

Evolution of root form endosseous dental implant-Transformation from bone anchored to ligament anchored implants and its neurological aspects

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Abstract

This review paper investigates the possible transformation of endosseous dental implant, primarily from the current osseointegrated to the future ligament anchored implant within which a new class of implants with enhanced feature of “neuro-ligament integration” may appear. Endosseous dental implants used presently to replace missing teeth get fused with bone but they do not have any periodontal ligament interface between the alveolar socket and the surface of the implant, which natural teeth do. Hence, they lack any proprioceptive sensation, which is important for discrimination, directional and masticatory sensation. Attempts have been made to regenerate periodontium around the implant in 90s, which was not completely successful. Thereafter, there has been limited research. However, recent advances in tissue engineering and biomaterials gave renewed hope of establishing sensory dental implants. In this review, various methods of regeneration of periodontium onto the surface of titanium implants have been discussed along with the possible types of neurological assessment and neuroimaging that could be carried out for validation of its afferent feedback. The review starts by giving background information of major stages and terminologies in the field of oral implants, its response to host tissue in bone, various surface modification of dental implants, stem cells that are used for periodontal regeneration, different approaches for regeneration of periodontium, concept of proprioception in periodontium, osseoperception of dental implants and concludes with neurophysiology of oro-dento-facial region in brain including its detection and measurements methods.

Glossary of important terms

Proprioception: Proprioception is a type of sensory function of periodontium. Proprioception, also called kinesthesia, involves awareness of the spatial and mechanical status of the musculoskeletal framework.

Osseoperception: The ability to identify kinesthetic sensation without the input from periodontal mechanoreceptors. This sensation is generated from the temporomandibular joint, masticatory muscle, mucosa, and periosteum, and provides sensory and motor information related to mandibular movements and occlusion.

Stereognosis: Stereognosis (haptic perception or tactile gnosis) is the ability to identify and discriminate various forms. It depends upon memory and intact somatic sensory system. Both, central analysis and peripheral receptors are involved.

Introduction

Dental caries is one of the commonest disease known to mankind [1]. Dental caries and periodontal pathosis results in destruction of tooth structure and attachment apparatus which ultimately leads to tooth loss. The edentulous space arising out of tooth loss leads to other complications like midline shifting of facial profile [2], supra-eruption of opposing tooth [3], masticatory imbalance [4], rapid bone loss [5], disruption of dynamic equilibrium of the masticatory apparatus [6], defective speech [7] etc. Hence, time immemorial people used various

substitute to replace the lost tooth in edentulous region. Probably, the first artificial implant were pieces of shells that were used as implants for mandibular teeth in Mayan population roughly around 600 AD [8].

In 1952, Per-Ingvar Brånemark, a Swedish orthopedic surgeon, while conducting experiments on intravascular rheology implanted titanium chamber on rabbit femur. However, after the completion of the experiment these titanium chambers could not be retrieved as surrounding bone fused with them permanently. He named this bone anchored phenomena as “osseointegration” [9]. He further stated that the surrounding bone approximates the implant surface very closely without any intervening connective tissue. “Osseointegration implies a firm, direct and lasting connection between the vital bone and screw-shaped titanium implants of defined finish and geometry-fixtures. Thus, there is no interposed tissue between fixture and bone. Osseointegration can only be achieved and maintained by a gentle surgical installation

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technique, a long healing time and a proper stress distribution when in function” [10]. For proper osseointegration to occur, the implant should not be loaded and left out of function during the healing period.

In 1986, Dr. Charles Wiess came up with another concept of implant biointegration which he termed as “fibro-osseous integration” [11]. According to him, when implant is subjected to micromotion, a type of connective tissue fibres *viz.* collagen fibres get interposed between the trabecular bone, weaving around the implant surface and then reinvesting into the trabecular bone on the other side. Early loading of such implants results in generation of bioelectricity (piezoelectric effect) due to polarity in the outer and inner surface of the investing collagen fibres resulting in differentiation of pluripotent cells present in the peri-implant area with predictable sequelae. He also suggested that dental implants integrated through fibro-osseous integration is superior to the osseointegrated implants. The fibro-osseous integrated implants showed initial success but in long term they failed as the collagen fibres were oriented parallelly. These collagen fibres cannot mimic the function of Sharpey’s fibres that were inserted in perpendicular fashion in the root cementum [12-14]. Schroeder *et al.* gave the term “functional ankylosis” to define osseointegration after he minutely examined the histological sections [15]. He opined that primary stability (initial fixation) is mandatory for functional ankylosis of the implant. This is achieved by the firm and frictional/contact relationship between the cortical bone and the implant surface.

De Putter stated that implant anchorage could be of two types-mechanical and bioactive anchorage [16]. Mechanical anchorage is seen in metallic implants such as titanium and is generated by interfacial tension of surface undercuts in the form of vents, slots, screws etc. The anchorage is purely physical and there is a direct contact between the metal surface and bone. Bioactive retention is achieved when the implant surface is coated with a bioactive material like hydroxyapatite which induces osteogenesis resulting in physico-chemical bond between implant surface and bone similar to ankylosis of natural tooth [13,14,16]. Further, peri-implant bone healing may elicits two types of mechanism - contact and distance osteogenesis. In contact osteogenesis bone starts forming from the implant surface while in distance osteogenesis, bone starts getting deposited on the old bone and move towards the implant surface in an appositional manner [13,17-19]. Although dental implants provides permanent solution to missing teeth, they have got their own limitations. The treatment is considered successful if the implant permanently fuses with the bone. This “ankylosed” process does not mimic the natural healthy tooth apparatus which contains the sensitive periodontium between the root of tooth and wall of the alveolar bone socket. Hence, dental implant ankylosed to alveolar bone do not display the functions of healthy periodontium as those found in natural tooth like defence and proprioception including sensation of mastication, occlusion, directional and discriminative abilities. Research is being conducted to regenerate functional periodontium¹ around dental implant to counter these drawbacks and this is a focus of this review paper.

Host response to implants

Dental implants are broadly classified into two types - endosteal (root form) implants and subperiosteal implants. Endosteal implants are placed in the jaw bone while subperiosteal implants are placed above it. We will focus on root form endosteal implants as these are the anatomic substitutes of dental root(s). A root form dental implant is placed in region of missing maxillary or mandibular teeth surgically, taking into consideration the systemic and oral health of the patients. After the implant has been placed in the biological system (alveolar

bone), water molecules are the first molecules to reach the surface of the implant [20]. Surface properties of the implant determines how water molecules behaves with the implant surface. The surface water shell determines the fate of biomolecules and proteins that adsorb later onto the implant surface. It has been suggested that biomolecules also have hydration water shells which interacts with surface water shells and drives the physicochemical process at the interface [20] (Figure 1).

Later as stated by Branemark in 1985, the microgap between the implanted surface and the wall of the drilled hole is filled by blood clot. Primary stability of the implant fixture leads to uneventful healing which was termed as “intramembranous bone formation” by Schenk and Hunziker [21] and “de novo bone formation” by Davies [17]. In intramembranous bone formation, blood clot surrounds the implant surface, followed by angiogenesis, osteoprogenitor cell migration, woven bone formation and compaction (deposition of parallel fibres and lamellar bone) and secondary remodelling [22]. There is a correlation between microdamage induced during the surgical placement of implant and bone remodelling. The damaged bone triggers cascade of healing response [23]. The interface between the implant surface and the inner wall of the osseous drilled hole follows the sequence of wound healing as depicted in the Figure 2.

Briefly, the local tissue response at the implant site depends on body’s response to surgical trauma induced by placement of root form endosseous dental implant fixture. Prognosis is better with optimal tissue response when there is minimal generation of heat (< 47°C for 1 min or less) during osteotomy procedures coupled with surgical precision. A vascular clot gets formed at the inflamed surgical site. This attracts macrophages/large phagocytes and undifferentiated mesenchymal cells from surrounding periosteum. Osteoblast, the polarized cells are known to be the chief bone matrix synthesizing cells. When they are completely covered by the matrix they are called osteocytes. Appositional bone growth occurs onto the implant surface by contact osteogenesis by these osteoblast cells. It has been suggested that with the initial placement of the implant a thin layer of bone (0.5 mm) becomes necrotic (even with optimal surgical technique) which will be replaced by woven bone with vascularization resulting in initial bone contact [24]. This woven bone matrix will be removed by hematopoietic derived osteoclastic cells by a process called remodelling. A mature haversian bone system is laid down by osteoblastic cells to form lamellar bone. This process is influenced by micromotion of the interface, local and systemic release of matrix regulating growth factors, local vascular supply etc. Later the space between the implant and bone is healed by a process called “creeping substitution” resulting in secondary stability of the implant [25]. Some authors categorized the above events as SIGMA phase consisting of Activation (A), Resorption (R), Quiescence or reversal (Q) and Formation (F) stages [12]. The final maturation and adaptation phase continues for years. Here the bone callus is resorbed and stronger bone structure develops in the regions of higher strain (Wolf’s law) to resist mechanical stress and strain [26]. The effect of many inflammatory mediators, eicosanoids, interleukins, chemokines on bone formation and osteoblast behaviour strongly implicates the post surgical inflammatory process in determination of bone formation.

Surface modification of titanium dental implants

Currently surface modification of the commercial endosseous dental implants is done to improve bone integration. No such instances have been reported where the implant surface or design was modified purely for ligament tissue proliferation and anchoring (Table 1).

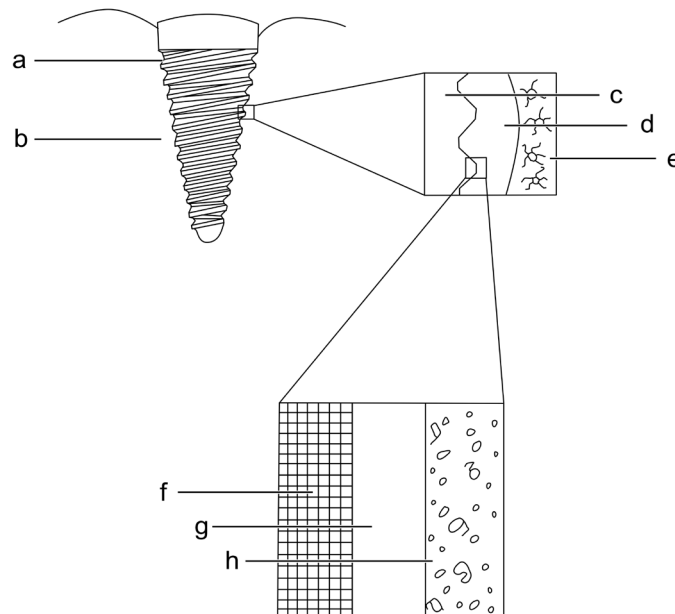


Figure 1. Biological response of endosseous dental implant: a- Titanium implant, b- Alveolar bone, c- Surface of titanium implant, d- Biofluid, e- Osteocytes and bone, f- Titanium, g- Titanium oxide, h- Biofluid with proteins and ions.

Table 1. Some work involving surface modification of titanium dental implant are listed in the following table.

Author and year	Aim	Surface modification	Process applied	Study	Conclusion
Bowers KT <i>et al.</i> 1992 [27]	Responses of osteoblast-like cells were studied on titanium surfaces	Roughness increased	Sandblast	In vitro	Increased osteoblast attachment were found in modified implant
Sul YT <i>et al.</i> 2002 [28]	Investigation of chemical properties of titanium surface for osseointegration	Altered surface chemical composition.	Electrochemical deposition of calcium ions	In vivo	Fast and strong osseointegration
Jimbo R <i>et al.</i> 2011 [29]	Investigation of in vivo bone apposition during the early stages of osseointegration	Increased hydrophilicity	Anodized porous titanium implants were modified with 0.175 wt% ammonium hydrogen fluoride solution (NH ₄ F-HF(2))	In vivo	Enhanced cellular response
Lee JK <i>et al.</i> 2013 [30]	Investigation of orthotropic bone formation and remodeling of dental implant surfaces with and without recombinant human bone morphogenetic protein 2	Bioinductive surface for osseointegration	Coated with bone morphogenic protein- 2	In vivo	Absorbed BMP-2 dose varied with implant surface characteristics, influencing local bone formation and remodeling.
Alghamdi HS <i>et al.</i> 2013 [31]	Study of osseointegration of Calcium Phosphate (CaP) coating in titanium implant in healthy and osteoporotic rats	Altered surface chemical composition	Radio-frequent magnetron-sputtered calcium phosphate (CaP) coating	In vivo	Thin CaP coating effectively improves osseointegration in both healthy and osteoporotic conditions.
Wennerberg A <i>et al.</i> 1996 [32]	Comparative study between different size of Al ₂ O ₃ on the titanium implant	Roughness increased	Blast with Al ₂ O ₃	In vivo	More bone-to implant contact and higher resistance to reverse torque in coarser implant
Perry R. Klokkevold <i>et al.</i> 1997 [33]	Acid etched implant surfaces are thought to enhance osseointegration	Roughness increased	Acid etching (HCl/H ₂ SO ₄)	In vivo	Resistance to reverse torque rotation implies enhanced osseointegration
Mustafa K <i>et al.</i> 2000 [34]	Responses of cells derived from mandible were studied	Roughness increased	Blast (TiO ₂)	In vitro	Rough surface showed increased cellular attachment

Stem cells used for periodontal regenerations

Regeneration of periodontal like tissue by using stem cells from various origin has been reported by numerous authors [35-37]. Hence, it becomes imperative to discuss stem cells in relation to periodontal regeneration. Briefly, stem cells are classified as embryonic (pluripotent) and adult (multipotent) stem cells based on their origin and differentiation potential and are isolated from inner cell layer of blastocyst and tissues that continuously replenish themselves

(intestinal epithelium, blood, skin etc.) respectively [38]. One of the most common source of stem cells are bone marrow stem cells (hematopoietic stem cells), stem cells derived from adipose tissue and bone marrow stromal cells (mesenchymal stromal stem cells). Bone marrow stem cells (BMSCs) and stem cells from adipose tissue have shown tissue regeneration having feature of periodontium, cementum and alveolar bone in experimental animal models [35,36,39]. Stem cells from dental origin have also been isolated and are classified into five types; dental pulp stem cells (DPSCs) [40], stem cells from exfoliated

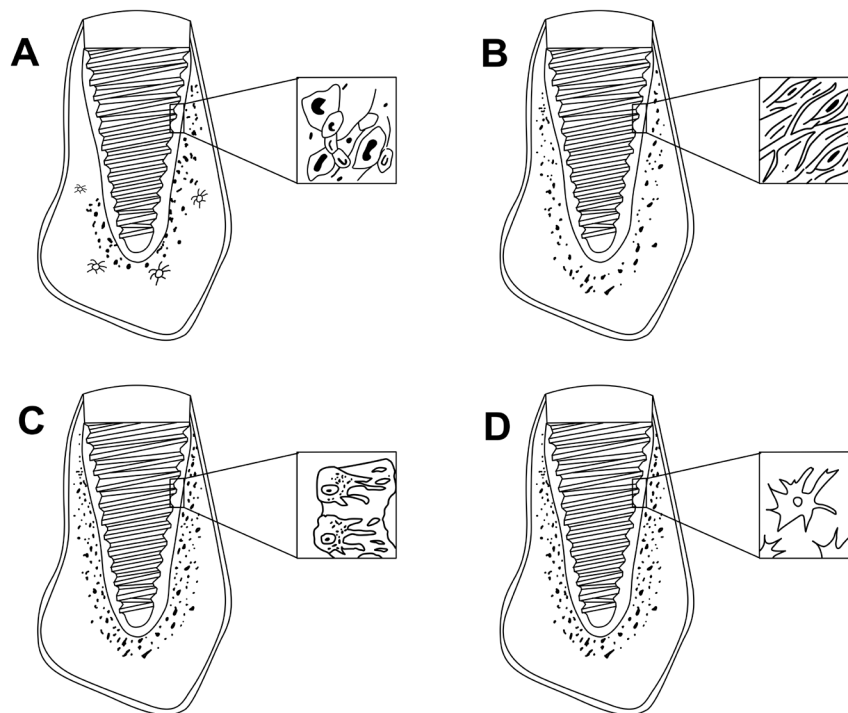


Figure 2. Healing events around endosseous dental implant: A- Formation of blood clot, B - Fibroblast and new capillaries, C- Osteoid formation, D- Mature bone.

deciduous teeth (SHED) [41], periodontal ligament stem cells (PDLSCs) [42], stem cells from apical papilla (SCAP) [43] and dental follicle progenitor cells (DFPCs) [44]. They all have mesenchymal stem cell properties and hence are capable of giving rise to various lineages of cells, like osteogenic, chondrogenic, adipogenic, myogenic and neurogenic cells [45]. Stem cells isolated from human periodontal ligament have been shown to give rise fibroblast like cells that may develop into adipocytes, osteoblasts-like, cementoblast-like cells in vitro and cementum-like and periodontal ligament-like tissue in vivo [42]. It has been reported that mesenchymal stem cells isolated from dental follicle can give rise to periodontal ligament like tissue [46]. Periodontal ligament regeneration in diseased tooth with periodontal pathology also employs progenitor cells for native tissue regeneration [47]. Scaffold based experiments in periodontally involved tooth have resulted in generation of PDL-like tissues in diseased areas [48]. However, exploration about the type of stem cells required for complete PDL regeneration is still insufficient.

Approaches for periodontal regeneration

There are many studies reported in literature which discusses periodontal regeneration of teeth in experimental animal subjects with periodontal pathology by using Guided tissue regeneration (GTR) membranes [49-52]. Further, Nayman et al. was successful in regenerating periodontium like tissues in periodontally involved human tooth by using GTR membrane [53]. A crucial factor in GTR is the presence of adjacent healthy periodontal ligament tissue, from which the slow growing cells are allowed to repopulate the diseased site while the barrier membrane excludes unwanted tissues like fast growing gingival connective tissue and epithelium to take part in the healing process [54].

Recently, various attempts have been made by researchers to regenerate periodontium onto the surface of the implants. Broadly three types of approaches have been reported in the literature (Table 2).

Regeneration of periodontium with residual root tip

Various researcher tried to regenerate periodontium by placing implants in contact with residual healthy root tips (Figure 3A.) [55-57]. Warrer *et al.* reported that regeneration of periodontium like tissue is possible in voids between alveolar bone and titanium implant surface when the implant is placed in contact with retained root tip [55]. Similar inference were also drawn by Guarneri [56]. Buser [57] also reported similar experimental findings in humans as well as in monkeys respectively.

Regeneration of periodontium with implant touching the root of adjacent tooth

In this approach, the titanium implant touches the root of adjacent tooth or they are placed between the roots to allow the growth of periodontium onto it (Figure 3B). Experimental studies conducted by Jahangiri *et al.* [58], Urabe *et al.* [59], Rinaldi JC *et al.* [60] have concluded that cementum and periodontium like tissues were regenerated on the surface of implants when this approach was explored. However, no studies have been published on the dental health of teeth whose root(s) have been used as a source of contact in regeneration of periodontium on the titanium dental implant.

Regeneration of periodontium with cultured cells

Periodontal ligament has also been regenerated by using stem cells seeded in appropriate biodegradable scaffold (Figure 3C). Choi *et al.* [37], Marei *et al.* [36], Lin *et al.* [39], have reported that regeneration of periodontal tissue is possible by seeding pluripotent stem cells in various types of scaffolds and implanting it in vivo. Gault et al. had reported that cells isolated from periodontium could be co-cultured with titanium pins in bioreactor which could later be implanted in monkeys to successfully regenerate periodontium like structures [61]. Piattelli *et al.* reported that periodontal ligament like structure

Table 2: Various work regarding regeneration of periodontium are listed in the following table.

<i>Author and year</i>	<i>Type of Animal subject</i>	<i>Experimental approach</i>	<i>Tooth selected</i>	<i>Maxillary/mandibular tooth</i>	<i>Type of Implant</i>	<i>Post-operative healing period</i>	<i>Histology</i>	<i>Conclusion</i>
Warrer <i>et al.</i> 1993 [55]	Monkeys	Implant touching the retained root tip	Premolars and molars	Mandibular Tooth	Self tapping titanium dental implants	3 months	Contact area showed cementum and periodontium	Formation of periodontium and cementum in voids present between the alveolus and surface of implant
Jahangiri <i>et al.</i> 2005 [58]	Beagle dogs	Implant touching the root of adjacent tooth	Premolars	Maxillary tooth	HA coated titanium implants	6 weeks	Periodontium like structures and cementum are seen	Formation of periodontal like tissues when implant touches the adjacent tooth
Nyman S <i>et al.</i> 1982 [53]	Human	Guided tissue regeneration	Incisor	Mandibular tooth	N/A	3 months	New cementum and principle fibres of periodontal ligaments like tissue are seen	GTR could be used to regenerate periodontium in periodontally involved tooth
Masaji U <i>et al.</i> 1999 [59]	Beagle dogs	Implant touching the root of adjacent tooth	Premolar	Mandibular tooth	Uncoated and coated titanium implant (coated with HA)	3 months	HA coated samples displayed periodontium and calcified cementum like tissues	Bioactivity of implants influence cell differentiation
Choi <i>et al.</i> 2000 [37]	Dogs	Implant cultured with periodontal ligament cells		Mandibular tooth	Titanium implant with PDLSCs		Cementum and collagen fibres	Possible method for periodontal regeneration
Takata <i>et al.</i> 1995 [50]	Rat	Guided tissue regeneration by using occlusive membrane	Molars	Mandibular tooth	Synthetic block of HA	6-8 weeks	Cementum and collagen fibres	PDLSCs can form connective tissue attachment on denuded root surface and non-dental inorganic material like HA block
Nyman S <i>et al.</i> 1982 [49]	Monkeys	Guided tissue regeneration	Lateral incisors, canines	Maxillary and mandibular tooth	N/A	6 months	New cementum with inserting collagen fibers was observed	Periodontal ligament cells possess the ability to re-establish connective tissue attachment.
A Doğan <i>et al.</i> 2002 [51]	Dogs	Guided tissue regeneration	Premolars	Mandibular Tooth	N/A	42 days	Formation of new connective tissue attachment with cementum formation	Regeneration in furcation defects by cell-seeding technique may be useful
H. Lang <i>et al.</i> 1998 [70]	Mini pigs	Cultured cells with various membranes	Premolars and Molars	Maxillary and mandibular tooth	N/A	Assessed after 10, 30 and 90 days	Formation of cementum and alveolar bone leading to the development of new attachment were observed	Replantation of cultured cells leads to formation of new cementum and bone, which, in turn, leads to formation of new attachment.
Kawaguchi H <i>et al.</i> 2004 [69]	Beagle dogs	Auto transplantation of MSCs in defects			N/A	1 month	Regeneration of cementum, periodontal ligament and alveolar bone	Auto-transplantation of bone marrow mesenchymal stem cells is a novel option for periodontal tissue regeneration.
Aukhil I <i>et al.</i> 1986 [71]	Beagle dogs	Guided tissue regeneration	Canines	Mandibular tooth	N/A	3 months	New connective tissue attachment was seen	Root dentin contact may be necessary for progenitor cell differentiation into cells like cementoblasts.
Akira Miyashita <i>et al.</i> 2005 [68]	Rats	Implants placed in extraction sockets	Molars	Maxillary tooth	Titanium dental implant	21 and 28 days	Cementum and collagen fibres	Placing implant into socket with periodontal ligament leads to formation of new connective tissue attachment apparatus
Guarnieri R <i>et al.</i> 2002 [56]	Human	Implant touching the retained root tip	Canines	Mandibular tooth	Titanium dental implant	1 year	A continuous layer of cementum adhering to the implant and innumerable cementocytes	Further studies are warranted as only cemental layer without CT and blood vessels in the PDL space were formed

Parlar A <i>et al.</i> 2005 [67]	Mongrel dogs	Custom-made, titanium implant was placed into the center of hollowed root	Canines	Maxillary tooth	Titanium implant	4 months	Presence of connective tissue layer between implant and dentinal wall	Presence of periodontal tissue prevents osseointegration
Marei MK <i>et al.</i> 2009 [36]	Goat	Implant covered by scaffold with Bone marrow stem cells	Canines	Mandibular tooth	Titanium implant	10 days and 1 month	Periodontal-like tissue with newly formed bone	Undifferentiated mesenchymal stem cells can give rise to periodontium and its associated structures in vivo
Rinaldi JC <i>et al.</i> 2010 [60]	Rats	Implant touching the root of tooth	Molars	Mandibular tooth	Titanium-mini implant	21, 30, 45, 60, 90 and 120 days	Cementum-like layer in samples subjected to prolonged healing time	Cementogenesis occurs in area where there was a contact between periodontium and implant
Gault P <i>et al.</i> 2010 [61]	Dogs	PDL cells cultured with titanium pins			Titanium pins		Ligament tissues were demonstrated in dogs	Could be a possible method for PDL regeneration around implant
Lin Y <i>et al.</i> 2010 [39]	Rats	Implant covered by scaffold with rat periodontal derived MSCs	Molars	Maxillary tooth	Titanium implant	8,12 and 18 weeks	Collagen fibers oriented perpendicular to the cementum surface, resembling naturally formed PDL and Sharpey's fibres	PDL-derived MSCs could potentially be used to regenerate autologous PDL tissues on titanium implants in vivo
Takamitsu kano <i>et al.</i> 2012 [66]	Rats	Titanium placed in extraction socket with and without occlusion	Molars	Maxillary and mandibular tooth	HA coated and non coated titanium implants	Histological studies were carried out after 28 days	Periodontal ligament like tissue formed on the HA coated implants subjected to occlusal loading	Remnants of PDL and occlusal loads to the HA-coated implants may induce regeneration of PDL-like tissue in the peri-implant area
Buser D <i>et al.</i> 1990 [72]	Monkeys	Implant touching the retained root tip		Mandibular tooth	Titanium implant		Cementing layers with inserting collagen fibres	Possible method for periodontal regeneration around dental implant
Buser D <i>et al.</i> 1990 [57]	Monkeys	Implant touching the retained root tip		Mandibular tooth	Hollow cylindrical implants with titanium plasma-sprayed	1 year	Layer of cementum on the implant surface and periodontal ligament with collagen fibres perpendicularly oriented to the implant surface	Possible scope for regeneration of all components of the periodontal attachment apparatus
Caiazza S <i>et al.</i> 1991 [65]	Rabbit	Implant placed surgically in the alveolus		Mandibular tooth	Modified titanium implant with polymethylmethacrylate and dacron	3 months	Complete incorporation of dacron filamentous tissue	New experimental supporting element has mechanical behaviour similar to PDL
Takata <i>et al.</i> 1994 [64]	Cat	Implants placed in root cavities	Canines		Bioactive (HA,Bioglass),Bioinert (titanium alloy, Zirconium)		Connective tissue layer on bioactive surface of implants	Formation of new connective tissue attachment is influenced by bioactivity of the materials.
Adriano Piattelli <i>et al.</i> 1994 [62]	Landrace pig	Implants placed in healed sockets	Premolars	Mandible	Titanium implants	3 months	Formation of mineralized tissue with similarities to cementum and separated from the bone by periodontal-like tissue	Further studies are warranted
Fulan Wei <i>et al.</i> 2013 [63]	Swine	Implants placed in healed sockets	Not mentioned	Mandible	PDLSCs sheet wrapping the HA/Tricalcium Phosphate/ Dental Pulp Stem Cells	6 months	PDL-like tissues were generated parallel to the dentin-like matrix structure in the autologous group and allogenic group	Possible way to regenerate dentinal tubule-like and functional periodontal ligament-like structures. Further studies are warranted

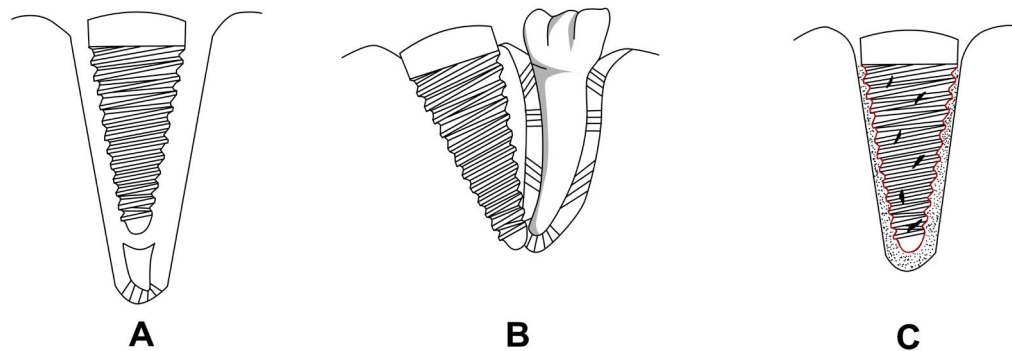


Figure 3. Various regenerative approaches of periodontium: **A-** Regeneration of periodontium with residual root tip, **B-** Regeneration of periodontium with implant touching the root of adjacent tooth, **C-** Regeneration of periodontium with cultured cells

could be regenerated when titanium implants are placed in alveolar sockets close to tooth buds [62]. Fulan Wei *et al.* reported that when periodontal ligament stem cells (PDLSCs) sheet was wrapped around hydroxyapatite/tricalcium phosphate (HA/TCP) with dental pulp stem cells (DPSCs) and are placed in extraction socket, they give rise to periodontal ligament like tissue when examined histologically [63].

Takata *et al.* believed that bioactive materials such as HA and bioglass are better suited for regeneration of periodontium when compared to bioinert material like titanium [64]. Studies showed that implant made of titanium, poly(methylmethacrylate) and dacron implanted into alveolus of rabbit could give rise to attachment apparatus whose mechanical behaviour was comparable to periodontal ligament [65]. Authors found that periodontal ligament (PDL) like tissues could be induced on HA coated titanium dental implants when subjected to occlusal load in rats [66]. Reports suggests that placing custom-made, titanium implant in hollowed roots with narrow slits, give rise to growth of periodontium like tissue onto it [67].

Studies demonstrates that when titanium implants were placed in immediate extraction socket in rats, cementum and periodontal like fibres were formed with adequate mechanical strength [68]. Reports suggest that when stem cells were placed in alveolar bone defects there was a possibility of regeneration of periodontal tissues [69]. Study also demonstrates that replantation of cultured alveolar bone cells leads to formation of new cementum and bone, which, in turn leads to formation of new attachment [70].

Periodontium and proprioception

Proprioception is a type of sensory function of periodontium [73]. Proprioception, also called kinesthesia, “involves awareness of the spatial and mechanical status of the musculoskeletal framework” [74]. The afferent nerve fibres (component of peripheral nervous system) concerned with proprioception are broadly classified morphologically as free, naked and non-encapsulated endings. The free nerve endings are further classified as simple (e.g. skin), elaborate (e.g. golgi tendon organ) and more elaborate (e.g. muscle spindle) nerve endings [75]. Functionally, they are divided into exteroceptors (receives stimuli from external origin mainly light pressure and touch), interoceptors (receives stimuli from visceral origin), proprioceptors (receives stimuli from joints, tendons, skeletal muscles, body wall etc.) [75].

Upon histological examination, PDL displayed two types of nerve fibres; thick fibres with spindle like endings in the periphery, probably concerned with tactile and pressure sensation and fine nerve fibres in the deeper region possibly relaying pain sensation [76]. The same

authors in another article discussed about the end organs found in the PDL of cats which were “spindle like in shape and were formed by nerve fibres twisted like a spiral spring. At intervals on the convolutions there were rounded thickenings” [77]. Reports also suggest that in guinea pigs upper two-third of the root contains fine nerve endings for pain sensations while lower third consists of nerve fibres ending in club-like fashion probably concerned with pressure and tactile sensation [78]. Allgood suggested three types of PDL receptors- (1) pressoreceptors related to consciousness (2) pressoreceptors unrelated to consciousness and (3) nociceptors [79]. It was also claimed that mechanoreceptors in periodontium are mainly two types of nerve endings which relay precise information to CNS regarding pressure [80]. Further, it was found that majority of nerves that relay pain are located in the pulp and those conduct pressure sensation are present in periodontal membrane [81]. Studies have shown that periodontal sensory units fire upon mechanical stimulation [82,83] suggesting that they are responsive to tactile or pressure stimuli [81,84]. Authors further suggests that the impulses were originated purely from periodontal ligament because registration of the impulse continued even after removal of dental pulp [81,85].

Recent studies have revealed that the Ruffini endings categorized as low-threshold, slowly adapting, type II mechanoreceptors are the primary mechanoreceptors in the periodontal ligament [86]. In the periodontal ligament Ruffini endings, the axon terminals have finger like projections called microspikes or axonal spikes, which invest into the surrounding tissue to detect the deformation of collagen fibres.[86]

The terminology that has been used in discussing mechanoreceptors has varied among authors. Freeman and Wyke distilled a number of reports and condensed the mechanoreceptors present in joints into four types [87] Table 3.

Type II and Type III mechanoreceptors in particular are believed to be linked to one’s sense of proprioception [89]. Very small forces applied to the tooth is registered and identified by the receptors present in the periodontium. Studies have shown that inserting very thin metal foil (10-30µm) during occlusion can be identified accurately. Micromotion of the tooth as low as in the range of 1-3 microns activates mechanoreceptors. Furthermore, if a particle of unregistered or unknown consistency is detected during mastication, the mandibular chewing movement is arrested reflexively. Later, temporomandibular joint (TMJ), masticatory muscles, etc. alters the mandibular chewing movement into mandibular opening movement [90] Figure 4.

Mechanoreceptors richly innervates the periodontium and their soma are located either in Trigeminal ganglion (TG) or in Mesencephalic

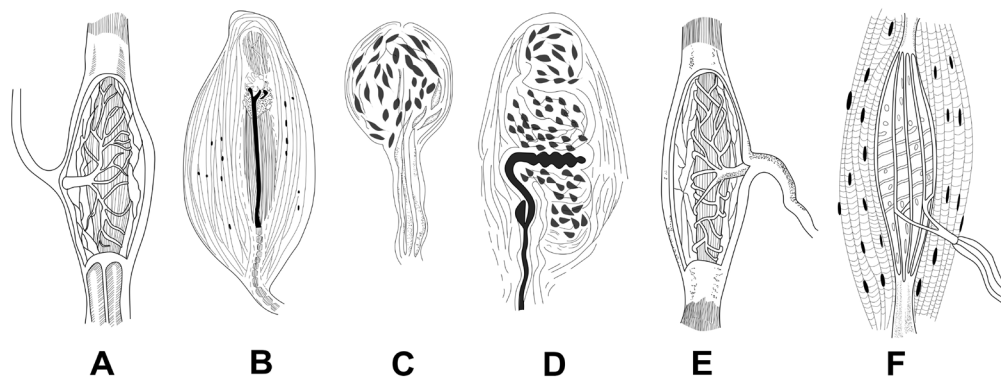


Figure 4. Sensory receptors: A- Golgi tendon organ, B- Corpuscle of Pacini, C-End bulb of Krause, D- Meissner corpuscles, E- Corpuscle of Ruffini, F-Muscle spindle, (adapted from [88]).

Table 3. Various feature of mechanoreceptors is listed in the table below, (adapted from [87]).

<i>Eponymous name</i>	<i>Type</i>	<i>Morphology</i>	<i>Location</i>	<i>Diameter of afferent fibres(microns)</i>	<i>Average size(microns)</i>	<i>Figures</i>
Ruffini, Golgi-Mazzoni	I	Globular, bulbous or ovoid corpuscle with thin capsule	Periosteum joint capsule, tendons ligaments,	5-8	100 X 40	E, B
Pacini, Krause, Vater-Pacini	II	Cylindrical or conical corpuscle with thick concentric laminated layers	Joint capsule	8-12	280 X 120	B, C, B
Golgi, Golgi-Mazzoni	III	Fusiform corpuscle with thin capsule	Ligaments, tendons	13-17	600 X 100	A, B
Not- reported	IV	Unmyelinated free nerve endings	Ligaments, tendons, blood vessels joint capsule, periosteum	0.5-5	0.5-1.5	-

(MS) trigeminal nucleus of central nervous system (CNS). TG and MS are different in central connections, functional significance and threshold levels but are similar in detecting stretch of periodontal ligament induced by micro or macromotion of tooth [91]. Studies have shown different distribution of MS and TG receptors in PDL of cat. Distribution of mechanoreceptors were found to be homogeneous and heterogeneous in the middle and apical portion of cat's tooth with their soma in TG and MS respectively [92]. Authors agreed by and large that periodontal ligament have two types of mechanoreceptors, rapidly adapting and slowly adapting. Some authors claimed that the third type of mechoreceptors viz. with spontaneously discharging and slowly adapting capability could be credited in part to cutting the sympathetic efferents [93]. It was claimed that surrounding peripheral tissues are loosely fit to rapidly adapting receptors resulting in easy gliding of tissues when forces applied. They are known to conduct signals from initial contact with food or antagonistic teeth. While slowly adapting receptors are firmly integrated to the surrounding tissues and are known for localizing of tooth being stimulated, direction of stimulus, intensity and pressure applied to tooth etc. Interestingly, when forces just above threshold are applied to slowly adapting receptors, they behaves like rapidly adapting receptors.

In another study, inferior alveolar nerve from nine cats were used for studying 127 periodontal mechanoreceptors (PDM). 105 PDM were found to be responded to both phasic and sustained component of force applied to crown and are classified under slowly adapting PDM. 22 PDM responded while the force is applied but did not fire during a sustained force and were classified as rapidly adapting PDM. Of these 127 PDM, 7 were rapidly adapting receptors and were near to the fulcrum than to apex, apical 3rd of the ligament contains 23 slowly adapting receptors and 30 were found to be located in the labial part of

the PDL [93]. Transmission of tactile sensation, pressure and pain are supplied by sensory fibres of periodontium via the trigeminal pathway into their trophic centre in trigeminal ganglion. Proprioceptive nerves have their tropic centre placed centrally i.e. in mesencephalic nucleus of CNS. Nerve bundles follows the porous alveolar bone and blood vessels, pass into the PDL from the peri-apical area and are divided into single myelinated fibres which loses their myelin sheath and ends in neural terminals.

Osseoperception and dental implants

Different author claims that endosseous titanium dental implants give rise to a form of "weak alternate sensation" when they are subjected to mechanical stimulation which they termed as osseoperception. Proprioception and osseoperception are different entity as in later no periodontal mechanoreceptors are involved. We now introduce the concept of osseoperception briefly.

Dental caries and periodontal diseases are among the primary cause of tooth decay, which is followed by extraction for preparation of prosthetic treatment [94]. Loss and damage of a large number of exteroceptors occurs during tooth extraction leading to impaired sensory perception and feedback, which tune the motor control for proprioception of stomatognathic system including mandibular movements [95]. The level of evidence indicate that dental implants are among the best option for treating edentulous conditions and prevents its associated complications [96]. However, patients with osseointegrated implants supported prosthesis displayed impairment of fine motor control of the mandible because of loss of afferent impulse from mechanoreceptors present in the PDL. Surprisingly, mechanical stimulus of osseointegrated implants in the jaw bone still elicits response [95,97-104]. Amputation of tooth along with intra-

dental and periodontal mechanoreceptors changes the sensory-motor coordination and results in faulty occlusal forces in masticatory system. Osseointegrated dental implants lack periodontal mechanoreceptors in peri-implant tissue which conducts tactile sensory input to the central nervous system (CNS), and are thought to play a key role in sensory discriminative capabilities and in the control of jaw functions in dentate individual [100].

Complete edentulous jaw restored with full denture demonstrates only partial function and hence is a compromised substitute when compared to implant supported prosthesis which have improved sensitivity directionally with better oral stereognosis [100,105]. Furthermore, evidence suggests that patients with implant supported prostheses displayed enhanced tactile discriminative capabilities and improved motor co-ordination compared to those who wore complete dentures. The detection of these unknown receptors responsible for this alternate “bony-perception” could probably be done by using somatosensory evoked potentials [101].

In a recent conference this alternate sensation named as ‘osseoperception’ was defined as “a change in central neural processing in maintaining sensorimotor function” [106]. Klineberg *et al.* also defined it as “the sensation arising from a mechanical stimulation of bone anchored prosthesis, transduced by mechanoreceptors that may include those located in muscle, joint, mucosal and periosteal tissues” [106]. Jacobs *et al.* stated that “clinical observations on patients with oral implants, have confirmed a special sensory perception skill. The underlying mechanism of this so-called ‘osseoperception’ phenomenon remains a matter of debate, because extraction of teeth involves elimination of the extremely sensitive periodontal ligaments while functional reinnervation around implants is still uncertain.” [99]. This findings may be attributed to the presence of some alternate peripheral feedback pathways to the sensory cortex coupled with receptors present in the periosteum/bone and has been termed as ‘osseoperception’ described for both skeletal and dental osseointegrated implants [95]. The term ‘Osseoperception’ is defined by Yan C *et al.* as “the ability to identify kinesthetic sensation without the input from periodontal mechanoreceptors. This sensation is generated from the temporomandibular joint, masticatory muscle,

mucosa, and periosteum, and provides sensory and motor information related to mandibular movements and occlusion” [107]. Klineberg defined osseoperception as “depending on central influences from corollary discharge from cortico-motor commands to jaw muscles, and contributions from peripheral mechanoreceptors in orofacial and temporomandibular tissues”[100].

Sensory discrimination in the orofacial region are of two types-passive discrimination and active discrimination. Periodontal mechanoreceptors determines passive discrimination and assessed by the application of definite and guided forces onto tooth surface. Active discrimination involves a number of mechanoreceptors present in the tooth, periodontium, jaw muscles, temporomandibular joints capsules and ligaments. It could be assessed by placing objects between the teeth. Both of these are age dependent and gradually decreases with increasing age [108-111]. Tests have revealed that passive discriminatory abilities are 10x higher in osseointegrated implants than that of natural teeth. (3.4 N and 0.3 N, respectively). Jacobs and van Steenberghe in 1993 reported that the osseointegrated implant threshold to be 50x higher than that of natural teeth [109]. Awareness of static and dynamic jaw position and forces for contraction of jaw muscles includes oral kinaesthetic and proprioceptive sensations.

It had been claimed that there are mainly two mechanism used by CNS for obtaining information regarding the position and movements of jaw and muscle contractions. The first is probably an input from Golgi tendon organs (GTOs) along with corollary discharge associated with jaw closing muscles is thought to be important in the sensation of voluntary biting. The second mechanism involves mechanoreceptors activated during different jaw movements. The input gives information about oral kinesthetics in relation to various jaw function and different contacts of opposing artificial tooth. These receptors are located in temporomandibular joint (TMJ), muscle, cutaneous, mucosal, and/or periosteum and provides mechanosensory information. It has also been claimed that although remnants of PDL mechanoreceptors are present in the peri-implant area, they do not contribute to osseoperception [100]. Presently, we have very little understanding of the neural inputs and pathways describing kinaesthetic perception in patients with implants (Table 4 and 5).

Table 4: Various theories of osseoperception.

Author	Year	Theory
Linden and Scott. [92]	1989	Suggests that periodontal receptors remains in the bone even after tooth extraction contributing to osseoperception
Bonte B <i>et al.</i> [112]	1993	Proposes that neural fibres reinnervates when implants are subjected to control loading leading to osseoperception
Klineberg I, Murray G. [100]	1999	Temporomandibular joint receptors take up the function in absence of periodontal receptors and performs osseoperception
Van Steenberghe D <i>et al.</i> [99]	2006	Periosteal receptors take up the function in absence of periodontal receptors and performs osseoperception
Weiner S <i>et al.</i> [113]	2004	Adjacent bone surrounding the implant contains nerve fibres which contributes to osseoperception
Rowe <i>et al.</i> [114]	2005	Pacinian corpuscles may act as osseoreceptors located in the periosteum but further studies are warranted.

Table 5: Contribution of various mechanoreceptors in osseoperception of jaw.

Type of mechanoreceptors	Anatomical location	Specifications	Functions
(1) Joint mechanoreceptors [115-117]	Joints like Temporomandibular joints and others	Low threshold (high-sensitive) mechanoreceptors	Joint receptors in TMJ acts as limited range receptors, others concerned with protective reflex
(2) Muscle mechanoreceptors [116,118-120] (a) Golgi Tendon Organs (GTO) (b) Muscle spindles	(a) Musculo-tendinous junction, arranged in series with extrafusal muscle fibres. (b) Belly of all skeletal muscles and arranged in parallel with extrafusal muscle fibres.	(a) High and low threshold mechanoreceptors. (b) Low threshold (high – sensitive) mechanoreceptors	(a) Senses pulling of muscle fibres (b) Provides information to CNS regarding length of muscle and rate of change of muscle length etc.
(3) Cutaneous mechanoreceptors. [121-125]	Skin (Hairy and glabrous)	Rapidly adapting and slowly adapting (type I and type II) mechanoreceptors	Relay information of kinaesthetic perception and skin deformation
(4) Mucosal mechanoreceptors [110,126]	Mucosal lining	Low threshold (high – sensitive)	Contributes to mucosal sensation
(5) Periosteal mechanoreceptors [83]	Periosteum	Low threshold (high sensitive)	Role in sensing periosteal deformation

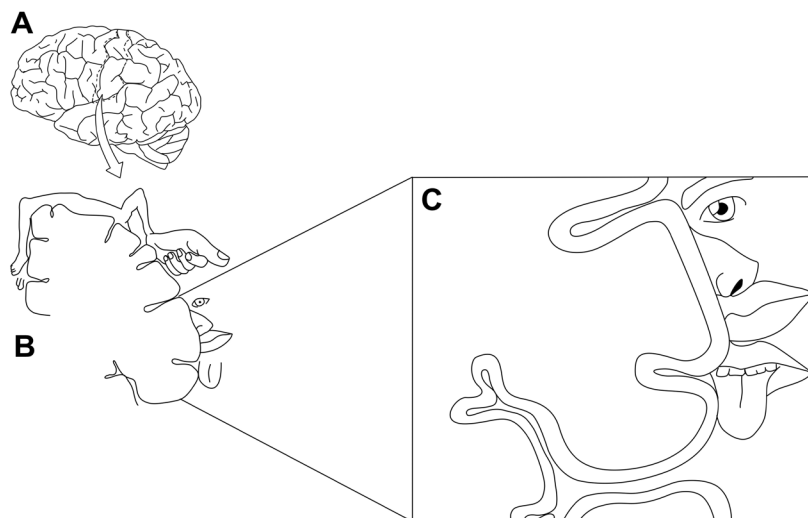


Figure 5. A- Primary somatosensory cortex , B- Sensory homunculus , C- Representation of oro-dento-facial region in sensory homunculus, (adapted from [128, 130]).

Oral sensations and somatosensory cortices

The sensory fibres originate from ophthalmic, maxillary and mandibular division of trigeminal nerve and insert into trigeminal ganglion present in the middle cranial fossa. The fibres later end at thalamus and cortex passing via trigeminal nuclei present at the level of pons in the brain stem [127]. All sensory inputs from these fibres are integrated and processed in somatosensory cortex which could be primary (S1) present in the lateral postcentral gyrus of parietal lobe in human brain or secondary (S2) present in upper part of sylvian fissure [128,129]

Representation of orofacial somatosensory inputs in Central Nervous System (CNS)

In 1937, Penfield and Boldrey published a paper comprising a physical representation of different anatomical parts in the human brain [130]. They named the map as cortical homunculus. There are two types of cortical homunculus; sensory and motor [128,130]. In this review we will be discussing very briefly about sensory homunculus; specifically the area which represents oro-dento-facial inputs (Figure 5).

It had been claimed by Penfield and others that cortical representation of the tooth was located superior to that of the tongue and inferior to that of the lip in somatosensory cortex [128,130]. Miyamoto et al. in 2006 studied the human brain by using fMRI and concluded that the teeth were represented in between the tongue (above) and lip (below) [131]; which was in accordance with the sensory homunculus proposed by Penfield. However, there was an overlap in the middle and caudal regions in postcentral gyrus. This change in response from the cranial to caudal region could probably be due to integration of various oral tissues [131]. Further it is believed that primary somatosensory cortex (S1) comprises of Brodmann's areas 1, 2, 3a and 3b [132,133]. Brodmann's area 1 occupies the top part of postcentral gyrus. The cranial border of the Brodmann's area 3a is in the nadir of the central sulcus, followed by 3b, 1 and 2 which ends in the nadir of post central sulcus respectively [132,133]. Area 1 and 3b receives primarily cutaneous afferents, and areas 2 and 3a receives more deep and proprioceptive inputs [133]. Secondary somatosensory cortex (SII) is believed to perform higher order functions including multisensory integration, memory, attention and learning [134]. Although advanced neuroimaging in humans for high resolution cortical somatosensory

mapping is possible, it is difficult to provide stimulation in precise and controlled manner on specific oral tissues in functional magnetic resonance imaging (fMRI) environment [135].

Studies (although limited) have reported that CNS has got extensive representation of orofacial inputs like muscle GTO present in TMJ, periodontal mechanoreceptors, mucosal mechanoreceptors and have been demonstrated at various level of afferent somatosensory pathway including primary somatosensory cortex (S1) etc. [124,136-138]. It had been suggested that these inputs could be used in muscle coordination for deglutition and chewing [139], precise control of facial and mandibular movements [140], reflexes [116] perceptual functions of oral kinaesthesia, oral stereognosis and tactile perception. [141,142]. Reports claimed that contribution of an elaborate cortical representation of cutaneous, mucosal, periosteal and deep somatosensory afferent can provide perceptual experiences associated with kinaesthetic sensibilities even in absence of PDL mechanoreceptors [100].

Information from mechanoreceptors are transmitted through somatosensory afferent pathways with high synaptic security and is represented in ventroposterolateral (VPL) thalamus and somatosensory cortex. Hence, in the absence of periodontal input, there is the possibility for adequate somatosensory information within the orofacial area, leading to kinesthetic and tactile perception and motor control of jaw and orofacial structures [143]. Reports suggest that specific somatosensory information is allowed to be transmitted to the cortex and hence leads to selective filtration of somatosensory stimuli [144]. Different types of stimuli are registered from dentate, implant supported and complete denture restored patients. The brain registers somatosensory input from implant supported prosthesis that will be different from that occurring from dentate individuals or from complete denture restored patients. It is believed that areas in somatosensory cortex in brain concentrate in these new specific sensory inputs and evolves to this new intra-oral environment [145].

Findings suggest that recent habits modify the details of representation of body surface in somatosensory cortical areas [146,147]. It has also been suggested by various studies that implants induces plastic changes in the somatotopic maps in the face motor and somatosensory cortical regions. These plastic behaviour tends to accommodate the new prosthesis in optimal functional status depending on oro-dental features and treatment standard [100].

Detection and measurement methods for afferent activity of oral cavity

The methods are broadly divided into neurophysiological and psychophysical methods.

Neurophysiological methods

Neurophysiological methods like trigeminal somatosensory evoked potentials (TSEPs), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), functional near-infrared spectroscopy (fNIR or fNIRS) could be used for detection of oral tactile sense perceptions.

Trigeminal somatosensory evoked potentials (TSEPs)

Trigeminal somatosensory evoked potentials (TSEPs), a non-invasive technique is used for registering electroencephalographic signals involving trigeminal nerve. Because of low amplitude signal and high amount of electrical signal, averaging improves noise to signal ratio. Results may be misrepresented due to high muscle activity and salivation in orofacial region [148]. TSEPs can be induced placing electrodes in intradental or intrapulpal, [149] periodontal ligament, [150] gingiva [151] and lower lip [152].

Functional magnetic resonance imaging, (fMRI) or microneurography

Functional magnetic resonance imaging (fMRI) is a noninvasive and safe technique for visualization of the activation of brain during cognitive tasks. The method depends on measurement of Blood Oxygen Level Dependent (BOLD) signal. By hemodynamic response, blood flows to active neurons at greater rate than inactive neurons and are thus visualized.

Recently, study demonstrated that osseointegrated maxillary implants upon mechanical stimulation activates cortical somatosensory areas which may possibly provide the explanation of osseoperception. The group inferred that dental implant substituting a natural tooth induces plasticity in CNS as represented by the difference in cortical network when stimulating either the implant or natural tooth precisely at same anatomical location [104]. Hence, a hypothetical representation of the prosthesis in the cerebral cortex is established leading to enhanced adaptation to motoneuron pool for trying to compensate for natural physiological function. The inhibitory reflex of masseter muscle in partially edentulous jaw is elicited in implant supported prosthesis with elevated threshold responses when subjected to mechanical stimuli. However, this "silent period" was not seen in fully edentulous patients. The probable reason for this could be the activation of distant neural receptors present in other tooth [153-156].

Magnetoencephalography (MEG)

Magnetoencephalography (MEG) non-invasively measures the magnetic field generated due to the excitatory postsynaptic electrical activity of neurons in the living brain by using highly sensitive superconducting sensors viz. superconducting quantum interference device (SQUID). A magnetically shielded room houses the equipment, and diminish the interferences. Nakahara et al. using MEG showed S1 represented separate cortical areas for lips and tongue, with no clear separate area for gingiva [157]. Kubo et al. used electrical stimulation on tooth pulp and recorded the results with MEG [158]. MEG was also used by Bessho et al. for studying three separate areas in hard palate [159] etc.

Functional near-infrared spectroscopy (fNIR or fNIRS)

Functional near-infrared spectroscopy (fNIR or fNIRS) is a non-invasive method for quantification of chromophore concentration in tissues mainly the chromophore haemoglobin (Hb) present in microcirculation (vessels < 1mm in diameter) in the brain. Deoxy-Hb and Oxy-Hb displays differences in absorption spectra which results in the measurement of relative changes in haemoglobin concentration. The cerebral blood flow was studied by Shimazaki et al. by using fNIR [160]. He used vibrotactile stimulation for various teeth and found out that apart from stronger response of molars compared to other tooth, the spatial resolution was insufficient for arriving at a conclusion Table 6.

Psychophysical evaluation

Psychophysical evaluation includes the study of sensation/perception and their respective influence when subjected to physical stimuli. Methods chiefly include threshold measurement, ideal observer analysis, and signal detection theory. For threshold level test, subjects are instructed to identify the pure stimulus from background noise [164]. Test are also carried out to verify if the threshold is active or passive. In passive threshold test, stimulation are passively applied onto the tooth surface or implant to stimulate mechanoreceptors present in periodontium or periosteum respectively [165]. In active threshold measurement, objects of different size are placed between antagonistic teeth or implants and participants are asked to manipulate those objects and report their sensations [166]. In this process, the tactile function of various mechanoreceptors from periosteum, mucosa, skin, muscle and periodontium (in case teeth is present) could be studied [142]. In humans passive threshold and active threshold is 60x and 6x higher for dental implants than natural teeth [110]. It has also been reported that one staged mandibular implants exhibited unchanged threshold during the healing phase in contrast to immediately loaded implants that showed enhanced passive tactile sensibility [167,168].

Stereognosis

Stereognosis (haptic perception or tactile gnosis) is the ability to identify and discriminate various forms. It depends upon memory and intact somatic sensory system. Both, central analysis and peripheral receptors are involved [169]. It is seen to be developed best in blind people. Oral sensory function changes with loss of tooth. It was found in dentate individuals that stereognostic ability decreases approximately 20% when bilateral mandibular block is given [170]. Further, natural teeth showed better stereognostic ability than patient with full denture [169,170]. Lundqvist reported patients, that were rehabilitated with oral implants showed improvement with stereognostic ability [166]. Stereognosis represents an overall sensor ability rather than identifying any particular group of mechanoreceptors.

Conclusion

Dental implants with functional periodontium is a distinct possibility in near future, as can be inferred from the extensive work reviewed in this paper. Other options like implanting tooth bud into jaw bone which later give rise to functional tooth has been explored but proper morphology of tooth and its occlusion etc. remains a massive challenge. Presently, it seems that modification of titanium dental implants having proprioception is the closest possible alternative to natural tooth, however to achieve this, inputs from implantology, neural sciences to biomaterials along with better design of the implants are warranted.

Table 6. Various studies upon stimulation of oral tissues by employing various neuroimaging techniques are listed in the table below.

Author and year	Region	Type of stimulation	Imaging/Detection modalities	Cortical projection/Analysis
Nakahara <i>et al.</i> (2004) [157]	Gingiva, lip and gum	Electrical stimulation	MEG	S1 showed separate cortical areas for lip and tongue, no separate area for gum
Miyamoto <i>et al.</i> (2006) [131]	Lips, tongue and teeth	Mechanical stimulation	fMRI	Postcentral gyrus showed two gradient. From primary towards higher processing a cranio-caudal gradient was followed.
Raab WH <i>et al.</i> (1991) [151]	Tooth	Mechanical stimuli	EEG	Interpretation of SEP-PA revealed change in perception following repeated periodontal stimulation at different rates.
Bessho <i>et al.</i> , (2007) [159]	Hard palate (3 regions)	Electrical stimulation	MEG	Merged region in S1
Kubo <i>et al.</i> (2008) [158]	Tooth pulp	Electrical stimulation	MEG	Specific region in S1
Chatrian GE (1982) [149]	Tooth	Electrical pulse	Questionnaires	Pulp can relay other sensations apart from nociception
Ettlin <i>et al.</i> (2004) [161]	Teeth	Vibration	fMRI	Activation of motor and insula bilaterally. No significant activation of S1
MH Bennett <i>et al.</i> 1980 [151]	Gum	Electrical stimulation	Triphasic wave	Muscle potentials did not significantly contribute to the characteristic response.
Jantsch <i>et al.</i> (2005) [162]	Teeth and hand	Mechanical stimulation	fMRI	S1 is activated bilaterally for tooth and contralaterally for hand respectively.
Barker GR <i>et al.</i> (1980) [152]	Lip overlying the 1 st premolar/ adjacent gingival margin	Electrical stimulation	Triphasic wave	Increase in latency period was associated with sensory impairment
Guest <i>et al.</i> (2007) [163]	Oral cavity	Thermal stimulation	fMRI	Bilateral activation of the somatosensory cortex
Shimazaki <i>et al.</i> (2012) [160]	Teeth	Vibrotactile stimulation	fNIR	Insufficient spatial resolution to reach a definite conclusion
Habre-Hallage <i>et al.</i> (2012) [104]	Teeth, endosseous implant	Mechanical stimulation	fMRI	Bilateral activation of S1 and S2

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Conflict of interest

The authors declare that they have no conflict of interest.

Foot note

1 Bellare Jayesh, Das Siddhartha and Soni Vivek P, Application for "Proprioceptive endosseous root-form dental implants," Indian Patent applied on March 9th, 2017.

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