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Review article

Periodontio Integrated Implants

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INTRODUCTION

The periodontal ligament is composed of a complex vascular and highly cellular connetive tissue that surrounds the tooth root and connects it to the inner wall of the alveolar bone. [1] Apart from its physical, formative and remodelling, nutritional, and sensory functions, the periodontal ligament also provides progenitor cells for alveolar bone formation and remodelling which plays the role of periodontium in the alveolar socket that faces the root of the tooth. [2, 3, 4, 5]

The periodontal ligament attaches to cementum and the alveolar bone and primarily consisting of collagen fibres, fibroblast, cementoblasts, osteoblasts, osteoclasts and their progenitors. The ends of PDL fibres are embedded in cementum and the alveolar bone called as the Sharpey's fibres and they are directed perpendicular to the tooth surface. This type of arrangement maintains the structural integrity of the PDL and also enables the distribution of masticatory forces onto the alveolar bone. [6]

Regeneration of lost periodontium can be done by the periodontal therapy especially in cases of severe destruction where attachment to tooth has been lost. Regeneration of periodontal ligament fibres and insertion of same into the root surface leads to formation of new attachment. The same concept of PDL regeneration has been carried out for replacement of lost tooth on the surface of dental implants.

Periodontal ligament having regenerative capacity and thus this concept is used to formulate tissue engineered periodontal ligament cells on the implant surface thus mimicking the natural tooth. This forms the new emerging era in the field of dentistry with implant and periodontal ligament together known as ligaplant. [7, 8]

HISTORICAL BACKGROUND

A lot of research and several experiments have been carried out to develop periodontal ligament around an implant, i.e., for the creation of a bio-root, which would provide ideal conditions for the implant-supported treatments in future. [9,10]

Nyman et al. [11] in 1982 suggested that the cells of the periodontal ligament possess the ability to re-establish connective tissue attachment. Nunez et al. [12] (2012) have further validated the regenerative potential of periodontal ligament-derived cells in a proof of principle study.

A study was conducted by Buseretal in 1990, in which he found that the periodontal ligament cells could be a source of regeneration as they have the ability to cover the surface of dental implants during healing period.

Several in vivo experiments have demonstrated the formation of cementum-like tissue with an intervening periodontal ligament, when the dental implants were placed in proximity to tooth roots by Buser et al.(1900), Caiazza et al. (1991), Warrier et al (1993). The mechanism of this phenomenon appeared to be due to the migration of cementoblast and periodontal ligament fibroblast precursor cells towards dental implants due to contact or proximity of the tooth-related cell populations to those implants. [13]

The potential for the clinical implementation of customized periodontal biomimetic hybrid scaffolds for engineering human tooth-ligament interfaces has been demonstrated by Park et al. [14] There is indeed a growing body of evidence validating the significant potential of the in vivo formation of ligamentous attachments to the biomaterials.

Piatelli et al. 1994 evaluated the potential of different cells of the forming tooth bud to induce formation of dental hard tissues and PDL around titanium implants and showed it is positive result.

Takata et al.,[15] in 1994 in an animal study examined whether connective tissue attachment could occur on implant materials by repopulating periodontal ligament derived cells and found that while new connective tissue attachment occurred on bioactive materials such as bioglass and hydroxyapatite, little or no cementum deposition was seen on bioinert materials such as titanium alloy and partially stabilized zirconium, i.e., the formation of new connective tissue attachment was influenced

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by bioactivity of the materials. Choi,(2000) [16] placed implants with the cultured autologous periodontal ligament cells in the mandibles of the dogs and histologically revealed that after 3 months of healing, a layer of cementum-like tissue with inserting collagen fibers had been achieved on some implant surfaces, demonstrating that cultured periodontal ligament cells can form tissue resembling a true periodontal ligament around implants.[10]

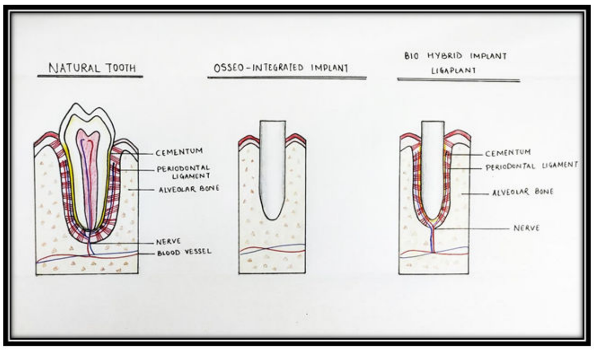
OSSEOINTEGRATED IMPLANTS VERSUS PERIODONTIO-INTEGRATED IMPLANTS

Localized osseointegrated represent a clinical challenge.[17]Excessive stress accumulating at the crestal region of the implants leads to bone loss at this region. [18] This concentration of stresses at the crestal region is mainly attributed to the lack of the periodontal ligament, which is essential for distributing the forces throughout the length of the root. Periodontal ligament additionally dissipates these forces through the compression and redistribution of its fluid elements, as well as through its fiber system and hence provides shock absorption and cushioning effect to the teeth in response to these forces.[19] Furthermore, the periodontal ligament has a sensitive proprioceptive mechanism and is therefore capable of detecting and responding to a wide range of forces applied to the teeth. When these forces are transmitted through the periodontal ligament, they result in the remodelling of the alveolar bone to allow tooth movements (as seen in orthodontics) or in the widening of the periodontal ligament space leading to an increase in tooth mobility in response to excessive forces (e.g., occlusal trauma).[20] The osseointegrated dental implants on the other hand, physiologically differ from natural teeth as they lack periodontal ligament support and hence when loaded mechanically, evoke a peculiar sensation, which has been termed as osseoperception.[10, 21]

Patients with osseointegrated implants will subjectively feel tangible sensation only when a force greater than that required to evoke sensation in natural teeth is applied. Hence, one of the reasons for the diminished ability of dental implants to adapt to occlusal trauma can be attributed to this lack of periodontal proprioceptive mechanism, which results in microfractures of the crestal bone and ultimately leads to bone loss.

Moreover, connecting teeth to osseointegrated implants presents a biomechanical challenge due to the differential support and mobility provided by the implant and the tooth and consequently have also shown a higher rate of failures and complications. [22] However, when tooth-implant supported restorations would be fabricated using support from periodontio-integrated implants higher success rates can be expected due to similar resilience of tissues supporting teeth and implants.

Figure1: Diagram showing difference between natural tooth, osseo-integrated implant and ligaplant.



PROCEDURE TO OBTAIN THE LIGAPLANT

Temperature-responsive culture dishes preparation

Polystyrene culture dishes were spread with N-isopropylacylamide monomer in 2-propanaol solution. Then these dishes were then subjected to electron beam irradiation with an Area Beam Electron Processing System. These temperature-responsive polymer-grafted (N isopropylacrylamide) dishes were subjected to cold water and rinsed to remove ungrafted monomer and sterilized with ethylene oxide. [2]

Cells isolation and cell culture

An extracted tooth is taken as the source of human periodontal cells and is isolate from the same.Periodontal tissue is scraped from the middle third of the root after extraction,with a scalpel blade. The harvested tissue is placed into culture dishes containing = Dulbecco's modified Eagle's minimal essential medium, supplemented with 10% fetal bovine serum and 100units/mL of penicillinstreptomycin.These outgrowth cells are then cultured in a humidified atmosphere of 5% CO_2 at 37°C for 48 hours which will allow attachment of the cells to the dishes. The dishes are washed to eliminate debris and the medium is changed at intervals of three times a week. For the harvestation of the cell sheet, human periodontal ligament cells are plated on temperature- responsive culture dishes(35 mm in diameter) at a cell density of $1x10^5$ and cultured at 37°C supplemented with 50mg/mL ascorbic acid 2-phosphate, 10nM dexamethasone and 10nM β-glycerophosphate that function as an osteo-differentiation medium. [2, 23]

Culture of PDL cells in a Bioreactor

Hydroxyappatite (HAP) coated titanium pin was placed in a hollow plastic cylinder leaving a gap of 3mm around the pin. Culture medium was continuously pumped through the gap. Single cells suspension (periodontal ligament cell suspension), obtained from human, are seeded first into plastic vessels under a flow of growth medium for a duration of 18 days. [2,23]

PRECAUTIONS WHILE PREPARING LIGAPLANT

Proper sterilization protocols must be maintained throughout the procedure. [7, 24]

Proper culturing and cell growth is necessary; otherwise it may to the formation of non- periodontal ligament cell types.

PDL formation is favoured by a cushion of appropriate thickness, but on the other hand, the prolonged cell culturing may favour the appearance of non-PDL type of cells. The bioreactor has been constructed with the aim to resemble the PDL situation during cell growth in order to preserve the cell differentiation state and to obtain adequate cell stimulation. [25]

Micromechanical movements of the growth medium are necessary for firm attachment of the cells to the implant. [7]

Cells are placed and positioned into a narrow space between the ligaplant and surrounding hollow cylinder. It is thereby expected that the phenotype of PDL is favoured by a tight attachment of cells to the implant. Thus, minute mechanical movements of the medium flow should be present in the preparation of ligaplants and space present in between the implants and the culture should be optimal. [25]

Adequate duration of surface treatment must be maintained for the success of the ligaplant which will bring big improvements to the implant system. [2]

ADVANTAGES

- Ligaplants have the advantage of mimicking the anatomy of natural teeth which has periodontal ligament around it along with the alveolar process. [26]
- Ligaplants become firmly integrated without interlocking and without direct bone contacts, despite the initial fitting being loose in order to spare the PDL cell cushion. Bone formation was induced and movements of ligaplants inside the bone suggesting an intact tissue communication between bone and the implant surface. [2, 25]
- Ligaplants can alleviate problems with implant usually faces such as infrabony defects, gingival recession of the missing tooth site. Thus it is possible to be applicable in periodontal bony defects, where conventional implants could not be installed.
- In cases leading to peri-implantis, amount of bone loss is reduced.

DISADVANTAGES

- It's a technique sensitive procedure. Hence, proper care must be taken.
- High cost. It is known to be costly procedure because of limited facilities and members to perform this research. [25]
- Host acceptance of the implant or PDL growth in the socket cannot be predicted. It may also lead to failure of implant by the host. [27]
- One should be cautious while culturing the ligaplants about the proper maintenance of temperature, duration of culture etc. All of these make it a cumbersome procedure. [26]

RECENT STUDIES ON LIGAPLANTS

In 2005, researchers such as Akira et al. Parlar et al., Jahangir et al. also explored the effect of remaining PDL and the feasibility of the the PDL around a dental implant.[28,29,30]

The performance of a tooth replacement by using a dental implant relies on the mechanical and biological capability of the anatomical substitute to restore lost physiological functions. L Carvalho et al. [2006] determined the PDL effects on the dynamic load transfer mechanism, from the tooth to the alveolar bone, evaluating the equivalent dynamic stiffness of the ligament structure. A porcine fresh mandible with a tooth was used within the study, applying an experimental procedure to identify the dynamic transmissibility of the entire system. The transmissibility function provided information about the stiffness and damping of the PDL, information that can assist the design of an improved dental implant system. [31]

In a yet another study done by Marei (2009), implantation of titanium fixture with porous hollow root-form poly (DL-Lactide-co-Glycolide) scaffold seeded with autogenous bone marrow-derived mesenchymal stem cells in goats exhibited periodontium-like tissue with newly formed bone both at 10 days and after 1 month, substantiating that undifferentiated mesenchymal stem cells were capable of differentiating to provide the three critical tissues required for periodontal tissue regeneration: Cementum, bone and periodontal ligament around the titanium implants.[32]

It was a scientific breakthrough when Gault *et al.* [2] in 2010 demonstrated for the first time the tissue engineering of the periodontal ligament and cementum-like structures on oral implants in humans, to promote the formation of implant-ligament biological interfaces or ligaplants capable of true, functional loading. One of the interesting facts in the Gault research-work was that periodontal ligament fibroblasts could be harvested from hopeless teeth of mature individuals and cultured in bioreactors to preserve their state of differentiation. Out of the eight implants inserted, one implant was still in place and functioning even after 5 years and even exhibited substantial bone regeneration in the adjacent bone defect 2 years after implantation. This implies that future clinical use of ligaplants might also be able to avoid bone grafting, its expense, inconvenience and discomfort to the patient.

Rinaldi and Arana Chavez in 2010 showed results by doing an animal study that that thin cementum like layer formed at longer times after implantation at the areas in which the PDL was in contact with the implant.

The clonogenic potential of human dental and periodontal tissues such as the dental pulp and the PDL and their potential for tooth and periodontal repair and/or regeneration was discussed by Javier Caton et al. (2011). They also proposed novel therapeutic approaches using stem cells or progenitor cells, which are targeted to regenerate the lost dental or periodontal tissue. [33]

Lately, Kano *et al.*(2012) suggested that implants surrounded by periodontal ligament-like tissue could be developed, when immediately after the extraction, tooth-shaped hydroxyl-apatite coated titanium implants were placed into the tooth socket where some periodontal ligament still remained; maintenance of original periodontal tissue domains most likely being the cause of prevention of osseointegration of the implants.[34]

Kiong and Arjunkumar in 2014 stated that ligaplants as tooth replacement have decisive advantages as compared with osseointegration devices, due to their periodontal tissue regeneration. [25]

It was confirmed that PDL-derived cells cultured with osteoinductive medium had the ability to induce cementum formation by Kaoro washio et al. (2018). Periodontal-like structure was formed around a titanium implant, which is similar to the environment existing around a natural tooth. The clinical application of dental implants combined with a cell sheet technique may be feasible as an alternative implant therapy. Furthermore, application of this methodology may play an innovative role in the periodontal, prosthetic, and orthodontic fields in dentistry. [35, 36]

The regeneration of lost periodontal tissue has been one of the most important subjects in periodontal research. Since their discovery, Kengo Iwasaki et al. [2019] used periodontal ligament stem cells (PDLSCs), and transplanted into periodontal bony defects to examine their regenerative potential. Periodontal defects were successfully regenerated using PDLSC sheets, which were fabricated by cell sheet engineering in animal models, and for which clinical human trials are underway. [36, 37]

CONCLUSION

Since the ligaplant is not tightly fitted to its site, the ligaplant surgery is relatively easy. Ligaplants has advantages compared to osseosintegration devices, due to their periodontal tissue regeneration capability. Patients however also have the advantage of not going through the inconvenience and discomfort of bone grafting, instead they can go for ligalants for a better outcome.

A major concern remains in the form of rational application of stem cell based tissue-engineering technology to be practiced in clinics. Apart from being a technique sensitive procedure, tissue engineering applications requires a considerable amount of cost and time. Although, a predictable and feasible method for producing dental implants with periodontal-like ligament has not been innovated, it has now been understood that generating a periodontal-like tissue around implants is possible and is the coming future in the field of implantology. This revolutionary approach to develop periodontio-integrated implants; however, opens up exciting possibilities for both periodontologists and oral implantologists and offers many interesting possibilities of utilizing ready-made, off-the shelf biological tooth replacements that could be delivered to serve as hybrid-material-living oral implants to patients.

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