyperlipidemia, however, alters the balance of bone formation and resorption particularly by increasing oxidative stress and low grade chronic inflammation due to increased osteoclast activity (6). Additionally, oxidized lipid remnants alter the fate of mesenchymal derived stem cells from the (early) osteoblastic direction limit early osteogenic progenitors necessary for regenerative hypotheses towards developing more adipogenic pathways (7, 8). For the most part the consequences of an interaction between hyperlipidemia biology and implants are important.

BIOLOGY OF BONES IN HYPERLIPIDEMIC STATUS

Bone regeneration occurs, largely, through differentiation of osteoprogenitor cells to osteoblasts, regulating these processes through key transcription factors such as Runx2, Osterix (Sp7), and β-catenin in the canonical Wnt signaling cascade (9–11). Hyperlipidemia will not only affect these pathways, but also can initiate additional inflammatory cytokine release, oxidative stressors, and additional downstream effects through a variety of processes (12). One potential mechanism being explored is oxidized low-density lipoprotein (oxLDL), which in vivo inhibited Runx2 and promoted PPARγ (a transcription factor promoting adipogenesis) (13–15). These inflammatory mediators, initiated from hyperlipidemia, are inhibitory to the regeneration process by further inhibiting osteoblast differentiation through an innumerable pathway (16, 17). These cytokines downregulated osteoblastic differentiation markers, alkaline phosphatase (ALP) and osteocalcin, which were further upregulated by the osteoclastogenic stimulating cytokine RANKL's expression in stromal supporting cells, facilitating osteoclastogenesis (18, 19).

This ultimately adds up to support a net resorptive bone reaction, instead of a net deposition. The Wnt/β-catenin pathway may be the most sensitive cascade to external influences like dyslipidemia. Hyperlipidemia is related to increased expression of antagonists to Wnt, like Dkk1 and sclerostin (3). The impairment of signaling, and consequently signaling fidelity, remains exacerbated through unfavorable levels of oxidative stress due to changes in lipid metabolism. Epigenetic reprogramming is an interference with transcriptional control (12). Hyperlipidemia is associated with, but not limited to, broadly altered patterns of DNA methylation and histone acetylation in MSCs (7). In these processes, microRNA also plays important mediating roles, as miR-204 and miR-211 both use Runx2 as a target, suggesting these are potentially elevated during hyperlipidemia states, and miR-29 is diminished (this miRNA promotes osteogenesis), indicating that hyperlipidemia provides a complex narrative for regulatory pathways (13, 20). There may be therapeutic opportunities using methods to normalize or reduce oxidative stress, and/or target those specific pathways of gene expression to improve osteogenic gene expression (12). Statins may show some efficacy in increasing osteogenic BMP-2 gene expression while inducing biosynthetic osteoblastic differentiation characteristics, probably context-specific (9). Monoclonal antibodies to sclerostin may offer some support through decreasing Wnt inhibition, although again requires targeted studies and clinical relevance when hyperlipidemia exists (3, 21). Going forward, defining these mechanisms will potentially provide clearer clinical paths for linking lipid therapies to regenerative occasions and possibly better translate to improved clinical outcomes to promote bone health, repair, and regeneration.

BONE HOMEOSTASIS UNDER HYPERLIPIDEMIA

Bone homeostasis is only achieved through the concerted actions of osteoblasts and osteoclasts (5, 10, 18); imbalance can come from a variety of systemic and cellular stimuli, of which oxidative stress and inflammation, and altered osteoblast/osteoclast activity, are significant contributing factors (12, 16). The effects of oxidative stress in patients with metabolic disease can largely be attributed to the neural link with systemic stressors and the convergence of interrelated influences implicated in compromised bone health and poor quality of repair (22).

High levels of reactive oxygen species (ROS), usually produced from a metabolic state such as hyperlipidemia, can damage DNA, proteins, and lipids of the bone cells (osteoblasts and osteocytes) (23). Osteoblasts are especially sensitive to oxidative stress due to their role in bone regeneration, and show reduced proliferation, differentiation, and mineralization capabilities (24). Higher oxidative stress will lead to an increase in osteoclastogenesis and this favors bone loss due to a tipping of the balance of bone health (12, 22, 23). In all of its forms, oxidative stress is a regulator of bone remodeling (25). In addition, low-grade inflammation has been directly associated with metabolic states characterized by higher levels of lipids (26). Inflammatory cytokines can directly inhibit the properties of the osteoblasts while promoting differentiation and/or activity of the osteoclast. TNF-α can inhibit Runx2 and Osterix, both genes that have an influence on the maturation of osteoblasts and promote RANKL-mediated osteoclastic differentiation (4, 18). Likewise, signalling for IL-6 can promote bone resorption activity as well as mobilization of osteoclast precursors via activation of the JAK/STAT signaling pathway (5). These

inflammatory signals will promote bone resorption during the normal regulatory bone remodeling process and together, these may negatively influence skeletal regenerative capabilities (18).

Metabolic dysfunction, oxidative stress and inflammatory signals lead to impaired osteoblast differentiation and increased osteoclast differentiation (12). Impaired osteoblast differentiation directly affects bone formation, increased osteoclast activity will mean more bone resorption, and both of these circumstances result in disequilibrium of osteogenic health and bone health (10). The impaired osteoblast properties due to TNF and the lipid signaling have been suggested to lead to greater levels of PPARγ, a fate-determining transcription factor that promotes adipogenic fate over osteoblastic fate in mesenchymal stem cells, by significantly decreasing osteoblast progenitor availability (15, 27). These mechanisms connect with a complex intersection of oxidative stress and inflammatory signaling (Tab. 1).

Oxidative stress has been effectively linked to inflammation through ROS and by activation of NF-kB signaling in bone cells, but inflammation can also promote ROS (22).

The already elevated inflammatory cytokines of TNF-α, IL-1β, and IL-6 during and/or after surgery further compromise osteoblast differentiation and function by decreasing the level of osteogenic markers necessary for new bone formation at the implant site, like alkaline phosphatase and osteocalcin (18). Markers such as malondialdehyde and protein carbonyls indicate an increased level of reactive oxygen species (ROS) production and cellular injury (21). High levels of ROS will inhibit critical transcriptional networks such as Runx2 and β-catenin, which are necessary for osteoblast commitment and also promote adipocyte differentiation via stimulation of PPARγ, which will decrease osteogenesis (13).

HEALTH STRATEGIES

There is compelling evidence for lifestyle related hyperlipidemia exacerbating bone health so smoking cessation and decreasing the quantity of alcohol consumption should be highlighted as part of an inclusive education program for the patient (28). Weight loss, to normalize body mass index, may be also important to health status improvement in obesity related hyperlipidemia (29).

Pharmacological management of hyperlipidemia is still an important foundation in reducing cardiovascular risk and enhancing bone healing capability. Statins, widely used lipid lowering agents, may promote osteogenic differentiation by enhancing the upregulation of the bone morphogenetic protein-2 (BMP-2) actions and inhibiting osteoclastic activity in the process of implant osseointegration (30). A systematic review provides an overview of new antioxidant agents and synthetic analogues that act through targeting oxidative stress and inflammation signaling pathways (31). It highlights new opportunities for the management of oxidative stress-related diseases in the clinic. Given the often-compromised bone health profile of patients, it is necessary for clinicians to consider a patient's health status before prescribing any of these agents to enhance regional and possibly systemic outcomes for implant surgeries.

Health promotion interventions can also be targeted and creative methods aimed at normalizing profile changes in microRNA expressions (miR-29 promoted, and miR-204 and miR-211 inhibited), or normalizing aberrant epigenetic changes such as, DNA methylation and histone acetylation that influence skeletal health (20, 32, 33). These options could help define methods or protocols advancing the osteogenic capability of potential regenerative cells such as mesenchymal stem cells and possibly

Tab. 1 Effects of TNF and lipid signaling on osteoblast differentiation and mesenchymal stem cell fate.

Parameter	Measure	Notes	Citation Number(s)	Model / Source
Oxidative phosphorylation in osteoblasts	Elevated levels of Reactive Oxygen Species (ROS) are present in inflammatory tissue of peri-implantitis lesions	In inflammatory settings, ROS production is associated with local tissue breakdown and bone loss, linking oxidative stress to clinical bone pathologies	34	Human
Effect of oxidative stress on osteoblast markers	Significant reduction in alkaline phosphatase (ALP) and Runx2 in oxidative stress-exposed bone stromal cells	ROS inhibits osteoblast differentiation signaling pathways (p38 MAPK, NF-κB, ERK)	22	In Vitro
Correlation of oxidative stress marker & bone density	Malondialdehyde positively correlates with reduced bone mineral density (r=−0.45) and ultrasound speed of sound (r=−0.39)	Increased oxidative stress is associated with a shift toward bone loss	12, 22, 23	Human
Osteoblast apoptosis rate under oxidative stress	FoxO3 overexpression reduces apoptosis rate by 25%; antioxidants reduce TNF-α-induced apoptosis	ROS is associated with osteoblast apoptosis via JNK signaling	22	In Vitro
TNF-α increase & bone resorption	TNF-α levels increase ~40% in hyperlipidemic mouse models, associated with increased osteoclast activity	TNF-α promotes osteoclastogenesis via NF-κB signaling under oxidative stress	2	Animal
High glucose-induced ROS and osteoblast apoptosis	Intracellular ROS increase correlates strongly (r>0.8) with apoptosis markers in osteoblasts	Hyperglycemia-induced oxidative stress is associated with osteoblast dysfunction	27	In Vitro

improve results for hyperlipidemic patients undergoing implant therapy. While very exploratory, incorporating molecular-level approaches into continuing clinical protocols could represent a path towards future therapies.

ANIMAL STUDIES

Animal experiments have indicated that lipid excess may alter osteogenic signalling and reduce the structural integrity of regenerated bone (2). Work assessing progenitor cell fate in vivo has also shown shifts toward adipogenic commitment under lipid-driven cues (7, 8). Studies examining bone healing in hyperlipidemic models describe delayed regeneration, weaker biomechanical properties, and reduced osseointegration, although partial recovery has been noted when lipid-lowering agents were introduced (2, 30).

HUMAN STUDIES

Human studies have reported altered osteoblast behavior under inflammatory hyperlipidemic conditions, including changes in key transcriptional regulators and reduced expression of markers linked to maturation (18, 19, 27). Clinical assessment and biochemical examination of peri-implant tissues have identified increased ROS and inflammatory mediators in affected patients, which may be related to impaired healing response (34, 35). Additional evidence from cultured human osteoblasts has shown shifts in osteogenic marker expression and signaling when exposed to metabolic or oxidative stress, suggesting that hyperlipidemia could influence bone turnover dynamics (18, 19, 27).

DISCUSSION

A distinction between animal and human findings has been included, as differences in physiology could influence how each set of results informs clinical interpretation (Tab. 2). Although animal experiments provide interesting insights, their applicability to human metabolism is limited due to interspecies differences, which may also affect data consistency.

The downregulation of the Wnt/β-catenin pathway via lipid mediated antagonists, as the Wnt/β-catenin pathway is one of the main pathways involved with osteoblast activity and matrix production (3, 16). There are also accounts that refer to epigenetic features, and with crosstalk from microRNA regulation, having additional roles in how hyperlipidemia mediates progenitor cell fate and function (7). Specifically, two significant osteogenic associated transcription factors, miR-204 and miR-211, which act to inhibit osteogenesis are upregulated, whereas miR-29 that supports osteogenesis is downregulated (10, 32). This supports the complexity of metabolic regulation on regenerative potential. This class of molecular changes may represent a limitation of progenitor cells to regenerate and adapt to an implant osseointegration. Both oxidative stress and inflammatory cytokines work interactively through several of the NF-kB signal pathways, which may cause a self-reciprocating loop that promotes progressive tissue impairment with a decrease in repair abilities (12, 25). This interaction could be especially impacting the peri-implant microenvironment due to the effect of chronic inflammation and ROS buildup due to peri-implantitis and early implant failure (34, 35). Elevated inflammatory cytokines and oxidative stress are leading indicators of osseointegration compromise in hyperlipidemia (1, 2, 16, 17, 26). While reports have been made that provide a widely phrased approach to describe the negative influences from TNF-α, IL-6, and ROS in osseointegration, there is also an opportunity for research to employ potential antioxidant agents, Wnt pathway modifiers, and lipid lowering drug to facilitate improved osseointegration in dyslipidemic patients (3, 5, 18, 21, 22, 30, 35). Explaining some of the mechanisms, along with the typical downstream metabolic conditions associated with hyperlipidemia, will be critical for managing conditions and limiting the multiple problematic facets of each condition in achieving dental implant success. The possibilities of management of hyperlipidemia lie among the multitude of antioxidant modalities to mitigate ROS trauma, along with other novel pathways to therapy via inhibition of inflammatory cytokine action, which all would have the potential to yield some improvement with osteoblast viability and performance. Recent findings provide evidence showing inflammatory cytokines and oxidative stress typically occur in conjunction with one another, evidenced by their pro-inflammatory states being characterized by a poor prognosis in chronic disease processes (12, 18, 22, 25, 26, 31, 35). Inflammatory cytokines' principal duty is to affect a site of immune activity, thus rising cytokine levels are frequently described with the state of inflammation, further demonstrating alterations with cells and tissue outcomes. Overproduction of cytokines, battling with ROS, increased mitochondrial dysfunction, along with additional stimuli, all perpetuate the stress state, causing activation of nuclear factor-kappa B (NF-kB). NF-kB leads to pro-cytokine activation, promoting inflammatory processes (17, 23, 35). The whole process relies on the interactive complexities of the transcriptional involvement signatures with signaling pathways, where the epigenetic modifiers interface clearly defined fates for the mesenchymal stem cells (MSCs) toward respective gleaned fates of osteogenesis and adipogenesis.

Maximizing postoperative management is imperative to limit the effects of hyperlipidemia oxidative stress induced negative microenvironment at implant sites. This would include controlling laboratory levels of lipids as tightly as possible prior to surgery, or any presurgical outcomes anticipate that it would be feasible to administer antioxidants to the patient before the surgical procedure to dampen reactive oxygen species, and therefore, inflammatory potentials. This could take on prior details, and proactive attention to approaching surgical outcomes in optimized management of systematic control postsurgically, along with local steps to limit peri-implantitis, will support osseointegration. Providing education to patients about their systemic health challenges such as hyperlipidemia, and understanding the potential contributions or

Tab. 2 Comparison of animal and human study findings with consideration of physiological differences.

Parameter	Animal Studies	Human Studies	Citations
Scope and Focus	Studies investigate the impact of hyperlipidemia on bone regeneration and mechanics in animal models. They explore oxidative stress, lipid oxidation, inflammation, and impaired osteoblast function, including pathways like Wnt/β catenin and transcription factors (Runx2, Osterix). Animal studies highlight altered microRNA and epigenetic changes affecting osteogenesis.	Clinical and epidemiological studies report associations between serum lipid abnormalities and reduced bone mineral density, altered bone formation markers, and increased resorption markers. Observations suggest that hyperlipidemia may influence oxidative stress, inflammatory cytokines, and bone remodeling outcomes, including in dental implant patients. Evidence for microRNA or epigenetic involvement in humans remains preliminary and largely indirect.	(1–3, 7, 11–13, 20)
Oxidative Stress Role	Animal models show that hyperlipidemia-induced reactive oxygen species cause DNA, protein, and lipid damage in bone cells, impair osteoblast proliferation, and increase osteoclastogenesis, tipping the balance towards bone loss.	Hyperlipidemia is associated with elevated oxidative stress markers (malondialdehyde, protein carbonyls) and higher inflammatory cytokines (TNF-α, IL-6), which correlate with reduced osteoblast activity and altered bone remodeling markers. Direct causal links have not been established.	(12, 21–26)
Bone Metabolism Markers	Impaired canonical Wnt/β-catenin signaling and upregulated antagonists are observed. Key osteogenic transcription factors such as Runx2 are inhibited, while adipogenic factors like PPARγ are promoted. Altered miRNAs affect differentiation: i) miR-204 and miR-211 typically function as inhibitors of osteoblast differentiation, while ii) miR-29 acts as a promoter of osteogenesis.	Elevated inflammatory cytokines are associated with reduced serum markers of osteoblast function, such as alkaline phosphatase and osteocalcin. Serum bone formation and resorption markers indicate dysregulated bone turnover in people with hyperlipidemia. Most evidence derives from circulating measurements rather than direct bone tissue analyses.	(3–5, 11, 13–15, 18–20, 27)
Therapeutic Interventions	In animal studies, therapeutic interventions involve dietary modifications such as high-fat diet regulation and the use of pharmacologic agents including statins and fibrates which have demonstrated efficacy in reducing lipid levels, oxidative stress, and improving bone regeneration outcomes	Lifestyle modifications, including smoking cessation and weight loss, along with pharmacologic lipid-lowering therapies such as statins, are emphasized. Approaches, including miRNA regulation and epigenetic modulation, remain experimental and are not yet established in clinical practice.	(2, 7–9, 28–33)
Data Interpretation	Insights from animal studies illustrate how hyperlipidemia induces oxidative stress and molecular signaling alterations detrimental to bone regeneration and strength.	Findings from human studies primarily show associations rather than causation. The insights from animal studies cannot be directly extrapolated, highlighting the need for clearer clinical evidence on the effects of oxidative stress on osteoblast metabolism.	(1, 2, 6, 16, 17)

risk to the surgical outcome, and concurrent with the provision of presenting medication and oral health maintenance instructions, may lead to improved compliance to their overall recommended health prescription which may improve fidelity toward long term implant stability.

Although there is evidence that elevated oxidative stress could interfere with osteoblastic activity, the current data are largely correlative, and a direct cause-and-effect relationship in vivo has not been confirmed. The animal studies were based on experimental models, and the human findings were presented as correlations rather than direct evidence. In some quantitative studies, levels of oxidative stress markers, such as malondialdehyde and protein carbonyls in peri-implant tissues and cultured human osteoblasts, have been observed to be higher under hyperlipidemia or an inflammatory condition (18, 19, 35). Markers important for osteogenic metabolism, such as alkaline phosphatase and osteocalcin, were decreased, and mineralization was impaired, which is suggestive of a directed effect on osteoblast metabolism by reactive oxygen species (18, 19, 27). However, without controlled longitudinal studies, definitive proof of causality is lacking. Future studies using antioxidants or lipid-lowering methods might observe concordance in levels of reactive oxygen species and osteoblast activity and measure the extent of this direct relation at the biochemical level (1, 2, 30, 35).

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