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Original Article

Stem Cell Surface Treatment on Dental Implant: A Review Article

Amit Siwach[1], Karanjyot Kaur[2], Irish Guangchuiliu Pamei[2], Anil Sharma[3], Reenu Sirohi[4]

[1]Professor, Department of Prosthodontics and Crown and Bridges, Kalka Dental College, Meerut, Uttar Pradesh, India, [2]Post Graduated Student, Department of Prosthodontics, Crown and Bridges, Kalka Dental College, Meerut, Uttar Pradesh, India, [3]Professor and Head, Department of Prosthodontics and Crown and Bridges, Kalka Dental College, Meerut, Uttar Pradesh, India, [4]Professor, Department of Public Health Dentistry, Kalka Dental College, Meerut, Uttar Pradesh, India

Abstract

Background: Dental implants are the most widely used treatment therapy for oral rehabilitation after tooth loss. Implant failures can be a result of many factors, with poor osseointegration being the main culprit and over the recent decades, there has been an important progress in the design and manufacturing of titanium implant surfaces with the goal of improving their osteointegration. Titanium implant surfaces are continuously modified to improve biocompatibility and promote osteointegration. The dental implant surfaces, subjected to specific treatments, perform better and allow for quicker healing times and better clinical performance. Stem cell therapy is a new age advancement which has led to quite promising results in the medical field. The implication of stem cells could lead to the unfolding of different dimensions of Biomimetic surface treatment leading to better results.

Aim: This present review article aimed to assess the studies done on the effect of stem cells on the osseointegration, osteoinduction, viability, cytotoxic response, and biocompatibility of dental implants. This study assimilated various studies done using human dental pulp stem cells in combination with autologous plasma components, for in vitro bone generation on biomimetic titanium dental implant materials. Eleven studies that fulfilled the criteria were examined and included in the study.

Results and Conclusion: All the included studies reported that the stem cells used with or without graft material acts as a great surface treatment on implant surface, and promoted osseointegration with higher levels of new bone formation. The mesenchymal stem attached to the implant surface facilitated cell proliferation which aided to boost bone formation and osseointegration at the bone–implant interfaces. A few selected studies showed a high risk of bias, indicating that caution must be exercised in their interpretation. These results highlight the significance of biomodified implant surfaces that in future can promote a better future for dental implants leading to reduced failures and better implant interface.

Key words: Dental Implant, Stem Cells Therapy, Osseointegration, Osteoinduction

INTRODUCTION

In the field of biology and medicine, one hears often about stem cells and their potential. The key property of all stem cells is that they are undifferentiated therefore; they can be replicated indefinitely and replace different types of damaged cells in the body.[1-4] Similar to mesenchymal stem cells (MSCs), literature shows that stem cells from the dental pulp share behaviors and characteristics from other tissues which could be used to repair damage throughout the body in the future as a regenerative medicine. The dental pulp is a connective tissue, contained within the pulp chamber and in root canals; it communicates with the periodontium through one or more apical foramina and through the lateral accessory channels of the roots.[9,10] The pulp is composed of cells immersed in an intercellular matrix characterized by a fundamental substance and fibers (especially collagen fiber types I and III).[11] The organic matrix represents about 25%, while the remaining 75% is made up of water. With advancing age, there is a progressive decrease in the cell population and a numerical and volumetric increase in collagen fibers, especially in the 2/3 apical roots. Two different types of stem cells are distinguished: Embryonic stem cells and adult stem cells.[12] After fertilization, the stem cells become totipotent: having morphogenetic capacity.

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Corresponding Author: Dr. Karanjyot Kaur, Post Graduated Student, Department of Prosthodontics, Kalka Dental College, Meerut - 250 103, Uttar Pradesh, India.

They are capable of giving rise to a complete individual, they have unlimited multiplicative and proliferative capacity (cell immortality), and they can differentiate into all cell types (differentiating ability).[13,14] A major breakthrough in dental history was achieved when Gronthos *et al.* found the odontogenic progenitor in the dental pulp. These cells were referred to as dental pulp stem cells (DPSCs). Since this discovery, several researchers have reported varieties of dental stem cells, which are isolated and characterized as:

1. DPSCs.[15]
2. SHED.[16]
3. Stem cells from apical papilla.[17,18]
4. Periodontal ligament stem cells (PDLSCs).[19]

At the implant surgery level, autologous bone derived from stem cells could replace the current materials used for guided bone regeneration.[20-23] In addition, the potential chances of having implants with ligament-anchored, or periodontal tissue implants surrounded, produced acknowledgement of tissue engineering, between bone and implant surface, arousing the interest of many researchers.[24-26] The characteristics of the implant surfaces have different implications in the integration that it will be possible to achieve, during rehabilitation, with both hard and soft tissues.[7,27] A rough implant allows for greater osseointegration rates than a smooth surface one. Equally important are the management of soft tissues and the transmucosal portion of the implant.[28,29] Scarano *et al.* recently demonstrated how faster osseointegration could be achieved in the presence of specifically treated implant surfaces, promising encouraging clinical outcomes.[30] Other related researches highlighted how the presence of stem cells applied to a dental implant surface could increase and accelerate the physiological osseointegration processes.[31,32] This review article is aimed to qualitatively assess the studies available in the literature, on dental implants coated with stem cells to enhance osseointegration.

MATERIALS AND METHODS

- Search Strategy: The articles were searched in relation to the role of stem cells in the osseointegration of dental implants. The search was restricted to the study of implant surfaces treated with mesenchymal types of stem cells derived from DPSCs.
- Focus questions: "Does the application of stem cells augment osseointegration of dental implants?"
- If so, then what are the advantages and differences achieved by coating the surface with stem cells?

Search Strategy

The following steps were performed for conducting the review:

(I) A broad electronic search was conducted of databases using the keyword combination "stem cell", "dental implant osseointegration", "different implant surface treatments" and "stem cell therapy on Implant". A manual search of the references in the selected full articles was complemented by the electronic search.
(II) Titles and abstracts were independently screened by reviewers to remove irrelevant articles and duplicates.
(III) Selection of the full-text articles was conducted manually with the inclusion and exclusion criteria in the following section.

Inclusion Criteria

In vivo studies and *In vitro* studies using stem cells (derived from humans, autologous stem cells, stem cells derived from the same species) to augment dental implant osseointegration, treatment of peri-implant–bone defects, and sinus augmentation for implant placement.

Exclusion Criteria

In vivo studies done on animals, stem cells derived from other species, and studies using stem cells other than mesenchymal type of cells.

Data Extraction

All studies fulfilling the inclusion criteria underwent a thorough valid evaluation. Reasons for rejection were recorded for each study. All reviewers have extracted the data independently with. Authors were also contacted to provide information, clarify data and permissions for further usage. The following data were extracted and recorded: number of patients, number of defects, defect size, and type, stem cell characterization, stem cell origin, defect location, length of follow-up, and treatment.

Quality Assessment and Data Synthesis

Both the reviewers were blinded to the authors, titles of journals, and institutions. The quality assessment of the included studies was independently performed by the reviewers.

RESULTS

Selection of Articles

A total of 100 articles were assessed including 53 from PubMed, 27 from MDPI, and 20 from Scopus were retrieved using the keywords. Title and abstract screening of the identified articles revealed that most of the articles were either duplicates or irrelevant to the topic of interest, and hence were excluded from the study. Out of the available full-text articles that were screened for eligibility, only 11 met the inclusion criteria, and hence were included in the review. Table 1 reports the characteristics of the final 11 retained articles.

Table 1: Summary of Data extracted from the included studies

Name of Author (s)	Origin of Stem Cells	Type and Size of Implants Used	Differentiation/Characterization/ Application of Stem Cells	Total Period of Observation	Results and Conclusion
Tonino Traini, Giovanna Murmura, Bruna Sinjari, Giorgio Perfetti, Antonio Scarano, Camillo D'Arcangelo and Sergio Caputi[27]	Small blood stem cells (SB cells), isolated from human peripheral blood	flat pentagonal grade V titanium	The samples surfaces were grit-blasted with 180 μm aluminum oxide at 0.25 MPa producing Ra values ranging between 1.5 and 2.5 μm and acid-etched in a solution of 5 N HNO3 and 5 N HF at room temperature (20 ◦C) for 20 min. A drop of whole blood without any addition of anticoagulant was immediately placed onto the surface of each specimen using a syringe. Contact time was 5 min at the room temperature; specimens were then rinsed with saline solution and fixed in a buffered solution of 2.5% of glutaraldehyde and paraformaldehyde at pH 7.2. Samples were washed again in a saline solution and dehydrated in an ascending alcohol series of 50%, 70%, 90%, 95%, and 100%. After dehydration, the specimens were treated in a critical point drying (Emitech K850 critical point dryer, Ashford, Kent, UK), mounted onto aluminum stubs and gold coated with a Emitech K550 sputter coater.	A week	***Contact angle:*** The difference between the two groups of −4.52◦ appeared to be not statistically significant different. ***Micro roughness:*** The difference between the two groups of 0.2 m was not statistically significant different (p = 0.248). ***Nano Roughness:*** The difference between the two groups of 60 nm was statistically significant different (p = 0.029). ***Blood Clot Extension:*** The difference between the groups of 15.9% was statistically significant different (p = 0.049). on ***Histomorphometric*** evaluation The anodized implant showed a prevalent lamellar bone in direct contact to the implant surface. This aspect indicates a contact osteogenesis process in which osteoprogenitor cells colonize on the implant surface and differentiate into mature, bone forming osteoblasts.
I. Irastorza, J. Luzuriaga, R. Martinez-Conde, G. Ibarretxe1 and F. Unda[33]	Human pulp stem cells (hDPSCs) were obtained from the third molar teeth of young healthy patients	Ti6Al4V ELI 2 mm thick discs were cut from a 5.5 mm-diameter bar, provided by Avinent Implant System SLU (Barcelona, Spain).	Cells were seeded at different densities for different assays on Ti6Al4V and BAS™ titanium discs.	14 days	The results obtained in this in vitro model of osteogenesis suggested a combination of biomimetic rough titanium surfaces, such as BAS™, with autologous plasma-derived fibrin-clot membranes such as PRF and/or insoluble PRGF formulations, but not with an addition of water-soluble supplements of plasma-derived growth factors, to maximise osteoblastic cell differentiation, bone generation, anchorage and osteointegration of titanium-made dental implants
Sheng-Wei Feng, Yi-Han Su, Yen-Kuang Lin, Yu-Chih Wu, Yen-Hua Huang, Fu-Hung Yang, Hsi-Jen Chiang, Yun Yen and Peter Da-Yen Wang[34]	Small blood stem cells (SB cells), isolated from human peripheral blood	Osseotite® double acidetched implants (Biomet 3i, Palm Beach Gardens, FL, USA)	SB cells and hydroxyapatite powder were added to the wound area and covered with an absorbable double layer collagen membrane Low Dose Group 1 patients received 1 × 105 CD61− Lin− cells /0.25 mL DPBS; Middle Dose Group 2 patients received 1 × 106 CD61− Lin− cells /0.25 mL DPBS, and High Dose Group 3 patients received 1 × 107 CD61− Lin− cells/0.25 mL DPBS.	12 week follow-up after GBR—implantation And 12 week follow-up after implantation	No severe adverse effects were observed for up to 6-month trial. Grade 1 leukocytosis, anemia, and elevated liver function were observed, The levels of cytokines and chemokines were detected by a multiplex immunological assay. Elevated levels of eotaxin, FGF2, MCP-1, MDC, and IL17a were found among patients who received SB cell treatment. . All patients who suffered from severe bone defect showed improvement from D3 level to D1 or D2 level. The HU score acceleration can be observed by week 2 after guided bone regeneration (GBR) and prior to dental implantation.

(*Contd...*)

Table 1: (*Continued*)

Name of Author (s)	Origin of Stem Cells	Type and Size of Implants Used	Differentiation/Characterization/ Application of Stem Cells	Total Period of Observation	Results and Conclusion
Roberta Di Carlo, Antonello Di Crescenzo, Serena Pilato, Alessia Ventrella, Adriano Piattelli, Lucia Recinella, Annalisa Chiavaroli, Silvia Giordani, Michele Baldrighi, Adalberto Camisasca, Barbara Zavan, Mirella Falconi, Amelia Cataldi, Antonella Fontana, and Susi Zara[35]	pulp mesenchymal stem cells (DPSCs)	Experimental pure (grade IV) titanium discs (cut at the elected dimensions of 5 mm diameter and 2 mm thickness. Both the two types of Ti implants were surface modified with GO to yield Ctrl + GO and Test + GO samples	DPSCs from the fourth or fifth passage were seeded on Ti discs at a density of 10,000 cells/cm2 and cultivated for 24 h in α-MEM. After 24 h, the standard medium was removed and replaced by a differentiating medium. Cells were cultured in differentiating medium for up to 28 days by refreshing it two times per week.	28 days	All the samples showed the deposition of extracellular matrix, more pronounced in the test and GO-functionalized test discs. GO-functionalized test samples evidenced a significant viability, with no cytotoxic response and a remarkable early stage proliferation of DPSCs cells, followed by their successful differentiation into osteoblasts
Francesca Diomede, Guya Diletta Marconi, Marcos F. X. B. Cavalcanti Jacopo Pizzicannella, Sante Donato Pierdomenico, Luigia Fonticoli Adriano Piattelli and Oriana Trubiani[36]	human Mesenchymal Stem Cells derived from human periodontal ligament biopsies	two different titanium disks surfaces (Resista, Omegna, VB, Italy) have been used: machined (CTRL) and dual acid etched (TEST).	TRL and TEST samples were seeded with hPDLSCs for 21 days and then were fixed for 4 h at 4 ◦C in 4% Glutaraldehyde in 0.05 M phosphate buffer (pH 7.4), dehydrated in increasing ethanol concentrations.They were then mounted on aluminum stubs and gold-coated in an Emitech K550 sputter-coater before imaging by means of a SEM	8 weeks	The present data, obtained under CLSM, evidenced an overexpression of RUNX2, an early osteogenic marker, and VEGF, an angiogenic protein, in TEST compared to CTRL sample. These results lead to hypothesis that the TEST surface had better osteogenic and angiogenic properties
Barbara Zavan ID, Letizia Ferroni, Chiara Gardin, Stefano Sivolella, Adriano Piattelli and Eitan Mijiritsky[37]	Mesenchymal stem cells (MSC)	MPI—Molecular Precision Implants with dimensions of 8 mm × 4.2 mm enriched with VEGF were used. The same implants without VEGF were used as control implants	Stem cells were seeded into the implant surface at a density of 1 × 105 cells per implant For treatment under inflammatory conditions cells were cultured on both type of implants in presence of TNF	Cells were maintained in culture up to 28 days, changing the medium twice a week	Presence of VEGF onto the implant surface is able not only to protect the cells from in vitro aging and from Reactive Oxygen Species (ROS) damage, but it also improves their osteogenic and endothelial differentiation, even in the presence of inflammatory cytokines. This study established a biologically powerful novel tool that could enhance bone repair in dental implant integration.
Pasqualina Naddeo, Luigi Laino, Marcella La Noce, Adriano Piattelli, Alfredo De Rosad, Giovanna Iezzi, Gregorio Laino, Francesca Paino, Gianpaolo Papaccio, Virginia Tirino[38]	Mesenchymal stem cells were obtained by the extraction of dental pulp tissue from third molars	Tri-Vent, purchased from TRI Dental Implants Int AG (Baar, Switzerland), and TiUnite, rom Nobel Biocare	DPSCs were seeded onto dental implants having either a rough surface (TriVent) or one coated with a ceramic layer mimicking native bone (TiUnite)	21 days	Both surfaces are equally biocompatible, preserve DPSC viability, stimulate osteogenic differentiation, and increase the production of VEGF. A slight difference was observed between the two surfaces concerning the speed of DPSC differentiation.

(*Contd*...)

Table 1: (*Continued*)

Name of Author (s)	Origin of Stem Cells	Type and Size of Implants Used	Differentiation/Characterization/ Application of Stem Cells	Total Period of Observation	Results and Conclusion
Kamal Khan Hoti, Muhammad Mansoor Ayub, Imran Saleem Qureshi, Sajid Hussain, Sahibzadi Fatima Tariq, Taimur Khan, Ali Hamad Khan, Noor Ul Amin[39]	CD61Lin cells/ 0.25ml DPBS)	e Osseotite® acid-etched implants	SB cells wer injected into the implant site and , an absorbable double-layer collagen membrane was utilized to cover the wound. A second treatment was performed following the removal of the granulation tissue. SB cells and hydroxyl apatite powder were used to fill the alveolar bone deficits, and repeated a third tim	six-month study period	There was no association identified between the stem cell transplant and any of the side effects. The inflammatory markers eotaxin, FGF2, MCP-1, MDC, and IL17a were elevated in patients treated with stem cells. Stem cells secrete cytokines and chemokines that aid in the healing of damaged tissue.
Luigi Laino, Marcella La Noce, Luca Fiorillo, Gabriele Cervino, Ludovica Nucci, Diana Russo, Alan Scott Herford, Salvatore Crimi, Alberto Bianchi,Antonio Biondi, Gregorio Laino,Antonino Germanà, Marco Cicciù.[40]	Mesenchymal stem cells were obtained by the extraction of dental pulp tissue from third molars.	Myth® (Maipek Manufacturer Industrial Care, Naples, Italy) is made of Grade 4 titanium. Titanium has a relative density of 4.5 g/cm	In order to achieve 3D tissue formation, cells were seeded at a density of 5 × 105 cells/implant onto dental implants that had been previously washed in PBS. Cells were resuspended in 100 µL of culture medium and plated as a drop on the scaffold placed in a 12-well plate, taking care not to spill the medium at the bottom of the plate, to allow cell attachment. After 1 h of incubation, the cell implant devices were transferred to 15 mL tubes with a cap filter and incubated with osteogenic medium in a humidified atmosphere at 37° C and 5% CO2 in a rotating culture apparatus (Wheaton Science Products, Millville, NJ, USA) at 6 rpm; cells plated in flasks were used as the control (2D culture)	30 days	***Cytotoxicity Test: Conditioned Medium:*** prove a total biocompatibility of the implants, suggesting that no particles that damage cells were released by them. ***Cell Proliferation Assay: MTT Tests:*** The implants promote cell proliferation approximately with the same values of the cell culture in standard conditions. ***Cell Adhesion: Immunofluorescence:*** The expression of osteocalcin is increased at 30 days, confirming the stability and osteogenic induction of the implant. ***Cell Adhesion: Scanning Electron Microscopy (SEM):*** the collected photos showed, adhered cells tended to spread onto implant surfaces acquiring an osteoblastic morphology. ***Bone Matrix Formation: Histological Analysis:*** cells seeded on Myth lay a quantity of calcified matrix greater than the control. ***Osteoinduction: qRT-PCR:*** The values of protein reported in Figure 8 show for the control (CTRL) a typical phasic trend, while the samples, collected by the implants, report an increase in concentrations at 30 days of culture with a value higher than the relative control. ***Vasculogenesis:*** Human-VEGF ELISA Test: The values relative to Myth show an increasing trend during the time, with the highest peak at 30 days of culture, but the concentration is lower than that of the control for the respective times

Characteristics of the Included Studies

- Geographical distribution: Of the 11 included studies, three are from Italy, one from Saudi Arabia, one from Spain, one from Canada, one from China, one from Brazil, one from Taiwan, one from Israel, and one from Pakistan.
- The source of stem cells: DPSCs, human MSCs, PDLSCs, blood clot extensions, and small blood stem cells.
- Types of implant used: Myth® (Maipek Manufacturer Industrial Care, Naples, Italy) is made of Grade 4 titanium, Osseotite® acid-etched implants, Tri-Vent, purchased from TRI Dental Implants Int AG (Baar, Switzerland), and TiUnite, rom Nobel Biocare, grade 2 Ti discs polished with silicon carbide abrasive papers and MPI—Molecular Precision Implants, Ti6Al4V ELI.
- The Follow-up period: The period of follow-up ranged between a week and 6 months.
- Outcome assessment: In all the 11 studies assessed different parameters. Some assessed DPSC isolation, culture, and characterization by flow cytometry, cell adhesion by scanning electron microscopy (SEM), cell viability in the presence of Calcein-AM (green fluorescence) and propidium iodide (red fluorescence), and analysis of osteoblastic differentiation markers by reverse transcription polymerase chain reaction. One did bone mineral density was measured by computer tomography scans. In one article, lactate dehydrogenase (LDH) cytotoxicity assay was used to evaluate membrane integrity of DPSCs, LDH was leaked into the medium and was quantified using a CytoTox 96 non-radioactive cytotoxicity assay, and enzyme-linked immunosorbent assay (ELISA) test was done for PGE2 secretion. In one article surface roughness test of the control and test were assessed by Atomic Force Microscopy. One article did Quartz Crystal Microbalance measurements for the assessment of albumin and amelogenin in TNS-modifies titanium. In one MTT colorimetric assay was also performed to assess cell adhesion and proliferation, and ELISA for h-osteocalcin, h-VEGF, and cell adhesion was evaluated by Immunofluorescence Test. In one article Bone Matrix Formation was done by histological analysis such as Alizarin Red S quantification.

Analysis of the Effect of Stem Cells on Osseointegration

All the included studies reported that implant coating with stem cells secrete cytokines and chemokines that aid in the healing of damaged tissue. They expressed excellent biocompatibility stimulate osteogenic differentiation, and increase the production of VEGF. No severe adverse effects were observed in patients who suffered from severe bone defect, moreover showed improvement from D3 level to D1 or D2 level. The results obtained in tests done for osteogenesis suggested a combination of biomimetic rough titanium surfaces, such as BAS™, with autologous plasma-derived fibrin-clot membranes such as PRF and/or insoluble PRGF formulations maximizes osteoblastic cell differentiation, bone generation, anchorage and osseointegration of titanium-made dental implants. The implants promote cell proliferation approximately with the same values of the cell culture in standard conditions and the expression of osteocalcin is increased at 30 days, confirming the stability and osteogenic induction of the implant.

DISCUSSION

The purpose of this review was to analyze the effect of stem cell-coated dental implants for osseointegration, cell proliferation, adhesion, and osteoinduction in humans and to further enumerate the advantages it holds compared to other coated or non-coated implant surfaces.

Most of the data done on such is done on animal models and very few on human-derived cells and thus were included in the study. Eleven studies were short-listed given the inclusion criteria. Three were from Italy, one from Saudi Arabia, one from Spain, one from Canada, one from China, one from Brazil, one from Taiwan, one from Israel and one from Pakistan.

In most of the studies, mesenchymal cells were used, derived from dental pulp or the third molar for coating the dental implants. Some used small blood stem cells (SB cells), isolated from human peripheral blood to coat the implant. Major studies used were *in vitro*. The SB cells were injected into the implant site and, an absorbable double-layer collagen membrane was utilized to cover the wound. A second treatment was performed following the removal of the granulation tissue. SB cells and hydroxyl apatite powder were used to fill the alveolar bone deficits and repeated a third time. In studies done with DPSCs, they were seeded onto dental implants having either a rough surface or one coated with a ceramic layer mimicking native bone. In one, cells were seeded at a density of 5×10^5 cells/implant onto dental implants that had been previously washed in PBS. Cells were resuspended in 100 μL of culture medium and plated as a drop on the scaffold placed in a 12-well plate, taking care not to spill the medium at the bottom of the plate, to allow cell attachment. The cell implant devices were transferred to 15 mL tubes with a cap filter and incubated with osteogenic medium in a humidified atmosphere at 37°C after 1 hour of incubation and 5% CO_2 in a rotating culture apparatus (Wheaton Science Products, Millville, NJ, USA) at six rpm; cells plated in flasks

were used as the control (2D culture). In another, DPSCs from the fourth or fifth passage were seeded on Ti discs at a density of 10,000 cells/cm^2 and cultivated for 24 h in α-MEM. After 24 h, the standard medium was removed and replaced by a differentiating medium. The culturing of cells is done in a differentiating medium for up to 28 days by refreshing it two times per week.

The samples of the respective studies were observed for a period of time ranging from a week-6 months. During the period various tests were performed to achieve the results. Tests including: Cytotoxicity test: Conditioned medium, cell proliferation assay: MTT tests, cell adhesion: Immunofluorescence, cell adhesion: SEM, bone matrix formation: Histological analysis and osteoinduction: Quantitative real-time-polymerase chain reaction. The studies showed that the results obtained were promising. It showed that coating implants with stem cells improve their osteogenic and endothelial differentiation, even in the presence of inflammatory cytokines. In a few, samples showed the deposition of extracellular matrix, more pronounced in the test and GO-functionalized test discs. Most studies prove a total biocompatibility of the implants, suggesting that no particles that damage cells were released by them, and the expression of osteocalcin is increased at 30 days, confirming the osteogenic induction of the implant and stability.

A moderate risk of bias was observed in a few studies and only one study had a low risk of bias. A note of caution is due here in the interpretation of these results, as there is a lack of homogeneity in the data. This indicates the urgent need for further well-designed, high-quality standardized studies.

CONCLUSION

In this present review article, we examined 11 published studies that investigated the application of stem cells on implant surfaces. Our analysis of the results revealed that stem cells when coated on the implant, promoted osseointegration with higher levels of new bone formation. These findings emphasize the role of the bioactive properties of these cells and for future use as surface treatment. The major limitation of the present review is the lack of homogeneity of the data in the selected studies, the amount of related studies along with the high risk of bias in the majority of the studies.

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