REVIEW ARTICLE

Role of Bone Marrow Mesenchymal Stromal Cells (BMMSCs) in Osseointegration among Diabetic Patients with Dental Implants

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Abstract

Aim: This review aims to explore the literature regarding the potential of bone marrow mesenchymal stromal cells (BMMSCs) in enhancing the osseointegration of dental implants among diabetic patients.

Background: Dental implants are a viable and popular option in oral rehabilitation. Various factors such as local, systemic, mechanical, and prosthetic factors play a crucial role in the successful osseointegration of dental implants. Diabetes mellitus (DM) is known to affect the survival of dental implants. Among the various methods developed to improve the survival rates in DM, bone marrow mesenchymal stem cells (BMMSCs) are gaining attention for their regenerative purposes. That could strengthen the osseointegration process in patients with DM.

Review results: This review identified significant studies describing the effects of diabetes on stem cells and thereby affecting osseointegration. We identified studies that reported DM to have a negative impact on osseointegration of dental implants. We also found evidence that BMMSCs can improve the implant survival rate by enhancing osseointegration. Further, various methods of stem cell culture and scaffolds are discussed. Though the BMMSCs-coated implants improve implant survival rates, we could find only a few studies of stem cell-coated implants in diabetes. They show a positive result in diabetic subjects.

Conclusion: Within the limitation of this comprehensive review, it can be concluded that BMMSCs enhance the osseointegration of dental implants among diabetic patients when their medical condition is wellcontrolled. Further double-blinded randomized controlled clinical trials are warranted to establish the clinical applicability of BMMSCs in dental implants in various systemic conditions.

Clinical significance: Though literature supports implants in DM, many studies have proven the impaired osseointegration in DM. This review elaborates on the impactful role of BMMSCs in promoting the osseointegration of the implants placed in well-controlled diabetic patients.

Keywords: Bone marrow mesenchymal stromal cells (BMMSCs), Dental implants, Diabetic patients, Osseointegration, Osteogenic potential.

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Introduction

Dental implants are highly predictable, widely accepted, and treatment options for replacing missing teeth in dentistry. Most of the long-term studies have reported a high survival rate. The field of dental implants has evolved worldwide with several novel techniques. The dental implant history stepped into modernization when Dr. Norman Goldberg collaborated with Dr. Aaron Gershkoff to design and produce the first-ever subperiosteal implant.[1] Dental implants are preferred mainly because of the sensory response demonstrated by osseointegrated implants, unlike conventional prostheses that do not transmit sufficient sensory signals. This osseoperception in osseointegrated dental implants is an important property in the proper functioning of dental implants. Osseointegration, a process that involves significant biological stages, results in the formation of new bone around the dental implant. This process begins soon after the implant loading until a new healthy bony union is formed. This process greatly determines the success of dental implants in healthy and diseased states. The survival rate of an implant is the rate at which implants are still present in the oral cavity at the time of examination. This doesn't consider the state of the prosthesis or the level of patient satisfaction. Today, implant treatment is considered successful when the survival rate is 95%.[2] However, the "cumulative survival rate" (CSR) for most of the studies is more compromised than the widely used "success rate."[3] Various local and systemic risk factors are responsible for most implant failures. One of the significant systemic factors is diabetes mellitus (DM), a chronic disease with diverse systemic and local side effects.[4] DM is associated with periodontitis leading to tooth loss. Implant prosthesis serves to meet this need. However, implants are relatively contraindicated in DM due to their increased risk of infection, delayed wound healing, and microvascular complications. Furthermore, studies have reported insufficient osseointegration and compromised success rate in diabetic patients.[5]

Advances in regenerative medicine have established the applicability of stem cells in dentistry to reconstruct tissues. Stem cells, also known as "progenitor or precursor" cells, are clonogenic

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cells capable of self-renewal and multi-lineage differentiation. BMMSCs are popular for enhancing bone, and bone grafts' regenerative capacity, especially in the osseointegration of implants in people with diabetes. Therefore, this comprehensive literature review aims to explore the literature regarding the potential of BMMSCs in enhancing the osseointegration of dental implants among diabetic patients. This review discusses the role of BMMSCs in osseointegration, how BMMSCs are affected in DM, how BMMSCs can be cultured or coated over the implants in DM, and finally, how one can assess the regeneration after osseointegration and its future directions.

BMMSC in Bone Regeneration and Osseointegration of Implants

What are BMMSCs?

Based on the origin, stem cells can be pluripotent embryonic stem cells (ESCs), undifferentiated multipotent mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs). These have found use in regenerative purposes such as the induction of osteoblasts.[6] It has been proved that dental tissues possess stem cells with the differentiation potential of mesodermal and ectodermal cell lineages.[7] The MSCs of the oral cavity can be isolated from the bone marrow of the alveolar bone, the oral mucosa, the periosteum, the salivary glands, the adipose tissue, the dental pulp, the dental pulp of exfoliated teeth, the periodontal ligament, the dental follicle, the dental germ, the apical papilla, and the inflamed periapical tissues.[8] The BMMSCs were called bone tissue progenitor cells.[9] The BMMSCs are close to hematopoietic stem cells, called 'bone marrow stromal cells'.[10] These cells can be isolated from suspensions obtained by aspiration of the bone marrow and have migration capacity.[10] Studies have validated that BMMSCs from the iliac crest differentiated into myogenic, osteogenic, chondrogenic, adipogenic, and non-mesenchymal neurogenic tissues.[11] Its main functions include maintaining and repairing cells and preserving the cell population,[9]

BMMSC in Osseointegration

"Osseointegration" was first described by Professor Branemark to explain the stable combination of biomaterials and bone tissue. It refers to the direct contact of the bone and the implant without any connective tissue as an intermediate layer.[9] A present-day definition describes osseointegration as a new bone formation to protect against a foreign body. The essential factors for successful osseointegration include the suitable environment for the osteogenic components to grow (osteoconduction), stimulation of undifferentiated cells to form osteoblasts (osteoinduction).[12]

The biological stages of osseointegration are:

- Integration by the formation of woven bone,
- Bone mass to load adaptation (lamellar and parallel fibered bone deposition) and
- Bone structure to load adaptation (bone remodeling).[13]

In adult life, the balance between bone formation and resorption is modulated by BMMSCs, differentiating into osteoblast and osteoclast. After any transplantation, these BMMSCs in the microenvironment act as potent modulators that exert anti-inflammatory effects that benefit the bone. Once the implant is placed, as a part of the host response similar to bone healing begins the activation of osteogenic processes regulated by various growth and differentiation factors at the bone-implant interface. Blood cells in contact with the implant surface induce clot formation.[14] The fibrin matrix serves as a scaffold for which the migrated osteogenic cells get differentiated. Osteoblasts and mesenchymal cells migrate to the implant surface, creating a non-collagenous matrix layer.[15]

Altered BMMSCs of Diabetes Mellitus Affects the Osseointegration of Implants

The osteoblast and osteoclast coupling, the vital cells of implant osseointegration, are reduced by increasing proinflammatory cytokines and mediators such as TNF - alpha and IL 6 in the chronic diabetes state.[16] Diabetes affects the regulators of osteoclast function by altering the ratio between the receptor activator of nuclear factor kappaB- ligand (RANKL) and osteoprotegerin (OPGs), leading to the bone resorption. Moreover, implants in diabetes fail due to the propensity of increased local and systemic infections.[16]

A study by Daubert et al. found the relative risk as 4.8 and 3.3 for peri-implantitis and diabetes,[17] and uncontrolled diabetics carried a 1.9 times more risk of peri-implantitis than the non-diabetes groups. A four-year follow-up study found a 2.57 times greater risk of implant failure in diabetes than in the non-diabetic group.[4] Another study in the systematic review by Naujokat et al. implied that endosseous dental implants in type 2 diabetics pose a marginal risk for implant survival for a long period.[4]

It is reported that hyperglycemia can weaken the osteoinductivity of BMMSCs.[18] When the possible causes for the delayed or failed osseointegration in DM were studied, it was found that DM, osteoporosis, or other systemic diseases show an elevated tumor necrosis factor (TNF) and reduced bone morphogenetic protein-6 (BMP-6).[19] Studies[20] have found a relation between the insulin levels in DM and BMMSC. Yamawaki et al. studied the effect of different glucose concentrations on the osteogenic differentiation of type 2 DM rat bone-derived BMMSCs and found that osteocalcin and calcium decreased at 8.0mM glucose but increased above 8.0mM glucose concentration.[5]

Another study found that these implants failed even in well-controlled glycemic states and attributed them to impaired wound healing. It claimed that the BMMSC changes in DM patients were not solely related to hyperglycemia and insisted on exploring the other factors affecting the osseointegration of implants in DM patients.[21] Another interesting finding by Sun et al. found that metformin promoted the implant osseointegration in a rat model by promoting the osteogenicity of DM–BMSC with the optimal concentration of 125 μm.[22] While the metformin concentration above 200 μm showed an inhibitory effect on DM–BMSC. Liang et al. demonstrated the reduced expression of BMP 4 in the blood of DM patients to be associated with the lesser osteogenic potential of BMSCs.[23] Numerous studies (Table 1) have shown various factors responsible for the failure of implants in DM. There is heterogeneity in the conclusions of the studies. These could be due to variations in study design, type of implant, and duration of follow-up. While most of the studies reported using narrow-diameter implants,[24–29] others did not mention it clearly. Different study designs have been mentioned in the methodology section of these studies, such as retrospective studies,[26] prospective studies,[24,25,27,29–32] case-control studies,[28,33] and cross-sectional studies.[34] The follow-up duration of the included studies ranged from 6 months[27] to seven years.[30] The results of these tables are inconclusive as some studies show increased bone loss around implants in DM patients,[30,33] while others showed acceptable results when meticulous oral hygiene and glycemic levels were maintained.[24–29,32] Nonetheless, the

Table 1: Role of type 2 DM in dental implant failure

Sl No	*Author*	*Study design*	*Aim*	*Type of implant*	*Duration of follow-up*	*Conclusion*
1	Alsahhaf et al., 2019 Saudi Arabia	Retrospective study	Assessment of clinical and radiographic parameters of narrow diameter implants in participants with different glycemic control levels.	Narrow diameter implant	3 years	Narrow diameter implant showed satisfactory results in terms of clinical and radiographic parameters when appropriate oral hygiene and glycemic levels were maintained.
2	Cabrera-Domínguez et al., 2020 Spain	Prospective case-control clinical study	Assessment of clinical performance of single-unit titanium-zirconium (TiZr) alloy narrow-diameter (3.3 mm) dental implants with a hydrophilic surface in patients with controlled DM compared with results in individuals without DM.	Single-unit titanium-zirconium alloy narrow-diameter (3.3 mm)	2 years	The narrow implants in patients with well-controlled HbA1c showed a marginal bone loss. The survival rates were similar to those of the control group.
3	Al-Sowygh et al., 2018 Saudi Arabia	Cross-sectional study	Assessment of inflammation of peri-implant soft tissues and crestal bone loss (CBL) among waterpipe smokers and never smokers with and without diabetes.	Not reported	No follow-up	Inflammatory parameters around peri-implant soft tissue and CBL were comparable among waterpipe smokers and nonsmokers with diabetes.
4	Al Zahrani and Al Mutairi, 2018 Saudi Arabia	Prospective study	Evaluation peri-implant bone loss and stability around submerged and non-submerged dental implants in patients with and without DM.	Straumann dental implant system, Waldenburg, Switzerland	7 years	There was an increased peri-implantitis bone loss around non-submerged single-tooth implant-supported restorations in DM patients.
5	Cabrera-Domínguez et al., 2017 Spain	Prospective study	Evaluation of changes of narrow diameter titanium zirconium alloy (3.3 mm) with hydrophobic surface in DM patients as compared to healthy control	Narrow diameter Straumann Roxolid SL Active	6 months	Patients with glycemic control and healthy individuals showed similar outcomes. Hence, narrow diameter titanium zirconium alloy can be used in anterior region of mouth in diabetes patients.
6	Abduljabbar et al., 2017 Saudi Arabia	Case-control study	Comparison of periodontal and periimplant inflammatory parameters along with marginal bone loss [MBL] among patients with prediabetes, DM and non-diabetic controls.	Not reported	No follow-up	Periodontal and peri-implant inflammatory parameters were worse among patients with prediabetes and DM compared with controls.
7	Al Amri et al., 2016 Saudi Arabia	Prospective study	Assessment of effect of oral hygiene maintenance on hemoglobin Alc (HbA1c) levels and peri-implant parameters around immediately loaded dental implants in diabetic patients.	Diameters ranging between 3.3–4.1 mm	2 years	Proper oral hygiene reduces hyperglycemia and peri-implant inflammatory parameters around immediately loaded dental implants placed in diabetic patients
8	Aguilar-Salvatierra et al., 2016 Spain	Prospective study	Evaluation of implant survival and primary stability parameters in patients with diabetes with different levels of glycosylated hemoglobin Alc.	Implants of 3.3–4.1 mm diameter	2 years	Patients with diabetes can receive implant-based treatments with immediate loading safely.
9	Gómez-Moreno et al., 2015Spain	Prospective study	Analysis of the changes produced in peri-implant tissues in type 2 DM patients with different glycemia levels.	Implants of 3.3–4.1 mm diameter	3 years	Implant therapies for diabetic patients can be predictable when HbA1c levels.
10	Tatarakis et al., 2014 United States	Prospective study	Assessment of putative local etiologic factors on implant bone loss in relation to DM, including clinical, microbial, salivary biomarker, and psychosocial factors.	Implant in function for a minimum of 6 months	1 year	Clinical, microbiological, salivary biomarker, and psychosocial profiles of dental implant patients with good diabetic control and regular maintenance are similar to those of non-diabetic individuals.
11	Bignozzi et al., 2013 Italy	Prospective study	Analysis of real-time polymerase chain reaction for possible differences in peri-implant microbiota of patients with and without DM.	Titanium, osseointegrated dental implants	2 years	A statistically insignificant correlation was empirically detected between gene expression profiles of microbial populations and history of DM.

entire mechanism of how DM affects the osseointegration of dental implants is not yet clear.[19,35] Therefore, the implants with physical changes alone are not sufficient to produce good implant osseointegration in DM.

Ways to Improve the Success Rate of Implants in Diabetes Mellitus

Gerritsen et al. reported that osseointegration in patients with DM could be achieved as in non-diabetic subjects by aiming to attain osseointegration at the early stages of healing.[36] In yet another study of type 2 DM, the authors promoted osseointegration in diabetic rats with a polylactic-*co*-glycolic acid (PLGA) based miR204 delivery system for the titanium implant models via promoting BMSCs osteogenesis *in vivo*.[19] A study in controlled diabetic patients under antibiotic coverage showed improved implant success.[37] A study by Aguilar-Salvatierra et al. found an association between elevated HbA1c and peri-implantitis. Therefore, it was proposed that people with diabetes with moderate HbA1c values can successfully receive implant treatments.[24] Another study in type 2 diabetic rodents suggested that osseointegration can be enhanced with an implant wrapped by osteoinductive MSC sheets.[38] BMMSCs possess the largest osteogenic capacity with maximum alkaline phosphatase action[6] and the ability to regenerate bone, as seen in an experiment on rat condyle.[11] *In vitro* and animal studies show that bone marrow mesenchymal stem cells (BMMSCs) can result in the successful osseointegration of bone and implant.[9] Some modifications were introduced for the BMSCs suspension or cell sheets to improve the outcome of dental implants. Since it had a complex procedure, few cells only survived, and the stability achieved was poor. In order to promote wound healing and tissue regeneration, in situ and *in vivo* delivery of growth factors has been introduced.[19,39–41]

Scaffolds for BMMSC

The 3D scaffolds mimic the extracellular matrix (ECM) in bone regeneration and can support the new bone formation and later degrade once the bone matures. The materials that are available to construct a scaffold can be of:

- Natural polymer- collagen, silk, chitosan, alginate, hyaluronic acid, and peptide hydrogels.
- Synthetic polymer- polyesters and copolymers.
- Ceramic- bioglass, calcium phosphate, and corals.
- Metal- stainless steel 316 L Co-based alloys and titanium alloys.
- Composites- Polymer/Ceramics, Metal/Ceramic, Metal/Polymer.

In composite scaffolds, it was found that calcium phosphate (CaP)/silk powders in silk scaffolds enhanced the porosity and CaP powders distribution. The scaffolds studied supported BMSC proliferation. One such study analyzed the possibility of enhancing bone regeneration by delivering hBMSC onto composite alginate scaffolds releasing vascular endothelial growth factor (VEGF)/bone morphogenic protein-2 (BMP-2) in a femur defect. They found an increase in the BV to TV ratio, and the trabecular number was also significantly increased.[41]

Stem Cells-based Scaffold-free Bone Regeneration

This approach gave better results than the usual scaffold. In an *in-vivo* model of pigs, wherein BMMSCs were harvested and cultured as a 3-layer cell sheet, enhanced mineralization levels and regeneration were noted. Also, a thick and large BV was found on the cell sheet's side.[6]

Decellularized Scaffold

In an experiment, periodontal ligament (PDL)—MSC were allowed to colonize the scaffold, followed by decellularization of the cells. Then MSCs from the umbilical tissue or PDL-MSCs were populated on the scaffold. This was followed by the application of BMMSCs, where a titanium structure was wrapped with a PDL-MSC cell sheet. This complex produced more cementum formation and increased bone regeneration.[6] Osseointegration of a BMMSC sheet-titanium implant complex in a rat model of osteoporosis recommended titanium implants with multilayer BMSC sheets for patients with systemic diseases.[38]

Co-culture BMMSCs with Oral Stem Cells

In an *in vitro* study, it was found that BMMSCs from the maxilla could increase the osteogenesis potential of PDL-MSC. The osteogenic capacity of BMMSCs increased when zinc ions were added, which was evident by elevated levels of collagen I, alkaline phosphatase, osteocalcin, and Runx2.[6] The study had combined the PD-MSCs and the BMMSCs into a calcium alginate hydrogel to produce effective osteogenic differentiation. It was found that the scaffold had kept the inflammation at a lower level locally.[20] In another animal study, which combined gingiva-derived mesenchymal stromal cells (GMSCs) and BMMSCs, the same amount of osteogenic differentiation could be attained by octacalcium phosphate ceramic (OCP) granules.[6]

Surface Modifications on Implants to Improve Osseointegration

Capoccia et al. proposed certain characteristics that favor osseointegration, such as sound and tight initial adhesion, support cell attachment and viability, and positively influence the osteogenic differentiation process.[9] Some surface modifications implicated so far include physical vapor deposition, sol-gel, ion implantation, anodization, and micro-arc oxidation. The effect of implant surface microtopography can be explained with two theories:[6] surface energy and the distortional strain.[1] The smaller the grain size on the surface, the higher is the surface energy, thus favoring cell adherence.[13]

Implant Surface Modification and BMMSCs

Biofunctionalization of an orthopedic implant with bioactive ceramic to regulate bone marrow mesenchymal stem cell behavior has been studied. Dimitrievska et al. used the plasma spray method and found that hBMSCs have stronger initial adhesion and osteogenic differentiation.[42] Shen et al. on the sol-gel method found that the micro/nano-level structure of large particles (80 nm) promotes the proliferation and differentiation of MSC.[43] Many researchers have studied the surface topography by chemical treatment, electrochemical anodization, plasma ion implantation, and deposition that can influence the bone marrow mesenchymal stem cell behavior.[9] Liu et al. found that the micro-arc oxidation (MAO) coating promotes adhesion and osteogenic differentiation of BMMSCs by mediating the integrin β1 signaling pathway.[19] When using the full spectrum (FS) laser to modify the implant surfaces, the BMSCs showed greater elongation with spindle-like morphology. They accelerated spreading speed.[9,41] Covalent immobilization of bioactive molecules like type I collagen, Hyaluronic acid (HyA), arginine-glycine-aspartic (RGD) peptide, and growth factors also impacted MSCs, affecting MSC osteogenic differentiation. Other authors studied the covalent immobilization of collagen on

titanium and found a more significant regulation effect on BMMSCs osteogenesis.[9] Ma et al. found that the PDGF-BB functionalized surfaces promote the BMSCs attachment and osteogenesis.[40] It has been proven that the local control release of bioactive molecules like L-3,4-dihydroxyphenylalanine (L-DOPA), dexamethasone, silicate nanoparticles have also been proven to affect the behavior of BMMSCs and promote osteogenic differentiation.[6,9,40]

In vitro studies have described the ability of BMMSCs to differentiate into osteoblast and demonstrated the expression of alkaline phosphatase, osteopontin, bone sialoprotein, osteocalcin, type I and III collagen.[6,40,43] It also shows how BMS sheets may be used to create a BMS implant. They were constructed with osteogenic potential *in vivo* and *in vitro*.[6,8,9,19,38] Few studies indicated that the platelet-derived growth factors also have the osteogenic potential to induce stem cells, especially MSCs of different origins.[1,7,9,38,41,44]

BMMSC-induced Osseointegration/Regenerative Outcome Assessment

Various methods can assess the quality of osseointegration of a dental implant. They include mechanical stability tests, imaging, histological evaluation, and Immunohistochemistry fluorescence.

Mechanical tests include surgeon's perception, cutting torque resistance analysis, insertion torque, and reverse torque test. Imaging includes X-ray, CBCT, Micro-CT, Field emission scanning electron microscopy, Microradiography. with these bone mineral density (BMD), buccolingual bone thickness, bone density index around the implants, BIC, bone volume (BV)/total volume (TV), trabecular thickness (Tb), trabecular separation (Tb.Sp), trabecular number (Tb.N), and bone surface (BS)/BV, quantitatively analysis, bone mineralization rate of the regenerated bone; the trabecular bone volume (BV/TV; %); the trabecular bone pattern factor (TBPf) can be measured.[45]

The histological evaluation uses light microscopy with Toluidine blue, Masson's trichrome, Alizarin Red-S, and von Kossa staining.[38,45] Immunohistochemistry uses cytokines, bone morphogenetic proteins (BMPs), collagen type I (an essential initial bone matrix protein), osteocalcin (a late marker of bone development), PCNA (correlates with cellular proliferation).[45] Fluorescence uses oxytetracycline, alizarin complex, calcein blue, and xylenol orange.[45]

A randomized control trial was conducted to estimate the efficacy of CD90+ MSCs and CD14+ monocytes in treating significant bone defects of the maxilla. They found that stem cell therapy yielded a better-quality bone correlated with the percentage of autologous CD90þ cells transplanted.[44] Efficacy of cell therapy with *ex vivo* expanded stem cell populations in regenerating significant alveolar defects in the cleft palate, and craniofacial trauma was reported in a phase 1/2 randomized controlled clinical trial. The average increase in bone width was 1.5 ± 1.5 mm in the stem cell therapy group and 3.3 ± 1.4 mm in the control group.[46] The study showed a successful ridge augmentation with ample bone deposition with well-integrated BCP granules for the dental implant. The bone marrow cells induced new bone formation with adequate volume, uneventful healing, satisfactory esthetic and functional results, and no side effects. Safe and predictable results were obtained with autologous MSCs in the clinical reconstruction of alveolar one and successfully osseointegrated implants.[47] Table 2 discusses recent research on coating stem cells in dental implants. Only a handful of studies have been reported in the literature. This includes one RCT,[48] animal studies,[39] and two clinical trials.[49,50] The randomized control trial[48] used coated the implant surface with platelet-rich fibrin matrix and peripheral blood MSCs while the animal used BMMSCs[39] Both the clinical trials used StemBios (SB) cell therapy.[49,50] Promising results have been found in these four studies.

Table 2: Recent studies showing coating of dental implants with stem cells

Sl No	*Author*	*Study design*	*Aim*	*Type of stem cell*	*Conclusion*
1	Singhal et al., 2022 India	RCT	To estimate how implant stability is affected by platelet-rich fibrin matrix with and without peripheral blood mesenchymal stem cells (PBMSCs)	PBMSCs	Promising results were found for implant stability with platelet-rich fibrin matrix and PBMSCs.
2	Alqahtani et al., 2020 Saudi Arabia	Animal study	To investigate the effect of BMMSCs on implant-bone osseointegration in type I diabetic New Zealand rabbits.	BMMSCs	Stem cell therapy with osteoinductive BMMSCs and platelet-rich plasma can enhance the osseointegration of dental implants in uncontrolled diabetic patients.
3	Ou et al., 2016 Taiwan	Clinical trial	To evaluate the osseointegration in low-density bone tissue for SLA (sandblasted, large grit, acid etched) treated implants with StemBios (SB) cell therapy.	StemBios (SB) cell therapy	The SLA modification enhanced osseointegration significantly, especially at early stages of bone tissue healing with SB cell therapy.
4	Weng et al., 2017 Taiwan	Clinical trial	To evaluate the early bone tissue healing in dental implants incorporating StemBios cell therapy.	StemBios (SB) cell therapy	A dental implant treated with (sandblasted, large grit, acid-etched (SLA) surface treatment, along with combination with StemBios cell therapy, promoted bone tissue healing, especially at early osseointegration compared with that of implants without StemBios cell therapy when monitored over a 4-month period.

Clinical Significance

Apart from treating the dental implants or the implant sites with BMMSCs to improve the osseointegration of implants, they are also used to treat maxillofacial bone defects, periodontal disease, congenital deformities, and traumatic injuries which require a bone graft. The osteogenic potential of a bone graft is governed by bone-forming cells, such as mesenchymal stem cells (MSCs), osteoblasts, and osteocytes. The osteogenic potential of a bone graft is governed by bone-forming cells, such as MSCs, osteoblasts, and osteocytes.

Limitations of Current Research

Diabetes mellitus has numerous complications which could have a role in the compromised osseointegration of dental implants. This review focused only on the altered BMMSCs in DM and their effect on osseointegration. We cannot be sure that only by improving the glycemic states of DM patients can an implant be successful. There would still be other factors like local infections, hypertension, etc., that were not taken into account, as that would be out of the scope of the present review.

Future Directions

Further double-blinded randomized controlled clinical trials are warranted to establish the clinical applicability of BMMSCs in dental implants in various systemic conditions.

Conclusion

This review has mainly highlighted the osteogenic potential of BMMSCs. Few of the experimental studies were animal studies that proved the capacity of BMMSCs can influence osteogenic potential. Though there exists literature that supports the use of implants in DM, many studies have proven the impaired osseointegration in DM. This review concludes with various clinical trials that showed that BMMSCs have an impactful role in promoting the osseointegration of the implants placed in well-controlled diabetic patients. Further double-blinded randomized controlled clinical trials are warranted to establish the clinical applicability of BMMSCs in dental implants in various systemic conditions.

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