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Vascularization of Peri-Implant Tissues: Literature Review

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Abstract: The modern implantology allows, through the new materials and the right technics, to restore the teeth that had been lost and so a natural occlusion. One basic step is the healing of the wound after the insertion of pins in the bond is to obtain a good vascularization. The literature review that is the object of this study, analyse the essential role of angiogenesis in the surgical wound also for a good osteointegration.

Key words: Peri-implant tissue, surgical wound, angiogenesis, blood vessels, growth factors

INTRODUCTION

Implantology is the answer to the common dream of both dental surgeons and patients: The reconstruction of teeth which have been lost in a way which is almost analogous to the natural process without having to rely on bothersome though sophisticated removable prosthesis (the so-called movable dentures or overdentures) or fixed prosthesis.

Dental implantology consists in the insertion of pins into edentulous sites in the maxilla or mandible. Once integrated with the bone itself, these can support an artificial tooth which is capable of carrying out its function.

Today, titanium pins are mostly cylindrical and of various lengths and diameters so that they can be adapted to the different configurations of bone segment available for their insertion. They are made of titanium, a metal which is widely used in surgery as its biological neutrality assures that the organism accepts it. Their surface is treated so as to augment the possibility of osseointegration, which has been well studied and verified in literature thanks to the use of the electronic microscope: there is no rejection in dental implantology given that there is no possibility of unfavourable immunological reaction, as happens in heterotransplants (from donors) (Brunski *et al*., 2000).

The dental implants have also overcome clinical tests in recent years through longitudinal studies on patients who have undergone treatment and who have testified to their reliability. They must be produced and manufactured according to the norms of European law and therefore, be accompanied by a certificate that can be seen and kept by the patient as a guarantee. The best modern implants come with a great number of connectors to the artificial tooth. These support it so as to guarantee not only that it can be cleaned perfectly, but also an optimal aesthetic appearance with respect to the contour of the underlying gingiva. This last factor is very important for the achievement of a good result in operations in areas exposed by the smile. According to the situation and to the model of the implant, the surgical operation can be carried out in one stage (leaving a small portion of the implant exposed after its insertion into the bone so as to subsequently connect it to the tooth) or in two stages, with the second stage being much simpler and shorter than the first (a small gingival incision is used to expose the most external part of the implant in the oral cavity so as to connect it to a porcelain or glass-polymer tooth). In the first case we refer to non-submerged implant and in the second a submerged implant, without referring to gingiva tissue because it is obvious that there must always be endosseus implantation. After the surgical operation, it is necessary to wait a varying length of time which, however, does not exceed four months, in order to be able to proceed with the prosthesization, that is, with the loading of an artificial tooth onto the implant. This can be made of porcelain-fused-to-metal, resin or glass-polymer, which are all materials of aesthetic value.

The dental implant of artificial roots firmly inserted into the bone succeeds in validly supporting a single crown or bridge (Sammartino *et al*., 2007).

Furthermore, the dental implant reproduces a functional stimulus which is typical of the natural root on the bone, allowing it to maintain its form and anatomy over time, avoiding therefore the process of resorption that follows the loss of teeth and which is even more noticeable under the stress caused by dentures.

Less recent implantology used implants of various forms whose aim was always to assure greater stability in

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different areas of the edentulous maxillary bone: screws, blades, needles, disks, grids and cylinders, made of various materials, were used, according to the knowledge available at that time. Today, modern implantology, sustained by rigorous scientific research, has shown that the best form for an implant is the one which simulates the root of a natural tooth, with some screw- like spirals on its surface to assure primary mechanical stability essential for the integration of the implant in the bone. Scientific research has not only dedicated its attention to the improvement of the form of the implants, but also and in particular, to the constituent materials and to the surface that is in contact with the bone. The screw implant with a root form can be of various lengths and diameters so that it is able to use greatest quantity of bone available. Today, titanium, a biomaterial, is the material that the international scientific community accepts as most suitable for use in implantology. The biomaterials used in the field of medicine that interact with the biological system (bone) are classified as biotolerated, bioinert and bioactive.

Biotolerated: Introduces fibrous material between the implant and the bone.

Bioinert: Introduces a direct contact between the bone and the implant (e.g. titanium).

Bioactive: Introduces a chemical-physical connection between the bone and the implant.

Titanium offers good biocompatibility given that its bioinertness is resistant to both the load and corrosion (Brunski *et al*., 2000). Modern implantology is quite predictable; we can affirm that we are able to achieve success in 96-97% of cases. It is important, however, to respect some principles.

Diagnosis: Examine accurately and evaluate the general health of the patient and the local conditions.

Local bone evaluation: Verify whether the quality and quantity of the bone is enough for the insertion of an implant.

General evaluation of the mouth: Investigate whether there are pathologies or illnesses in progress and whether hygiene is good.

Radiograph evaluation: Analyze the radiographs to verify the real quality and quantity of bone and the presence of any possible anatomical limitations or pathologies.

Surgery: Operate in sterility (performers of surgery, patients, instruments, environment). Perform surgery with the least possible invasiveness required for the operation and with respect for the consolidated protocols.

Material: Use implants that correspond to the standards of quality, safety and guarantee.

Follow-up: Require and carry out periodic check-ups.

Prosthesis: Apply prosthesis on implants that satisfy the criterions of occlusion, function, aesthetics and load (Sammartino *et al*., 2007).

ANATOMY OF THE PERIODONTAL TISSUES

The periodontium is the name given to the hard tissue (cement and alveolar bone tissue) and soft tissue (periodontal ligament and gingiva) that surrounds the tooth and contributes to its stabilization in the alveolar arch. The periodontium, also called "attachment apparatus" or "support tissue of the tooth", forms a unitary whole for development, biology and function. It undergoes some changes, depending on age and is in addition subject to morphological and functional alterations, as well as to correlated modifications due to changes in the oral environment. The gingiva is that part of the masticatory mucosa that covers the alveolar process and surrounds the cervical portion of the teeth. It can be divided into two parts: The free gingiva and the attached gingiva. The free gingiva surrounds the tooth, from which it is separated by a circular groove called the free gingival sulcus and together with the adjacent teeth forms the gingival or interdental papilla. The attached gingiva is so called because the tissue adheres tightly to the alveolar bone and to the underlying cementum through connective tissue. It extends from the free gingival sulcus, in an apical direction, up to the mucogingival junction. The periodontal ligament is the soft, cellular and richly vascularized connective tissue that surrounds the roots of the teeth and connects the cementum around the root with the hard lamina or the alveolar bone proper, through a great deal of densified collagen tissue arranged in well defined principal layers; these cross the periodontal space and penetrate the alveolar bone tissue and the cementum with their terminal parts, or perforating tissue. Thanks to the presence of the periodontal ligament, it is possible to distribute and to absorb the stress which comes from its function or during other contacts of the teeth, in the alveolar process, through the alveolar bone proper (Lindhe, 2002). The ligament secures the tooth to the adjacent structures (bone and cementum) but at the same time “hangs” it in the alveolus, acting as a "shock absorber". The cementum is a specialized calcified tissue that covers the surface of the teeth. It is a periodontal tissue and as such has a

supportive role for the tooth. It has various functions: it attaches the tissue of the periodontal ligament to the root and contributes to repairs following damage to the surface of the root. The alveolar process is defined as the portion of the mandible and maxilla that form and support the alveoli of the teeth. The alveolar bone is endowed with a high level of "plasticity" and is thus able to adapt itself, modifying its structure, to the different functional needs; its principal function is to distribute and to absorb the stress produced during mastication or other contacts between the teeth. The vascularization of the periodontal tissues is assured by the dental artery channel of the upper and lower alveolar artery; before entering the root channel, the dental artery gives origin to other channels that supply blood to the apical portion of the periodontal ligament. The gingiva receives its supply of blood from the supraperiosteal vessels that, during their course towards the free gingiva, emit numerous channels towards the subepithelial plexus situated below the oral epithelium of the free and attached gingiva. The subepithelial plexus sends out some thin capillary loops that are found in every connective papilla that projects itself into the oral epithelium. The number of these capillary loops is constant through time and is not altered by the application of epinephrine in the gingival edge. In the free gingiva, the supraperiosteal blood vessels anastomize with the blood vessels that originate from the periodontal ligament and from the bone. Under the junctional epithelium there is the plexus of blood vessels called the dentogingival plexus. In the healthy gingiva capillary loops are not found in the dentogingival plexus (Lindhe, 2002).

IMPLANT SITE

The insertion of an implant represents a surgical manoeuvre that attacks the entire organism and produces a generalized reaction in it. For one thing, due to the use of cutters and screws, the insertion in situ causes an increase in the temperature of the bone that must be opportunely cooled. It is critical to avoid reaching the temperature of 47 °C given that it may cause necrosis of the bone (Simion and Maiorana, 2003). The fundamental mechanisms of recovery from an implant are tissue encapsulation and ankylosis. The first method, also called osseointegration, involves the presence of tissue made up of healthy and dense collagen tissue, placed between the screw and the new bone tissue of the alveolar. The assemblage of the collagen tissue is tangent to the external surface of the implant and similar to a reactive application of a foreign body rather than to an organization similar to the periodontal ligament, where, however, the cells which generate the new tissue are

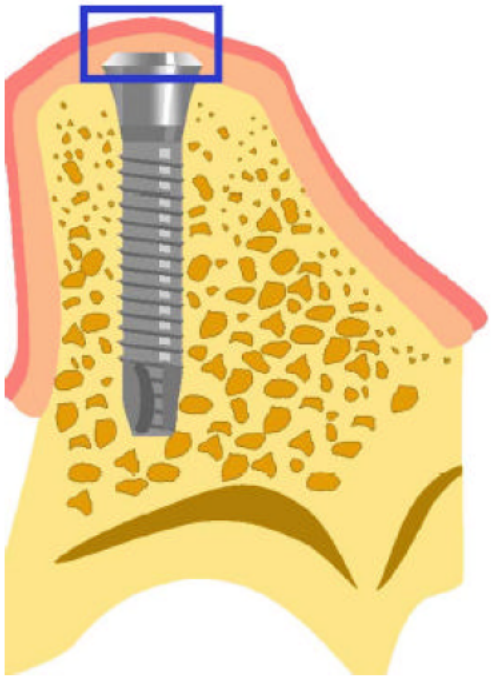

Fig. 1: Schematic section of the implant site after recovery (Schultze *et al*., 2006)

activated. The recovery is almost always through ankylosis, as by now universally recognized and confirmed by long term follow-ups (Fig. 1) (Schultze *et al*., 2006). In particular, the decisive factors for a greater orientation of the type of recovery are the substitution of the necrotic area that is created around the surgical defect and the characteristics of the material used.

Biotolerant materials create osseogenesis from a distance, or rather, a fibrous capsule of varying thickness ranging from 200- 500 microns between bone and implant, made up of collagen fibers and hyaline areas. Bioinert materials create contact osseogenesis, the osseogenesis being without connective tissue (Simion and Maiorana, 2003). The osseogenesis that is produced matches post-fractural osseogenesis, with the initial presence of haematic clots, the migration of mesenchymal cells from the endostal surface and the relative production of osteoid and bone tissue and continuous remodelling for osteoblastic and osteoclastic activity up to six months after the insertion of the implant (Shimada, 1989).

Finally, the bioactive materials (ceramic made from calcium phosphate) which create the osseogenesis of bone attachment or rather a real integration of bone-implant with the formation of a real chemical bond with the tissue substance, thanks to the action of the hydrossiapatite that creates a cuticle which is external to the implant (Simion and Maiorana, 2003).

PERI-IMPLANT TISSUES

The mucosa area of the peri-implant has the junctional epithelium around the surface of the implant attached by hemidesmosomes. The dental gingiva and the peri-implant mucosa have some common characteristics, but they differ in the composition of their connective tissue, the alignment of the layers of collagen fibers and the distribution of the vascular structures in the apical area of the junctional epithelium. In the implant site, the upper-alveolar tissue is assembled entirely in a different way in comparison to dental tissue. First of all, cementum is not present on the surface of the titanium body and accordingly, the collagen fibers of the peri-implant mucosa either insert themselves in the periostium of the crest bone and project themselves in a direction parallel to the surface of the implant, or they assemble in large strips that present a variable route which is, however, more or less parallel to the surface of the bone. The upper-alveolar part of the peri-implant mucosa at the connective tissue/titanium interface closely resembled scar tissue, being rich in collagen and poor in cells. In the implant site there is no periodontal ligament and so also no periodontal vascular plexus. The vascular system of the peri-implant mucosa has its origin exclusively in the large supra-periosteal blood vessel that is found in the external part of the alveolar crest. This vessel emits branches that form the capillary plexus and venules and is present under both the oral and junctional epithelium. Moreover, it has been seen that in the peri-implant mucosa, the connective tissue in the upper-alveolar, apical to the junctional epithelium, did not have almost any vascular supply (Abrahamsson *et al*., 1996).

The insertion of an implant in the alveolar process involves a series of events. The inflammation of the peri-implant mucosa, in which there is a statistically significant increase of TGF-b, IL-1b and VEGF and the resorption of the traumatized tissue around the implant followed by the formation of new tissue. The transforming growth factor-b attracts the fibroblasts, monocytes and macrophages to the site of the inflammation. During the formation of the new tissue, it induces the expression of integrate that controls the migration of the keratinocytes. Furthermore, it stimulates the synthesis of collagen during the healing process of the injured tissue. Interleukin 1-beta(IL-b) has an important role in the inflammatory process; it is produced by the monocytes and by the macrophages and acts as the principal stimulus for the catabolism of the extracellular matrix, the production of collagenesis and proteinosis and the degranulation of neutrophil granulocytes. The Vascular Endothelial Growth Factor (VEGF) is a glycoprotein which is capable of inducing the

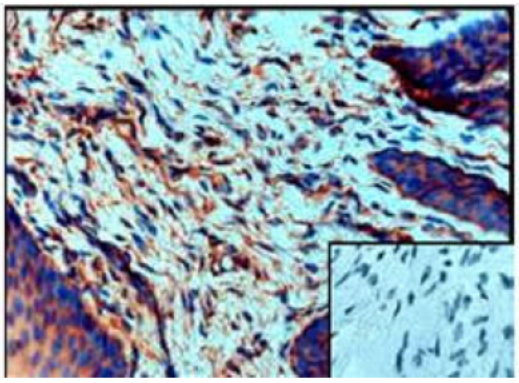

Fig. 2: VEGF expression in the peri-implant tissue: Polyclonal VEGF-specific goat IgG antibody directed against VEGF120, VEGF164 and VEGF188, hematoxylin counterstaining, magnification 400X (Schultze *et al*., 2006)

microvascular permeability and angiogenesis; it is activated by conditions of hypossia and also by IL-1b and TGF-b (Schultze *et al*., 2006). A study conducted by Schultze-Mosgau *et al*. (2006) showed that following the insertion of an implant there is a statistically significant increase of the levels of VEGF, capable of inducing neoangiogenesis in the injured peri-implant tissue. Immunohistochemical analysis of the VEGF epitope has been evaluated through the incubation of slides with polyclonal VEFG-specific goat IgG antibody (Fig. 2).

The endothelial cells are able to participate in the inflammatory response through the secretion of cytokines and chemotactic substances and through the recruitment of molecules of cellular adhesion. Furthermore, the ECs have the ability to form new blood vessels (Angiogenesis). Angiogenesis has a fundamental role during a person's development (embryogenesis and growth). In life it is regulated by complex interactions among endothelial cells and other types of cells (monocytes, macrophages, fibroblasts, smooth muscle cells, pericytes and osteoblasts) and other substances such as cytokine and growth factors, molecules of the extracellular matrix and molecules of cellular adhesion. An ample number of angiogenetic and anti-angiogenetic factors have been recognized, but with the regulation of the process of angiogenesis coming in various phases, it is highly complex and still not well understood.

In particular, VEGF, that is, the vascular endothelial growth factor, has been isolated in both ex vivo studies and in vitro studies. This is a glycoprotein secreted from the keratinocytes and from the endothelial cells and has an initial role in the process of angiogenesis. It contemporarily forms a paracrine and autocrine system. In

fact the smooth muscle cells which produce VEGF are found in the vascular wall close to the endothelial cells; the latter produce VEGF and are at the same time their target (Risau, 1997).

The VEGF causes vasodilatation and increase the permeability of vessels. Furthermore, it stimulates the action of metalloproteinases (Shubayev *et al*., 2004) produced by various cells, among which fibroblasts and inflammatory cells that by acting on the basal membranes of the endothelial cells, degrade them and form capillary fenestration and invade the adjacent stroma. In addition, VEGF acts in the release of nitrous oxide and in the production of enzymes such as serinprotease and interstitial collagenesis that seem to be involved to the vascular neoformation. VEGF binds itself to some proteins of the membrane, forming the FGF-1 and FGF-2 complex (Walsh and Pearson, 2001).

The VEGF-receptor system is not always active; it is silent and is activated in particular situations in the healthy adult, such as in the formation of the corpus luteum or in response to angiogenic stimuli, among which are ischemia and hypossia. Hypossia derived from an imbalance between the metabolic demand and the offer of oxygen from the tissue is the principal factor of induction of angiogenesis in the adult (Stefano *et al*., 2004). Following proteolytic degradation, the endothelial cells called leaders migrate through the matrix where fibrin is found in notable quantity. This is a necessary substratum for EC activity. The fibrin that is found in abundant quantities outside the vessel is produced by the degradation of the plasminogen that becomes plasmin through a proteasic action.

The migrated endothelial cells start to proliferate through the action of numerous growth factors. Immediately after, the proliferative action of the endothelial cells is drastically reduced and the first newly formed vascular islets begin to appear (Bonnet and Walsh, 2005).

A study conducted by Matsuo *et al*.(1999) has in fact shown that vascularization is an important factor for the remodelling of the bone. The purpose of this study, was to clarify the process of osseointegration through the observation of the changes of the vascular architecture and the apposition of bone. Total twelve beagle dogs were used and 2 types of implants were inserted in the jaw. Subsequently histological sections were used to study the vascular architecture and it was possible to observe the osseointegration of the implant with the peri-implant tissue using Indian ink; it was extremely difficult to appreciate the vascular network three-dimensionally using thin histological sections and it was in fact impossible to make a distinction between the arteries and the veins. The microvascular "resin cast" method was useful to observe the vascular structure three-dimensionally. The basic technique consists in injecting a synthetic resin, dissolving the peripheral tissue through the proteinosis and observing a sample through the use of a SEM. This technique, which only highlights the form of the vessels and the bone, has various advantages with regards to the observation of the hystologic sections:

- The complete structure of the vascular system, arteries, veins and capillaries can be observed.
- It is possible to make a distinction between the arteries and the veins through the observation of the structural difference in the endothelium, as indicated in the surface of the injected resin.
- It is possible to observe arteriovenous anastomosis.
- The direction of the blood flow can be established according to the orientation of the venous valves.
- The increase of the vascular permeability caused by an acute inflammation can be observed. Unlike the method which uses sodium hydroxide and potassium removal from the soft tissue, the action of proteinosis does not demineralize the newly formed bone. A vascular injection was made at 14, 30 and 120 days from the surgical operation. The soft tissue was digested with proteinase solution and the samples were examined through scanning electron microscopy.

In the TPS (Titanium Plasma-Sprayed) implants the neoformation of bone occurred along the uneven surface of the fixture. With the threaded implants, the apposition of bone occurs along the coils. The precipitation of calcium salts in the haematoma is the first step for the regeneration of tissue and the bone is formed from a continuous process of revascularization and mineralization.

The fibroblasts aligned themselves according to the characteristics of the surface of the implant that can be either smooth or rough. In this study, it was possible to show that the cortical bone adheres to the cervical portion of the threaded implant. There is no space in the interface between the bone and implant for the regeneration of blood vessels. Thus the vessels stem out from the medullar and spongy bone and from the oral mucosa, they distribute themselves towards the fixture and form the vascular network. The vessels are flat and the diameter varies between 3-the 80 μms. The form of the regenerated vessels seemed to be of a hemispheric type. This form is not the result of an incomplete filling with resin but rather points out that the vessels are formed through the multiplication of the endothelium. Instead, with the TPS

implant, the vascular network regenerates in the microscopic spaces of the bone and in the uneven surface of the implant. At 14 days from the insertion of the implant, the spherical and laminar particles in titanium were surrounded by a ramification of new vessels which on average had a diameter of between 10 and 50 μm. In this study the formation of new vessels was observed in the threaded implants 14 days after the surgical operation and in the TPS implants after 7 days; the formation of the vascular network occurred in the intermediate time. The uneven surface of the TPS implant made it simpler for the vessels to invade the surface of the fixture. The study has shown that there are significant differences in the generation of new blood vessels and in the bone around the implants in TPS in comparison to the threaded implants, due to their structure and the characteristics of their surface. The formation of vessels was confirmed after 14 days in both groups; osseointegration was had after 120 days. Using the vascular method with the injection of resin, the nuclei of the endothelial cells were considered to be the elements from which vessels originate. Similar results were reported in studies on cancer of the tongue in hamsters, for which the vascular technique with injection of resin was used. In this study it was possible to see the formation of new vessels; in fact new endothelial cells developed during the formation of new vessels. This is due to an increase of the permeability of the venous system as a result of the release of VEFG.

It is thought that the vascularization of a wound has its origin in the venous blood flow. The vessels are subject to pressure, so much so that they become flattened. Some of them tighten at the terminal part of the vassal lumen. This deficiency in microcirculation leads to an exfoliation of the endothelium and to thrombosis. With the SEM, the narrowing of the diameter of the vessels provokes an image of stasis of the blood flow. Osseointegration is thought to occur in this way, although many of these vessels do not appear in this form. Furthermore, they must still remain on the surface of the bone for the remodelling of the bone (Matsuo *et al*., 1999).

A study by Berglundh *et al*. (2007) has wanted to illustrate the morphogenesis of the peri-implant tissue following the insertion of a titanium implant. The study was conducted in the premolar area of the extracted jaw in 20 Labrador dogs. After a period of recovery of 3 months, non-submerged implants were inserted. During the initial phase of the recovery, neutrophils infiltrate and degrade the clot present in the interface between the mucosa and the implant (Fig. 3). Two weeks after the surgical operation the fibroblasts and vascular structures were the predominating population of cells in the interface of the connective tissue, in the marginal portion of the tissue, proliferation of epithelium had occurred and the first signs of a barrier (junctional) epithelium were observed (Fig. 4).

After 4 weeks a diminution in the density of the fibroblasts was noticed. Tissue maturation and collagen fiber organization was evident from 6-12 weeks of healing and the formation of barrier epithelium was completed between 6 and 8 weeks (Fig. 5). A dense layer of elongated fibroblast formed the connective tissue interface to titanium. In connective tissue compartments

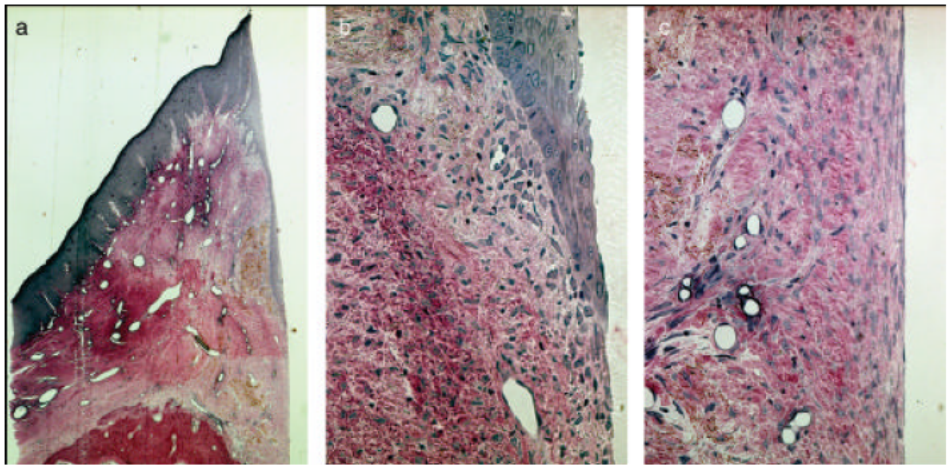

Fig. 3: (a) Peri-implant mucosa at 4 days of healing. Decalcified section, original magnification×50. (b) Detail of .(a), original magnification×100. (c) Detail of (b). Leukocyte-infiltrated fibrin tissue in the interface to titanium, original magnification × 400 (Berglundh *et al*., 2007)

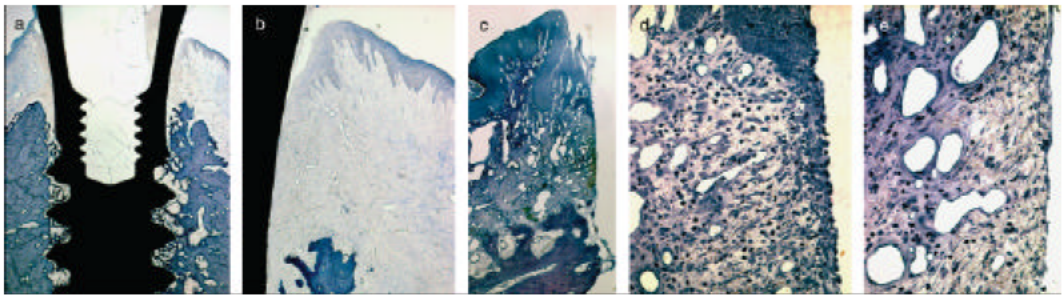

Fig. 4: (a) Ground section of implant and surrounding hard and soft tissues representing 2 weeks of healing, original magnification × 16. (b) Detail of (a), original magnification × 50. (c) Peri-implant tissues at 2 weeks. Formation of barrier epithelium in the marginal portion of the mucosa. Decalcified section, original magnification×50. (d) Detail of (c). Marginal portion of the soft tissue interface to titanium, original magnification×100. (e) Detail of (c). Apical portion of the soft tissue interface to titanium, original magnification×100 (Berglundh *et al*., 2007)

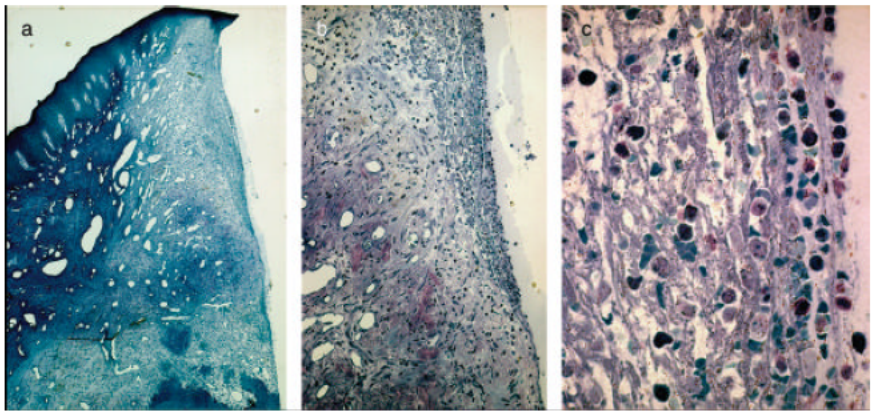

Fig. 5: (a) Decalcified section of peri-implant tissues representing 8 weeks of healing. Formation of barrier epithelium completed, original magnification×50. (b) Detail of (a). Apical part of the barrier epithelium, original magnification ×200. © Detail of (a). Connective tissue interface to titanium, original magnification×200 (Berglundh *et al*., 2007)

lateral to the implant interface, few vascular structures were found. Fibroblast were interposed between thin collagen fibers, the direction of which was mainly parallel to the implant surface (Berglundh *et al*., 2004).

A study by Berglundh *et al*. (1991) on beagle dogs compared the implant mucosa with dental mucosa. The implants were inserted using a two-stage technique in a site on the mandible and biopsies of the dental mucosa and of the peri-implant mucosa were performed at 4 months from the connection to the abutment. It was highlighted that the attachment of the soft tissue to the teeth and to the implants included both long zones similar to the junctions of the epithelium and connective tissue. The connective tissue found immediately adjacent the implant was characterized by a high density of collagen fibers and a low density of blood vessels (Berglundh *et al*., 1991).

CONCLUSION

The vascularization of peri-implant tissue is a very important parameter both for the remodelling of the bone and for the preservation of a dental implant after its insertion. The relationship between the bone and the organization of the vascular network is still unknown (Traini *et al*., 2006). Further investigations will be necessary in the future in order to appraise the vascular architecture of the peri-implant tissue and to clarify the role of neoangiogenesis during the process of osseointegration and the healing of the mucosa.

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