REVIEW ARTICLE

Factors affecting Osseointegration: A Literature Review

Manish Goutam, GS Chandu, Sunil Kumar Mishra, Madhvi Singh, Brajendra Singh Tomar

ABSTRACT

The purpose of this literature review is to collect the published data concerning factors affecting osseointegration. Popularity and large demand of dental implant makes this study essential because success of dental implant is directly related to the principle of osseointegration, a process of implant-bone interaction that finally leads to bone-implant anchorage.

To identify relevant literature an electronic search was performed using term osseointegration and dental implant on PubMed central. Titles and abstracts were screened and articles that fulfilled the inclusion criteria were selected for full text reading.

Review of selected articles enabled us to enlist various factors which have significant effects on osseointegration either by enhancing or inhibiting it.

Based on the review literature, it is concluded that there are factors which when considered may increase osseointegration which in turn will increase success of dental implant and some factors play an inhibiting role for bone-implant contact.

Keywords: Osseointegration, Bone and implant, Factors of osseointegration, Titanium and osseointegration.

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INTRODUCTION

Dental implant treatment modality has become a routine procedure in todays health care delivery system. High success rate and patience acceptance has contributed to the fame of dental implant. The major contributing factor for this fame is the concept of osseointegration. This concept has been described by Branemark, as consisting of a highly differentiated tissue making 'a direct structural and functional connection between ordered living bone and the surface of a load-carrying implant'[1,2] Branemark showed that titanium implants could become permanently incorporated within bone that is, the living bone could become fused with the titanium oxide layer of the implant that the two could not be separated without fracture. It occurred to this investigator that such integration of titanium screws and bone might be useful for supporting dental prostheses on a long-term basis.[1]

So, this article aims to review the literature on factors effecting osseointegration either by promoting or inhibiting.

MATERIALS AND METHODS

A literature search was performed of the PubMed Central database using the following key word: 'osseointegration', 'bone and titanium', 'hormones and osseointegration'. The searches were limited to articles in English and between 2007 and 2012 and those with an associated abstract.

Some methods which have been applied to affect osseointegration:

1. Modification in implant properties
2. Use of laser and bio-active molecule on implant
3. Use of systemic bone regulating hormones
4. Use of local osteogenic factor
5. Application of bone source to augment fixation.

REVIEW OF THE LITERATURE

Factors considered by different authors have been discussed below in the tabular form (Table 1).

Modification in Implant Properties

Plecko et al[3] evaluated four different metallic implant material, either partly coated or polished were tested for their osseointegration and biocompatibility in a pelvic implantation model in sheep. Materials to be evaluated were: cobalt-chrome, cobalt-chrome/titanium coating, cobalt-chrome/zirconium/titanium coating, pure titanium standard, steel.

Surgery was performed on 7 sheep, with 18 implants per sheep, for a total of 63 implants. After 8 weeks, the specimens were harvested and evaluated macroscopically, radiologically, biomechanically (removal torque), histomorphometrically and histologically.

This study demonstrated that cobalt-chrome and steel show less osseointegration than the other metals and metal-alloys. However, osseointegration of cobalt-chrome was improved by zirconium and/or titanium based coatings being similar as pure titanium in their osseointegrative behavior.

Use of Laser

Marticorena et al[4] irradiated pure Ti foils using a pulsed Nd:YAG Laser under ambient air, in order to produce and characterize a well controlled surface texture (Roughness and Waviness) that enhance osseointegration. The laser treated Ti foils were implanted in the tibia of 10 male Wistar rats to study the peri-implant healing process response. The histological analysis after 14 days postimplantation showed a tendency to more bone formation compared to the untreated control implants. The formation of a layer of tin on the surface and the obtained roughness, have been demonstrated to improve bone response.

$T_{(02)}$treatment showed a more beneficial response and more areas of bone interlocking compared to $T_{(01)}$. Due to the high difference in topography between $T_{(01)}$ and $T_{(02)}$ surfaces, it indicates the importance of both spatial and height dimension of surface roughness for implant incorporation.

Where,

$T_{(01)}$—Tin foil with 200 laser shots per site

$T_{(02)}$—Tin foil with 500 laser shots per site

Mavrogenis et al[5] in their review study on biology of implant osseointegration explained several factors effecting osseointegration.

- He concluded in his review that cell types, implant and bone tissues, growth factors and cytokines are involved in a coordinated manner during the inflammatory, formation and remodeling phases of bone healing. This means that osseointegration should be regarded not as an exclusive reaction to a specific implant material but as the expression on the endogenous basic regenerative potential of bone.
- The final goal is controlled, guided, and rapid peri-implant bone healing which leads to fine and fast osseointegration for direct structural and functional connection between living bone and the surface of an implant into bone allowing early implant loading. A better understanding of the complex biological events occurring at the bone-implant interface will ultimately lead to improved biologically-driven design strategies for endosseous implants.

Table 1: Factors considered by different authors

Authors	*Factors affecting osseointegration*
Marco et al[6]	Implant design chemical composition, topography of the implant surface material- shape and length, diameter, implant surface treatment and coatings
Linder et al[7]	Status of the host bone bed and its intrinsic healing potential
Soballe et al[8]	Mechanical stability and loading conditions applied on the implant
Khan et al[9] Arrington et al[10] Younger et al[11]	Use of adjuvant treatments such as bone grafting, osteogenic biological coatings and biophysical stimulation
Eberhardt et al[12] Basarir et al[13]	Pharmacological agents such as Simvastatin and bisphosphonates

Sakso et al[14] attempted to improve the bone-implant interaction by (1) adding surface micro scale topography by acid etching, and (2) removing surface-adherent proinflammatory agents by plasma cleaning. Implant fixation was evaluated by implant osseointegration and biomechanical fixation.

The study consisted of two paired animal substudies where 10 skeletally mature Labrador dogs were used. Grit blasted titanium alloy implants were inserted press fit in each proximal tibia. In the first study grit blasted implants were compared with acid etched grit blasted implants. In the second study grit blasted implants were compared with acid etched grit blasted implants that were further treated with plasma sterilization. Implant performance was evaluated by histomorphometrical investigation (tissue-to-implant contact, peri-implant tissue density) and mechanical push-out testing after 4 weeks observation time.

Neither acid etching nor plasma sterilization of the grit blasted implants enhanced osseointegration or mechanical fixation in this press-fit canine implant model in a statistically significant manner.

Effect of Bioactive Molecule

Petrie et al[15] applied fibronectin-mimetic coating which enhanced osseointegration of titanium implants. The bioadhesive ligands examined in this study were: (i) a recombinant fragment spanning the 7th to 10th type III repeats of human fibronectin ($FNIII_{7-10}$), (ii) human plasma fibronectin (pFN), and (iii) a linear RGD peptide (GRGDSPC). $FNIII_{7-10}$ was expressed in *E. coli* and purified.

Study concluded that, $\alpha_5\beta_1$-specific $FNIII_{7-10}$ biomolecular coatings significantly enhance *in vitro* osteoblastic differentiation and implant osseointegration in a rat cortical bone model over full-length fibronectin coatings and the clinical orthopedic 'gold standard'. Importantly, this biomolecular coating relies on simple physiosorption of bioactive ligands onto biomedical-grade titanium as a simple, clinically-translatable, implant biofunctionalization strategy to enhance tissue healing responses.

Effect of Hormone

Daugaard et al[16] studied the effect of human PTH*(1-34) on the cancellous osseointegration of unloaded implants inserted press-fit in intact bone of higher animal species. Twenty dogs were randomized to treatment with human PTH (1-34), 5 µg/kg/day subcutaneously, or placebo for 4 weeks starting on the day after insertion of a cylindrical porous coated plasma-sprayed titanium alloy implant in the proximal metaphyseal cancellous bone of tibia. Osseointegration was evaluated by histomorphometry and fixation by push-out test to failure (Table 2).

Table 2: Surface fraction of woven bone at implant interface

PTH group	*Control group*
15%	11%

*PTH: parathormone

Mechanically, the implants treated with PTH showed no significant differences in total energy absorption, maximum shear stiffness, or maximum shear strength.

In conclusion, findings support the concept that PTH (1-34) treatment improves histological cancellous osseointegration of orthopedic implants in normal bone. At the observed time point, no additional improvement of the initial mechanical fixation was observed. This was found in the context of porous coated titanium alloy implants inserted non-weight bearing and press-fit in cancellous bone of dogs.

Effect of Local Osteogenic Factor

Xu et al[17] worked on hypothesis that bone marrow stromal cells (BMSCs) participate in cellular and molecular events in osseointegration process, and that osterix (Osx) promotes implant osseointegration. To prove this hypothesis they tracked double-labelled BMSCs in implantation sites created in nude mice transplanted with these cells. They also inserted implants into the femurs of our established transgenic mice after local administration of viruses encoding Osx, to determine the osteogenic effects of Osx.

Immunohistochemical results demonstrated that BMSCs can recruit from peripheral circulation and participate in wound healing and osseointegration after implantation.

Microcomputed tomography (micro-CT) analysis revealed an increased bone density at the bone-to-implant interface in the Osx group, and histomorphometric analysis indicated an elevated level of bone-to-implant contact in the Osx group. They concluded that exogenous BMSCs participate in the osseointegration after implantation, and that Osx overexpression accelerates osseointegration.

Yan et al[18] assessed effect on osseointegration of titanium implant after the local delivery of transcription factor SATB2 and the quantitative real-time RTPCR results demonstrated that:

- *In vivo* overexpression of SATB2 enhanced expression levels of potent osteogenic transcription factors and bone matrix proteins.

  It was also found that 21 days after implantation, there were no significant differences in the expression levels of SATB2, Osx, Runx2, COLI, OC, and BSP between the RCAS-Satb2 group and the RCAS group.
- Histological analysis showed that SATB2 overexpression significantly enhanced new bone formation and bone-to-implant contact after implantation.
- IHC staining analysis revealed that forced expression of SATB2 increased the number of BSP-positive cells surrounding the implant.

  Micro-CT analysis demonstrated that *in vivo* overexpression of SATB2 significantly increased the density of the newly formed bone surrounding the implant.

These results conclude that *in vivo* overexpression of SATB2 significantly accelerates osseointegration of titanium implants and SATB2 can serve as a potent molecule in promoting tissue regeneration.

Effect of Bone Source Augment

Timperley et al[19] assessed whether the use of hydroxy apatite (HA) paste at the cement-bone interface in the acetabulum improves fixation.

They performed a randomized study involving 22 sheep that had BoneSource hydroxyapatite material applied to the surface of the acetabulum before cementing a polyethylene cup at arthroplasty. We studied the gross radiographic appearance of the implant-bone interface and the histological appearance at the interface.

They concluded that the application of HA material prior to cementation of a socket produced an improved interface. The technique may be useful in humans, to extend the longevity of the cemented implant by protecting the socket interface from the effect of hydrodynamic fluid flow and particulate debris.

Table 3: Studies on factors inhibiting osseointegration

Authors	*Factors inhibiting osseointegration*
Giori et al, Pilliar et al[20,21]	Excessive implant mobility and micromotion
Otsuki et al[22]	Inappropriate porosity of the porous coating of the implant
Kudo et al, Sumner et al[23,24]	Radiation therapy
Sakakura et al, Eder et al, McDonald et al[25-27]	Pharmacological agents such as cyclosporin A, methotrexate and cis-platinum
Callahan et al[28]	Warfarin and low molecular weight heparins
Dahners et al, Pablos et al.[29,30]	Non-steroid anti-inflammatory drugs especially selective COX-2 inhibitors
Rosenqvist et al, Zhang et al, Mombelli et al, Wong et al [31-34]	Patient's related factors such as osteoporosis, rheumatoid arthritis, advanced age, nutritional deficiency, smoking and renal insufficiency

DISCUSSION

Success in implant dentistry depends on several parameters that may improve considering both biologic and mechanical criteria. To explain the micromechanisms involved in osseointegration is necessary to know concepts of biology, physiology, anatomy, surgery and tissue regeneration. This means that osseointegration should be regarded not as an exclusive reaction to a specific implant material but as the expression on the endogenous basic regenerative potential of bone.

Bioactive materials bond to bone tissue through bridges of calcium and phosphorus. On the other hand, the chemical bond between noncoated titanium implants and living tissue occurs through weak van der Waals and hydrogen bonds.

Use of laser and bioactive molecule gives a broad scope for researchers and more studies are needed to improve osseointegration more efficiently. Moreover, modification in implant surface by coating with titanium and using different implant design also helps to improve bone-implant contact where as acid etching and grit blasting has no significant effect on this union.

Local administration of osteogenic factors and systemic administration of PTH (1-34) proved to be quite beneficial for better osseointegration where as systemic diseases can adversely affect the osseointegration in dental implant which comes under patient's related factors such as osteoporosis, rheumatoid arthritis, advanced age, nutritional deficiency, smoking and renal insufficiency and this should be considered during procedure which in turn will affect success rate of implant.

CONCLUSION

Studies on factors affecting osseointegration can be concluded as a set of factors which are boosting osseointegration and factors which inhibit osseointegration (Table 3) and we can summarize it in a tabular form (Table 4).

Table 4: Factors involved in increase and inhibition of osseointegration

Factors enhancing osseointegration	*Factors inhibiting osseointegration*
Implant design, shape and diameter	Excessive implant mobility and micromotion
Titanium coating on Co-Cr metal implant	Nonsteroid anti-inflammatory drugs especially selective COX-2 inhibitors
Laser treatment of Implant Surface	Warfarin and low molecular weight heparins
Human PTH (1-34)	Inappropriate porosity of the porous coating of the implant
Ostetrix factor	Osteoporosis, rheumatoid arthritis
Local delivery of transcription Factor	Radiation therapy
Bone source augment to socket	Smoking
Mechanical stability and loading conditions applied on the implant	Advanced age, nutritional deficiency and renal insufficiency
Pharmacological agents such as simvastatin and bisphosphonates	Pharmacological agents such as cyclosporin A, methotrexate and cis-platinum

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ABOUT THE AUTHORS

Manish Goutam (Corresponding Author)

Postgraduate Student, Department of Prosthodontics, Rishiraj Dental College, Bhopal, Madhya Pradesh, India, Phone: 8878615099, e-mail: drmanishgoutam@yahoo.com

GS Chandu

Professor and Head, Department of Prosthodontics, Rishiraj Dental College, Bhopal, Madhya Pradesh, India

Sunil Kumar Mishra

Reader, Department of Prosthodontics, Rishiraj Dental College Bhopal, Madhya Pradesh, India

Madhvi Singh

Postgraduate Student, Department of Peridontics, People's Dental Academy, Bhopal, Madhya Pradesh, India

Brajendra Singh Tomar

Postgraduate Student, Department of Prosthodontics, Rishiraj Dental College, Bhopal, Madhya Pradesh, India