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# The signaling pathway in modulating bone metabolism after dental implant in diabetes

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**Key words:** Diabetes, Osseointegration, Titanium, Wnt, ROS, Adiponectin, PPARγ, Dental transplant

**Abstract:** Diabetes Mellitus is a systematic disease with complications in multi-organs, including decreased implant osseointegration and a high failure rate of dental transplants. Accumulating evidence indicates that the signaling pathway directly impacts the process of bone metabolism and inflammatory response implicated with dental implants in diabetic patients. This review summarizes the recent advance in signaling pathways regulate osseointegration and inflammatory response in dental transplantation, aiming to identify the potential therapeutic target to reduce the dental transplant failure in diabetes patients, with emphasis on the surface characteristics of the implant, inflammatory signaling, AMPK, PPARγ, WNT, ROS, and adiponectin signaling.

## Abbreviations

**T2DM:** type 2 diabetes
**NTs:** nanotubes
**$H_2O_2$:** hydrogen peroxide
**APN:** adiponectin
**ROS:** reactive oxygen species
**ALP:** specific alkaline phosphatase
**AGE:** advanced glycation end products
**PDLSCs:** Periodontal ligament stem cells
**SLA:** acid-etched
**HA:** hydroxyapatite
**Ch-GNPs:** chitosan gold nanoparticle
**LPS:** lipopolysaccharide
**RIP3:** receptor interaction protein 3
**MLKL:** lineage kinase domain-like
**AMPK:** AMP-activated protein kinase

## Introduction

Type 2 diabetes (T2DM) is a chronic metabolic disorder featured by hyperglycemia and insulin resistance. With the increase in life expectancy and changes towards a sedentary lifestyle, the global prevalence of diabetes, particularly of T2DM, has been increased steadily over the past decade (Hasegawa *et al.*, 2008). It is predicted that by 2040, the number of diabetes patients worldwide will reach 632 million, which will be 10% of the total population (Luo *et al.*, 2015). In general, both types I and II diabetes mellitus (DM) encounter a high failure rate of dental transplants, especially with poorly controlled hyperglycemic patients. Accumulating evidence demonstrated that DM is associated with periodontitis and decreased implant osseointegration (McCracken *et al.*, 2000; Oates *et al.*, 2009; Chrcanovic *et al.*, 2016; Hashiguchi *et al.*, 2014), reflected by loss of bone mass, inhibition of bone mineralization and reduction of bone turnover (Farr *et al.*, 2014; Botero *et al.*, 2012). Therefore, elucidation of the molecular mechanism of hyperglycemia on bone metabolism will provide guidance for better clinical practice to stabilize the dental implants in diabetes patients.

## Osseointegration is Impaired in Diabetes Patients and Animal Models

Osseointegration is defined as a direct structural and functional bone to implant connection without any interposition of a connective tissue layer (Marx and Garg, 1998; Bryant and Zarb, 1998). Osseointegration is essential to the long-term stability of dental implants, and the success rate of implants in healthy individuals is very high (about 95% to 100%) (Cakarer *et al.*, 2014). For those with healthy bone metabolism, the process of osseointegration is normally initiated and maintained once the titanium implants are placed into the specific surgical loci (Fontanari *et al.*, 2014). However, diabetes patients had a higher failure rate of orthopedic implants (Le *et al.*, 2011; Moraschini *et al.*, 2016;

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Oates *et al.*, 2013; Annibali *et al.*, 2016) mainly caused by impaired bone regeneration and healing process at the titanium-bone interface (Zou *et al.*, 2012; Foretz *et al.*, 2010).

The adverse impact of DM on osseointegration of dental implants had been confirmed by a substantial number of studies; however, the molecular mechanism behind impaired bone healing in DM remains largely unknown. One study pointed out that a hyperlipidemic environment impacted the osteoblasts function during the osseous formation process, reflected by suppressed differentiation, proliferation, and bone-forming capacity of osteoblasts (Fiorellini and Nevins, 2000). Eventually, these patients suffered from a lower bone-to-implant contact ratio, which caused an increased risk of implant failure during osseointegration (Schlegel *et al.*, 2013; Annibali *et al.*, 2016). In particular, despite the normal or even high bone mineral density level, T2 DM patients displayed a surprisingly high risk of fracture and implant failure (Leslie *et al.*, 2012).

According to the epidemiological data, sex also seems to be an interference factor for the prevalence of DM. In general, men showed a slightly higher rate of DM than women, a phenomenon that is believed to be associated with variation of insulin sensitivity and regional fat distribution (Gale and Gillespie, 2001; Glosel *et al.*, 2010) Nevertheless, women tend to have different and poor prognoses. DM women normally showed a relatively higher incidence of complications, such as coronary heart disease, than men (Huxley *et al.*, 2006). Therefore, the sex difference may also impact bone turnover and thus the osseointegration in dental transplants. Menopaused women showed a much rapid bone loss and a higher prevalence of osteoporosis, which indicated that estrogen exerted a protective role against bone turnover (Compston, 2001). Such beneficial effects of estrogen may also impact the growth of bone tissue during the osseointegration process in dental transplants. Rather surprisingly, the limited studies on the impact of sex on overall implant survival rates showed marginal or even no differences between men and women (Chrcanovic *et al.*, 2016; French *et al.*, 2015). To improve health outcomes for both genders, future preclinical studies need to be conducted, which will accurately reflect the conditions of males and females.

Currently, animal studies had been generally utilized to investigate the impact of hyperglycemia on bone metabolism and osseointegration (King, 2012; Kanazawa *et al.*, 2009; Krakauer *et al.*, 1995; Shu *et al.*, 2012). Several animal models had been proved to reflect the natural disease progression of T2DM and metabolic changes in the bone tissue, particularly, bone turnover, bone mineral density, and bone micro-architecture (King *et al.*, 2016). Abnormal bone metabolism had been reported in DM rats, which showed impaired bone maturation, sparse bone trabeculae formation, as well as minimal growth of new bone compared to normal rats (Lee *et al.*, 2017).

In rats, hyperglycemia reduced bone formation, reflected by alterations of bone formation marker, such as bone-specific alkaline phosphatase (bALP osteocalcin) procollagen and type 1 N-terminal propeptide (Shu *et al.*, 2012). Meanwhile, hyperglycemia also inhibits bone resorption with elevated serum osteoprotegerin (OPG) and C-terminal telopeptide of collagen type I (Achemlal *et al.*, 2005; Knudsen *et al.*, 2003). Hyperglycemia also contributes to the overall deterioration of bone quality by interfering with the production of advanced glycation end products (AGEs) (Vashishth, 2007; Garnero *et al.*, 2006). Accumulating evidence has shown that AGE not only enhances the osteoclast-related bone resorption (Miyata *et al.*, 1997) also affects collagen structure and the subsequent organic bone matrix quality (Kume *et al.*, 2005), which results in an overall deterioration in bone quality. The detrimental effects of hyperglycemia on osteoblast function has also been confirmed in primary human osteoblasts (Kume *et al.*, 2005).

Regarding bone mass, accumulating evidence suggests that cortical bone is more profoundly affected in T2DM, characterized by increased cortical porosity, while the minimal impact was observed in the trabecular bone (Burghardt *et al.*, 2010). Such findings had also been confirmed in a diabetic tibia dental transplant rat model, which showed a similar preference for cortical bone reduction compared to trabecular bone reduction around dental implants (Hasegawa *et al.*, 2008). The reduced bone turnover rate, combined with alteration of cortical structures and organic matrix, leading to an overall deterioration of bone quality and resilience.

## Surface Characteristics Impact the Success of Dental Implants in Diabetes

The features of implant surfaces were regarded as one of the most influential factors for the success of dental implants (Ogle, 2015; Smeets *et al.*, 2016). Over the past decades, to improve both the short and long term osseointegration of titanium implants in diabetes patients, many studies have attempted to stimulate osseointegration and to stabilize implants, normally via promoting osteoblast adhesion and enhance new bone formation, by modifying the titanium alloys (Henningsen *et al.*, 2018; Smeets *et al.*, 2017; Kim *et al.*, 2008; Liu *et al.*, 2005).

Titanium and its alloys are widely used for orthopedic implants due to their unique features: high corrosion resistance, biocompatibility, and mechanical properties (Tabata *et al.*, 2019). However, implant failure, frequently caused by improper osseointegration, is a serious complication that requires repeated surgeries or even implant removal (Chrcanovic *et al.*, 2014). To tackle such clinical challenges, researchers have explored potential ways to modify the surface of the implants with new biomaterial (Tabata *et al.*, 2019; Ogle, 2015). Nowadays, as many as 1300 different combinations that vary in shape, dimension, topography, surface material, and chemical features had been reported (Junker *et al.*, 2009; Ogle, 2015). Specifically, $TiO_2$ nanotubes (NTs) fabricated on titanium implant surfaces by electrochemical anodization has arisen extensive interest, with the advantage of their excellent biological properties and resemblance to bone collagen fibrils in dimensional scale (Ottria *et al.*, 2018). $TiO_2$-NTs were recently shown to activate bone cell viability in vitro, enhance implant osseointegration, and prevent osteoclast genesis (Pellegrini *et al.*, 2018). In particular, $TiO_2$-NTs may serve as an ideal delivery vehicle for drugs, including antibacterial materials, growth factors, and bioactive elements (Souza *et al.*, 2019). The resulting $TiO_2$-NTs had been shown to exert anti-bacterial functions as well as facilitating osseointegration

(Li *et al*., 2018). Strikingly, $TiO_2$-NTs could also be used as a unique platform for enabling the slow release of therapeutic agents in situ (Mi *et al*., 2017).

To improve the osseointegration in individuals suffering from metabolic disorders, researchers had been explored various surface modifications options (Chouirfa *et al*., 2019). The sandblasted and acid-etched (SLA) surface (microroughness of 2.5 mm) provides a moderately rough structure that is supposed to be attractive for cell attachment. The hydroxyapatite (HA)-coated surface (microroughness of 5.1 mm) might serve to create a very osteoconductive surface. These surface modifications had been shown to improve osseointegration in T2DM rats. In one study, osseointegration around titanium implants with SLA surface and implants with an HA-coated surface were compared with that of machined surface (less than 0.8 mm). Indeed, a substantial increase in the volume of new bone formation, bone-to-implant contact, as well as increased surface roughness, were observed in the 2 implant groups (SLA and HA) compared with the machined surface implant group. The machined implants, which had been extensively investigated in the past, serves as a nice control for evaluating the modern implant surfaces (Dasmah *et al*., 2014).

The successful dental implant is not merely evaluated by the volume of newly formed bone alone, but also determined by the pattern of new bone formation and bone maturation (Alenezi *et al*., 2018). In the T2DM rat model, the SLA and HA treated group showed more extensive bone formation, covering the flanks and even the crests of the thread, while the machined surface group displayed isolated islets of bones especially within the roots of the threads (Zou *et al*., 2012; Wang *et al*., 2010). Moreover, the bone maturity level to the whole length of the implants appeared to be in a better condition in surface-modified groups. Indeed, a substantial increase of bone-to-implant contact in the medullary region was reported in the HA coating group compared to the machined implants in T2DM rats (Hasegawa *et al*., 2008; Alenezi *et al*., 2018).

In addition to the beneficial effects of the mechanical surface modification, accumulating evidence indicates that gold nanoparticle, such as chitosan gold nanoparticle (Ch-GNPs), linked to genes with bioactive characteristics were excellent tools for facilitating dental implants osseointegration without provoking an immune response (Pasparakis and Vandenabeele, 2015; Li *et al*., 2018; Tsuda *et al*., 2012). In dental implant animal models, target DNA can be conjugated with Ch-GNPs and delivered into bone cells from titanium surfaces; by this pathway, the bioactive molecules could exert modulation effect for bone regeneration.

The stability of the bone implant is determined by the healing process as well as the local environment of the bone-interplant interface (Mathieu *et al*., 2014). Therefore, several recent studies have been focusing on improving the osseointegration under diabetes conditions by targeting the micro-environment of the dental implant, including stem cell sheet-implant complex (Yu *et al*., 2011) local insulin infusion around titanium (Wang *et al*., 2011) and bioactive material coating on titanium (Ma *et al*., 2014; Li *et al*., 2015). Diabetes has been shown to exert adverse effects on the micro-environment of bone metabolism, damages the bone structure, and increases the risk of fracture (Gilbert and Pratley, 2015). One study indicated that overproduction of ROS, as observed in diabetes patients, contribute to the osteoblast damage on titanium surface (Feng *et al*., 2013). In clinical studies, insulin treatment of T2DM demonstrated beneficial effects on the osseointegration. However, the beneficial effects of insulin still need further validation in studies including proper controls, for example, subjects who have successful dental implants which develop diabetes in the future.

## Signaling Pathways Regulating the Dental Implants in Diabetic Conditions

*RIP3/caspase 8 signaling*

Diabetes patients are more susceptible to infection with a much higher periodontitis rate compared with the general population. In general, apoptosis and necrosis are regulated as the two major processes of cell death involved in the regulation of periodontitis. More recently, necroptosis, a newly discovered type of cell death, has been identified to be involved in the pathology of periodontitis (Pasparakis and Vandenabeele, 2015). Periodontal pathogens may rely on necroptosis to acquire a constant supply of substrate for bacteria growth. Meanwhile, the release of DAMPs may activate the inflammatory response of the immune cells, causing the breakdown of the periodontal tissue. Necroptosis can also release the intracellular bacteria into the extracellular microenvironment, which can facilitate immunologic recognition and clearance (Li *et al*., 2018).

Necroptosis can be induced by various stimuli, including lipopolysaccharide (LPS), the most extensively studied mediators, Toll-like receptors as well as intracellular RNA and DNA sensors. Necroptosis requires the activation/phosphorylation of receptor interaction protein 3 (RIP3). The process of necroptosis requires RIP3 phosphorylation, and the downstream protein mixed lineage kinase domain-like (MLKL) (Tsuda *et al*., 2012). RIP3-MLKL can induce necroptosis under LPS stimulation, and it regulates the immune response in which IL-1β participates through NLRP3 (an inflammatory corpuscle) (Huang *et al*., 2009). Caspase-8, known as the cysteine protease critical in the regulation of cellular apoptosis, is inactivated in this stage (Rayamajhi and Miao, 2014). RIP3 can directly strengthen the inflammatory response through the production of inflammatory cytokines when the caspase-8 activity remains weak (Zou *et al*., 2012).

Recent findings indicate that RIP3/caspase-8-dependent necroptosis promoted the LPS-induced periodontal inflammatory microenvironment through enhancing inflammation. Inhibiting RIP3/caspase-8 plays a protective role in the biological characteristics of periodontal ligament stem cells (PDLSCs) (Hao *et al*., 2013). The osteogenesis differentiation ability of PDLSCs declined in necroptosis, which is supposed to be regulated by the RIP3/caspase-8 signaling pathway. After necroptosis occurred, PDLSCs' osteogenesis ability decreased significantly, while inhibition of the RIP3/caspase-8 pathway partially recovered the downward trend (Dinarello, 2011; Hao *et al*., 2013). In

addition, inhibiting RIP3/caspase-8 can reduce the inflammatory reaction and immune characteristics of PDLSCs (Tsuda *et al*., 2012). Moreover, PDLSCs could form new cementum, and inhibiting RIP3/caspase-8 raised expectation of periodontal regeneration (Yan *et al*., 2018). Thus, inhibiting necroptosis by targeting the RIP3/caspase-8 pathway might improve the osseointegration of the dental transplant in diabetes patients. Given that apoptosis and necroptosis can be converted to each other, and RIP3 is a molecular "switch," the combined inhibition of both apoptosis and necroptosis might achieve better results for dental transplant in diabetic conditions.

*PPARγ signaling*

Diabetes patients encounter decreased bone density and increased risk of fracture combined with chronic inflammatory response, PPARγ, a transcription factor which belongs to the nuclear receptor family, is an important modulator for glucose homeostasis and inflammatory response in various tissues (Walton *et al*., 2015). In the clinic, PPARγ agonist rosiglitazone and aleglitazar are generally applied pharmaceuticals for glucose control in diabetic patients (Lei *et al*., 2015; Dubois *et al*., 2017). The application of PPARγ on dental transplant had been proved to enhance osseointegration in diabetes rat models and human cells (Lee *et al*., 2015; Lee *et al*., 2013). In experimental diabetes rat models, PPARγ delivery stimulated bone adherence on the surface of implants, as determined by P and Ca deposition onto the target tissue. PPARγ also facilitated the formation of new bone trabecular and increase bone mineral density, as indicated by elevated new bone formation biomarkers including OPG, BMP-2, BMP-7, and osteocalcin. Moreover, PPARγ inhibits peri-implantitis and alleviates the production of inflammatory stimuli (IL-1β, TNF-α, and RANKL). In summary, these studies pointed out that PPARγ activation might increase the longevity of the dental implant by improving the micro-environment of the regional implant sites in DM patients.

The beneficial effects of PPARγ in dental transplant had also been attributed to its role in improving diabetic pathogenesis (Cock *et al*., 2004; Lei *et al*., 2015) by reducing the inflammatory response and oxidative stress. Diabetes induces chronic inflammation, which impacts the biological performance of osteoblastic cells on implant surfaces. PPARγ agonists, such as pioglitazone and thiazolidinediones, had been used in the clinical practice for the treatment of DM (Gandhi *et al*., 2014). It is believed that PPARγ functions through the modulation of signaling pathways involved in the insulin signaling and inflammatory response, such as protein kinase B (AKT) and extracellular-signal-regulated kinase (EKR) pathways (Banks *et al*., 2015). Some studies pointed out that DM impairs osteoblastic adhesion through the inhibition of AKT phosphorylation/activation (Hie *et al*., 2011). Treating cells with PPARγ agonists had been shown in many studies to activate p-AMPK signaling as well as p-AKT signaling. The AKT signal was considered to be involved in the regulation of self-renewal and maintenance during tissue regeneration (Sen *et al*., 2009). Therefore, the induction of regional PPARγ gene expression may provide a suitable therapeutic strategy for dental implants in DM.

Of note, despite the beneficial effects of PPARγ agonist on the dental transplants, studies had also shown that prolonged administration of thiazolidinediones had an adverse impact on bone metabolism (Chen *et al*., 2015; Schwartz and Sellmeyer, 2007; Adil *et al*., 2017). In adipose tissue, inhibition of PPARγ signaling activated the osteogenic process and enhance bone formation (Li *et al*., 2011). In the bone marrow, suppression of PPARγ had also been reported to stimulate osteogenesis (Smith *et al*., 2015; Adil *et al*., 2017). In contrast, the administration of rosiglitazone in rodents model stimulated the osteoblastogenesis and enhanced osteocyte apoptosis, thus disturb the microstructure of the bone (Mabilleau *et al*., 2010; Takada *et al*., 2009). The PPARγ agonist induced bone loss was considered to be mediated through the activation of ERK and P38 pathways (Mieczkowska *et al*., 2012). Therefore, caution should be taken regarding the potential clinical application of PPARγ agonists to improve the outcome of dental transplants. Further studies also need to be performed to elucidate the molecular mechanism of the PPARγ signaling through dental implants.

*Adiponectin signaling*

Adiponectin (APN), an adipose-derived adipokine with anti-diabetic efficacies, directly contribute to the maintenance of mitochondria homeostasis and cellular redox balance, especially in pathological conditions (Liu *et al*., 2015; Lin *et al*., 2014; Gan *et al*., 2015; Huang *et al*., 2014; Zorov *et al*., 2014; Takada *et al*., 2009; Mieczkowska *et al*., 2012; Pu *et al*., 2016). In T2DM, plasma APN concentrations were substantially decreased (Yu *et al*., 2015; Kanazawa, 2012; Khan et al., 2015). Given that diabetes induced mitochondria malfunction and oxidative stress stimulated the osteoblasts damage, APN functions to improve bone metabolism by maintaining mitochondrial function. APN also stimulated bone formation on titanium surface through inhibiting the apoptosis of osteoblasts as well as improving the function of osteoblast (Pu *et al*., 2016; Chen *et al*., 2015). A previous study in a diabetic mouse model showed that APN treatment alleviates ROS-caused DNA damage and improves bone regeneration around the titanium (Khan *et al*., 2015).

The molecular mechanism of the APN function in the titanium implant is mainly associated with its function in regulating bone metabolism. APN had been reported to be actively involved in the reorganization of the micro-structure of the bone matrix through stimulating the differentiation of osteoblasts, inhibition of osteoclast activity and bone resorption, as well as enhancing tissue repair by mobilization of bone marrow-derived mesenchymal stem cells (Kanazawa, 2012; Bai *et al*., 2004; Chen *et al*., 2015; Yu *et al*., 2015). Several signaling pathways had been identified to regulate bone formation while AMP-activated protein kinase (AMPK) signaling being the most extensively studied (Katsiki *et al*., 2017; Yanai and Yoshida, 2019; Yang *et al*., 2013). Activation of AMPK signaling further promoted the osseointegration via inducing autophagy, mitochondrial formation and fission, as well as stimulating the antioxidation process (Wu *et al*., 2014).

AMPK is generally known as a conserved sensor of cellular energy status, which is sensitive to the cellular energy alteration (Yamauchi *et al.*, 2014). AMPK signaling could switch on the catabolism process in response to stress and meanwhile switching off biosynthetic pathways to preserve energy homeostasis (Okada-Iwabu *et al.*, 2013). The function of AMPK also included promoting mitochondrial proliferation (Mieczkowska *et al.*, 2012), mediating mitochondrial fission in response to energy shortage (Murphy *et al.*, 2016) and eliminating the damaged mitochondria through autophagy (Yoon *et al.*, 2011). In diabetic conditions, however, the AMPK level is substantially inactivated, which contributes to the development of diabetic complications (Chen and Zweier, 2014; Patti and Corvera, 2010). Such suppression of AMPK signaling contributes to the mitochondrial dysfunction and defective cellular antioxidant stress in osteoblasts, which ultimately caused osteoblasts apoptosis and necrosis (Yoon *et al.*, 2011).

APN, however, could effectively reverse diabetes induce inhibition of APMK in osteoblasts at the titanium-bone interface (TBI). APN could also alleviate the mitochondrial damage and oxidative stress of osteoblasts, thus ameliorating the diabetes-induced osteoblasts impairment, stimulated osteoblasts proliferation, and promoted the osseointegration of titanium.

In addition, APN has also been reported to promote the osseointegration by modulating the inflammatory response and angiogenesis. APN had been shown to be negatively correlated with circulating MCP-1 levels (Yanai and Yoshida, 2019). In addition, the cardiovascular-protection effects of APN were also linked to its function of alleviating inflammatory response and stimulating angiogenesis (Katsiki *et al.*, 2017). Likewise, the impact of APN on the osseointegration of titanium in diabetes may also involve the angiogenesis for tissue repair at the implant bone interface. APN may function as an important pharmaceutical target to improve the outcome of dental implants in diabetic patients.

Recently, adiponectin has been delivered through various routes into the dental implant loci to promote the osseointegration of titanium implant and reduce implant failure in diabetes. In a surgical menopause OVX rat model that displayed faster bone loss and delayed bone healing, adenovirus-mediated APN delivery into the dental implants' area markedly enhanced the new bone formation and accelerated the osseointegration surrounding the titanium implants (Yin *et al.*, 2019). In addition, adiponectin had also been delivered through nanoparticles to the implant site. To boost the APN expression, chemical compounds, small-molecule agonists of APN receptors, such as AdipoRon or microRNA antagonist of APN, had also been tested (Okada-Iwabu *et al.*, 2013; Yamauchi *et al.*, 2014). It is likely that in the near future, novel delivery pathways that could mediate the slow and durable release of APN to the dental implant site will be available to prevent dental implant failure in diabetic patients.

*ROS signaling*

An abnormally high glucose level generates a large amount of hydrogen peroxide ($H_2O_2$) and reactive oxygen species (ROS), which subsequently stimulates oxidative stress in cells (Yang *et al.*, 2013). In diabetic patients, especially the uncontrolled hyperglycemia patients, the excessive amount of ROS adversely affects the biological function of osteoblasts on titanium alloy surface, featured by impaired osteoblast adhesion, decreased cell proliferation and osteoblastic differentiation, as well as increased apoptosis. Interestingly, the beneficial effects of PPARγ on osteoblast viability were also attributed to the attenuation of pathological $H_2O_2$ and NO production (Lee *et al.*, 2015). The ROS induced disruption of the cellular oxidant-anti-oxidant balance was considered as the main cause of impaired titanium osseointegration in DM (Murphy *et al.*, 2016; Yoon *et al.*, 2011; Chen and Zweier, 2014; Patti and Corvera, 2010; Zorov *et al.*, 2014). Hyperglycemia-stimulated ROS had been reported to be associated with various pathways, such as activation of protein kinase C isoforms and enhancing the formation of advanced glycation end-product. Accumulating evidence proved that ROS induce severe damage to cellular DNA, RNA, and protein, which further results in the decrease in cell proliferation, differentiation, and apoptosis (Bai *et al.*, 2004; Xiao *et al.*, 2015).

Dysfunction of mitochondria enhanced the ROS production and directly impact the differentiation, function, and survival of osteoclasts, osteoblasts and osteocytes (Jin *et al.*, 2014; Chen and Zweier, 2014; Gan *et al.*, 2015; Gan *et al.*, 2014), especially in the diabetic conditions. In contrast, inhibition of oxidative stress markedly improved bone metabolism. Alpha-lipoic acid, a potent scavenger for some ROS, prevented bone loss in various cell and animal models (Cui *et al.*, 2012). The protective effects of Alpha-lipoic acid were attributed to its protection against ROS induced oxidative stress and inflammation by restoring the endogenous antioxidant defenses and mitigating inflammation-induced cell death in osteoblasts (Kondo *et al.*, 2013). Moreover, in the $H_2O_2$-induced osteoblast injury models, modulation of the mitochondrial function via blockade of Drp1, the major regulator in mitochondrial fission, suppressed ROS production and subsequently restored oxidative stress-induced osteoblast dysfunction (Gan *et al.*, 2015). In summary, mitochondrial dysfunction induced ROS production might be the main cause of the impaired osteoblasts osseointegration on TBI.

*Wnt signaling*

Wnt ligands are a group of secreted proteins with a variety of functions and expression patterns (MacDonald *et al.*, 2009). Wnt interacts with receptors that activate several intracellular, canonical and non-canonical signaling pathways. The characteristics of canonical Wnt signaling is the stabilization of the β-catenin in the cytosol (Kulkarni *et al.*, 2006). Wnt/β-catenin pathways have been proven to control bone formation and remodeling through promoting osteoblast proliferation while inhibiting osteoclast activity (Zancan *et al.*, 2015; Wang *et al.*, 2015). Studies in animal models also confirmed that activation of Wnt signaling by strontium significantly enhanced the deposition of extracellular matrix and bone formation *in vivo* (Yang *et al.*, 2011).

Given that Wnt signaling functions like a growth factor for bone formation, it has been proposed that stimulation of

WNT pathways may improve implant osseointegration. Peri-implant tissues treated with liposomal Wnt3a showed a significant up-regulation of collagen type I and ALP. Moreover, Wnt3a treated sites exhibited more bone-to-implant contact surface, with mineralized osteoid matrix in close proximity to the implant surface, thus demonstrating that transient exposure to WNT3a induces peri-implant cells to rapidly commit to an osteogenic lineage (Popelut *et al*., 2010).

Accumulating evidence indicated that diabetes directly suppressed Wnt/β-catenin signaling in osteoblast, which subsequently impacts the proliferation, differentiation, and osteogenesis capacity at the bone-implant interface during the healing process. It is believed that the compromised osseointegration and high failure rate of the titanium implant in diabetes was considered at least partially due to the impaired Wnt/β-catenin signaling (Ma *et al*., 2014). Recent findings suggest the inactivation of the Wnt/β-catenin signaling in osteoblast is associated with diabetes induced oxidative stress and ROS overproduction (Ma *et al*., 2018). According to these reports, control of Wnt signaling appears to be a promising therapeutic approach to improve implant osseointegration in the clinic.

However, Wnt signaling, as a potential inducer for osteogenesis, has been challenged by some studies. One study reported that up-regulation of Wnt/β-catenin signaling, especially the canonical pathway alone, may not be sufficient for bone matrix development despite its beneficial effects in bone healing (Kim *et al*., 2007; de Boer *et al*., 2004; Boland *et al*., 2004). Indeed, as reported in LRP5 or β-catenin deficient cell and animal models, depletion of any Wnt mediators could not induce the complete interruption in osteoblastogenesis, indicating the presence of a redundant and coordinate network of the different Wnts (Hill *et al*., 2005; Chung *et al*., 2004). Interestingly, Dkk1 and Dkk2, the inhibitors of WNT canonical signaling, are essential for the complete osteoblastic differentiation (Li *et al*., 2005; van der Horst *et al*., 2005; Qiang *et al*., 2008; Heath *et al*., 2009). In summary, Wnt signaling may exert very sophisticated effects in the regulation of osteoblast differentiation under various physiological situations (Zhang *et al*., 2008).

## Concluding Remarks

Diabetes Mellitus is a systematic disease with complications in multi-organs, including the high failure rate of dental transplants. Signaling pathways directly impact the process of bone metabolism and inflammatory response associated with dental implants in diabetic patients. PPARγ, WNT, ROS, and adiponectin signaling pathways have been reported as the major pathways modulating the dental transplant process through improving the general insulin sensitivity, limiting inflammatory response, or stimulating bone formation. In addition, those signaling molecules might also improve the general diabetic conditions in these patients. For example, PPARγ also involved in energy metabolism and inflammatory response in adipose tissue, liver, and skeletal muscle to improve glycemic control. Therefore, these signaling molecules might serve as potential therapeutic targets for implant in DM.

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