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Review

Peri-implant osteogenesis in health and osteoporosis

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Abstract

Long-term clinical success of endosseous dental implants is critically related to a wide bone-to-implant direct contact. This condition is called *osseointegration* and is achieved ensuring a mechanical primary stability to the implant immediately after implantation. Both primary stability and osseointegration are favoured by micro-rough implant surfaces which are obtained by different techniques from titanium implants or coating the titanium with different materials. Host bone drilled cavity is comparable to a common bone wound. In the early bone response to the implant, the first tissue which comes into contact with the implant surface is the blood clot, with particular attention to platelets and fibrin. Peri-implant tissue healing starts with an inflammatory response as the implant is inserted in the bone cavity, but an early afibrillar calcified layer comparable to the lamina limitans or incremental lines in bone is just observable at the implant surface both in vitro than in vivo conditions. Just within the first day from implantation, mesenchymal cells, pre-osteoblasts and osteoblasts adhere to the implant surface covered by the afibrillar calcified layer to produce collagen fibrils of osteoid tissue. Within few days from implantation a woven bone and then a reparative trabecular bone with bone trabeculae delimiting large marrow spaces rich in blood vessels and mesenchymal cells are present at the gap between the implant and the host bone. The peri-implant osteogenesis can proceed from the host bone to the implant surface (*distant osteogenesis*) and from the implant surface to the host bone (*contact osteogenesis*) in the so called *de novo* bone formation. This early bone response to the implant gradually develops into a biological fixation of the device and consists in an early deposition of a newly formed reparative bone just in direct contact with the implant surface. Nowadays, senile and post-menopausal osteoporosis are extremely diffuse in the population and have important consequences on the clinical success of endosseous dental implants. In particular the systemic methabolic and site morphological conditions are not favorable to primary stability, biological fixation and final osseointegration.

An early good biological fixation may allow the shortening of time before loading the implant, favouring the clinical procedure of early or immediate implant loading. Trabecular bone in implant biological fixation is gradually substituted by a mature lamellar bone which characterizes the implant ossoeintegration. As a final consideration, the mature lamellar bone observed in osseointegrated implants is not always the same as a biological turnover occurs in the peri-implant bone up to 1 mm from the implant surface, with both osteogenesis and bone reabsorption processes.

Keywords: Implant surface; Biomaterials; Osteogenesis; Bone; Osteoporosis

Contents

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1. Introduction

Endosseous dental implants are widely inserted in maxillae and mandibles as substitutes for teeth in prosthodontic therapy to restore or replace function in partially or completely edentulous patients. Osseointegration has been claimed to be the clinical condition allowing the functional loading of dental implants (Adell et al., 1981; Nevins and Langer, 1993) and consists in direct histological bone-implant contact (Branemark et al., 1977; 1985).

The tissue responses giving rise to implant osseointegration depend on various factors such as implant surface, anatomical site, surgical trauma, time of specimen observation, and the animal species. Consequently a reliable literature evaluation in is not always possible (Listgarten, 1996; Masuda et al., 1998; Lu et al., 1998). Nevertheless, a description of the biological events occurring at the implant-bone interface may help to shed light on peri-implant osteogenesis. When inserting a medical device into a bone cavity a sequence of different biological events takes place at the bone-implant interface until the implant surface appears finally covered with a newly formed bone. The final goal of surgical procedures is controlled, guided, and rapid healing which leads to the integration of an implant into bone (Puleo and Nanci, 1999). Osseointegration has been considered the most appropriate bone-implant interface.

In implant dentistry the biomechanical, biochemical, functional, and aesthetic demands of the implanted material are fundamental to ensure long-term clinical success (Elligsen and Lyngstadaas, 2003). The different materials, shape, length, diameter, implant surface treatment and coatings have been proposed to enhance clinical performances so that dentists can now choose from more than 1300 different types of implants (Binon, 2000).

Cell types, tissues, growth factors and cytokines are involved in a coordinated manner during the inflammatory, formation and remodelling phases of bone healing. This means that osseointegration should be regarded not as an exclusive reaction to a specific implant material but as the expression on the endogenous basic regenerative potential of bone (Linder et al., 1989). Moreover, the mechanical and biological factors involved in the healing process of bone are certainly affected by senile and post-menopausal osteoporosis (Augat et al., 2005). Whether fracture repair is impaired in aged and osteoporotic patients remains an open question, but osteoporosis just influences fracture healing (Kubo et al., 1999; Meyer et al., 2001; Wang et al., 2005; Xu et al., 2003).

Nowadays, senile and post-menopausal osteoporosis are widespread and could have important consequences on the success of the osteosynthesis device, prostheses for total joint replacement and dental implant surgery. Many clinicians and researchers have observed that biomaterial osseointegration is slower in osteoporotic subjects, with an increased rate of prosthetic device failures both in dental and orthopaedic reconstructive surgery (Hayashi et al., 1989; 1994; Fini et al., 1997; 2001; 2004; Pan et al., 2000; Rocca et al., 2001; Nicoli Aldini et al., 2002; Duarte et al., 2003; Qi et al., 2004; Zhang et al., 2004).

2. Implant surface

The design, chemical composition and topography of the implant surface can influence peri-implant tissue healing (Pilliar, 2003). Commercially pure titanium (Ti) is widely used as a dental and orthopaedic metallic implant material as it is highly biocompatible material (Breme et al., 1988; Browne et al., 2000) with good resistance to corrosion, no toxicity on macrophages or fibroblasts, and lack of inflammatory response in peri-implant tissues (Rae, 1975; 1981; Brune et al., 1982; Breme et al., 1988). However, other materials like tantalum (Alberius, 1983), nionium (Johansson and Albrektsson, 1991), zirconium (Thomsen et al., 1997) and hafnium (Mohammadi et al., 2001) have been proposed as substitutes of titanium. The smooth or machined implant surfaces, largely used in the past, have today been replaced by modified rough surfaces obtained with different techniques like spark erosion grit blasting with different materials, etching, titanium plasma spraying, chemical coatings and physical vapour deposition (Wisbey et al., 1987; Aspenberg et al., 1996; Hendry et al., 2001; Giavaresi et al., 2003a; 2004). The methods used to modify surface topography may affect the implant's chemistry and vice versa, altering adhering cell shape and cytoskeletal organisation through the modulation of fibronectin expression (Chou et al., 1995).

Among the different variables influencing peri-implant osteogenesis, the morphology of the implant surface is particularly important (Thomas and Cook, 1985). Rough surfaces have been proposed to enlarge the implant area in contact with host bone favouring primary stability (Vercaigne et al., 1998; Hansson et al., 1999) and enhancing peri-implant bone formation compared to smooth surfaces (Buser et al., 1991; Cochran et al., 1996; 1998; Mustafa et al., 2000; 2001; Weng et al., 2003). Surface topography and roughness positively affect the osseointegration process, encouraging favourable cellular response by means of protein-surface and cell-surface interactions (Anselme et al., 2002; Borsari et al., 2005). Surface roughness in particular seems to have a direct effect on osteoblast attachment and subsequent proliferation and differentiation (Martin et al., 1995; Wen et al., 1996; Boyan et al., 1998; Lohmann et al., 2000; Korovessis et al., 2002; Fini et al., 2003). Osteoblast-like cells adhere more readily to rough surfaces and appear more differentiated on rougher surfaces, with regards to morphology, extracellular matrix production, alkaline phosphatase activity and osteocalcine production, and response to systemic hormones such as 1,25-(OH)2D3 (Batzer et al., 1998; Lohmann et al., 1999; Schwartz et al., 2001). Roughness also influences the synthesis of two local

factors, TGFβ1 and PGE2, which can act on the osteoblastic cells as autocrine regulators, and modulate the activity of bone resorbing cells via paracrine mechanisms (Orsini et al., 2000; Schwartz et al., 2001; Boyan et al., 2002). The observations by Schwartz et al. (2001) suggested that the roughness-dependent regulation of osteoblast proliferation, differentiation and local factor production is related to the activation of integrin receptors by substrate, thus regulating phosphokinase C (PKC) and A (PKA) through phospholipase C (PLC) and A_2 (PLA_2) pathways (Boyan et al., 1999). The rough surfaces also favour both platelets (Park and Davies, 2000; Park et al., 2001) and the monocytes adhesion (Soskolne et al., 2002) better than machined surfaces. Generally, at the micrometer level of evaluation, moderately rough surfaces favour peri-implant bone growth better than smoother or rougher surfaces (Albrektsson and Wennerberg, 2004a).

Rough surfaces can be divided into surfaces roughened with a coating [titanium plasma-sprayed (TPS) or hydroxyapatite (HA)], or without a coating [sandblasted or/and acid-etched (SLA)] (Zechner et al., 2003). Even if implant surface topography plays a more important role in promoting early peri-implant healing than variations in surface chemistry (Davies, 2003), coating the metallic implant surface with calcium phosphate, such as hydroxyapatite (HA), may accelerate peri-implant osteogenesis (Cook et al., 1988; Shirakura et al., 2003) and provide a mechanical barrier to metal ion release (Ducheyne et al., 1988) or titanium particles detachment (Martini et al., 2003). In addition to the plasma spray technique, other methods have been applied for depositing dense HA, including electrophoretic deposition, laser deposition and radio frequency magnetron sputtering (Jones, 2001). Calcium phosphate materials may increase the protein adsorption on the implant surface favouring both the platelet adhesion-activation and fibrin binding by accelerating implant healing (Davies, 2003). Calcium phosphate ceramics coatings increase the implant surface (Dhert et al., 1991; Caulier et al., 1995; Wheeler, 1996) and some of them are considered to bind to bone as biomimetic materials (Hench et al., 1972; Osborn, 1979; Yan et al., 1997; Geesink et al., 1988; Chang et al., 1999), where bone-bonding is generally considered a chemical interaction between the newly formed collagen and the chemically active surface (Figs. 1 and 2). Bone formation is higher in beta-tricalcium phosphate (TCP) cylinders implanted in rabbit femur compared to HA ceramics with the same pore size. Among different pore sizes, a pore size above 80 μm improves bone ingrowth in both HA and TCP materials (Galois and Mainard, 2004). HA-coated implants show an early formation of bone vs. grit-blasted titanium implants by removal torque tests, histomorphometric and morphometric analyses (Park et al., 2005). However, the implant-bone interface, consisting in a thin calcified afibrillar layer, is similar in both metal rough surfaces and hydroxyapatite-coated implants, suggesting that bonding is achieved by micro-mechanical interdigitation of the cement line with the material surface (Davies, 2003).

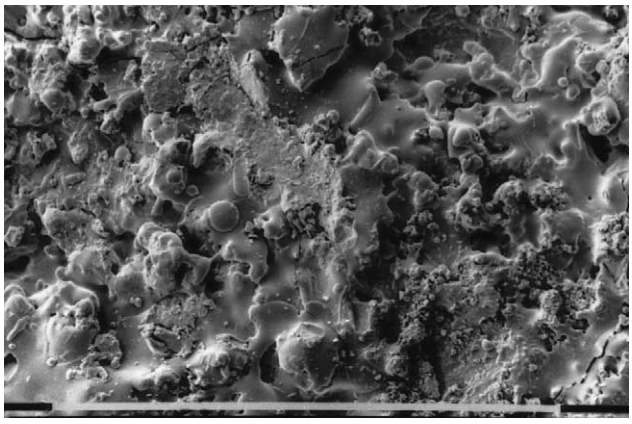

Fig. 1. Scanning electron microscopy of a hydroxyapatite-coated titanium dental implant. The HA surface looks irregular and shows a microporosity which increases the implant surface and plays an important role in favouring early peri-implant osteogenesis. Bar = 100 μm.

Even though literature is critical on the long-term performance of HA coating, a human study reported that, despite a 22.75% loss of the HA coating after 10 years, implants appeared well osseointegrated, with an adaptation of the bone to the exposed titanium surface (Trisi et al., 2005).

Certain calcium phosphate materials with a specific porous structure have been reported to be osteoinductive, i.e. able to induce bone formation at extra-skeletal sites where normally no bone is deposited (Chang et al., 1999). However, it was clearly demonstrated for the first time that a porous titanium block can be osteoinductive if implanted in dorsal muscles of beagle dogs, suggesting that the porous structures of a material are useful for tissue regeneration acting as a scaffold for growth factors and/or osteogenic cells (Fujibayashi et al., 2004).

Electrochemical modification of implant surfaces like anodic oxidation (Kurze et al., 1986; Becker et al., 1991; Larsson et al., 1996; Hall and Lausmaa, 2000) or titanium

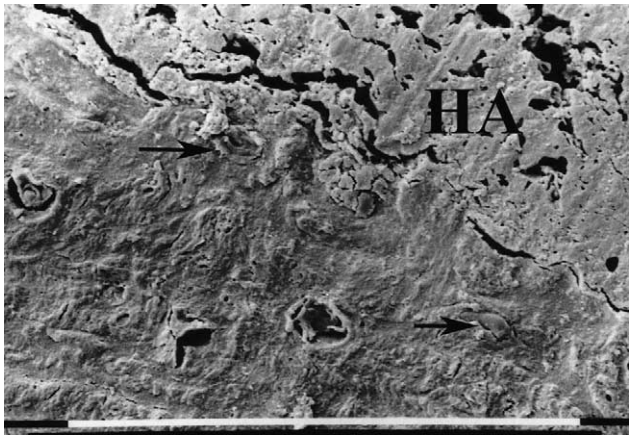

Fig. 2. HA-coated titanium dental implant from human. The newly formed mature lamellar bone is in close contact with the HA-coating surface (HA): no gap or soft tissue are present at the interface. Young osteocytes recognizable in wide lacunae are aligned parellel and next to the implant surface (arrows). Bar = 100 μm.

treated with NaOH (De Andrade et al., 2000; Jonasova et al., 2004) have recently proposed to boot apatite formation as biomimetic surfaces. The evolution of anodic spark deposition (ASD) techniques led to the development of inorganic glass-ceramic-like coating structures on metal surfaces with adhesive strength up to 25 MPa (Ishizawa et al., 1995; Schreckenbach et al., 1999; Zhu et al., 2002; Chiesa et al., 2003). By shear loading tests and histological analysis it was suggested that a micro rough surface treated by sandblasting and anodic oxidation on a macro rough surface structure favours bone formation and fixation of the implant (Yamagami et al., 2005). However, surfaces modified by anodic oxidation have shown a bone-to-implant contact similar to that reported in HA-coated implants (Zechner et al., 2003), while calcium-incorporated oxidized implants probably allowing a chemical bonding with the newly formed bone better favour osseointegration than machined implants (Sul et al., 2004). The secondary application of a biomimetic process (BSP) to ASD surfaces improved the physico-chemical properties of the Titanium surface generating a tiny fibrillar morphology at nanoscale level and changing also the chemical nature of the surface (BioSpark™), achieving a higher Ca/P ratio (2.9) (Sandrini et al., 2003; Sandrini et al., 2005). The BioSpark™ process improved titanium biocompatibility by enhancing its bioactivity and osseointegrative properties, without introducing any detrimental effects on the mechanical properties of the material (Sandrini et al., 2005). In general implant industries often introduce new implant surfaces that clinicians adopt in clinical practice. However, clinical follow-up studies of anodized or sandblasted and acid-etched implant surfaces limited to a few years, and long-term clinical reports are required (Albrektsson and Wennerberg, 2004b).

3. Primary implant stability

The first clinical outcome of surgical procedures is the primary stability of the medical device, which consists in a rigid fixation of the implant within the host bone cavity together with a lack of micro-motion of the implant (Branemark et al., 1977; Adell et al., 1981; Futami et al., 2000; Meyer et al., 2004). In fact, an excessive mobility of the device may improve a fibrous membrane formation around the implant (Pilliar et al., 1986; Soballe et al., 1992) and cause displacement at the bone-implant interface inhibiting osseointegration. Primary stability depends on surgical techniques, implant design and implant site (Sennerby, 1991; Butcher et al., 2003; Saadoun et al., 2004; O'Sullivan et al., 2004; Sevimay et al., 2005) and is related to the biomechanical properties of the adjacent host bone; cortical bone allows a higher mechanical anchorage to the implant than cancellous bone (Sennerby, 1991). Implants inserted in the posterior maxilla undergo failure more often than implants positioned in the anterior mandible due to a higher ratio of compact to cancellous bone (Adell et al., 1981; Lazzara et al., 1996). For this reason, it would be reasonable to engage the cortical bone at the implant site even with a few threads using a screw implant (Sennerby et al., 1992). In human cadaver tapered implants showed a higher primary stability than cylindrical ones when both were placed in soft bone (O'Sullivan et al., 2000). Mechanical interlocking of the threads with cavity bone ensures secure fixation of the implant (primary stability) (Meyer et al., 2004). However, in some areas evident gaps are present between the implant and bone of some hundreds of micron and filled by blood cell and tissue remnants are present (Berglundh et al., 2003; Franchi et al., 2004a,b). A close contact between implant and host bone may not serve to enhance osteogenesis because in these areas no early bone formation has been described (Futami et al., 2000; Berglundh et al., 2003; Shirakura et al., 2003; Franchi et al., 2004a,b) (Fig. 3). On the other hand, excessively wide gaps of more than 500 μm are predict a reduction in the quality or quantity of the newly-formed bone and delay the rate of gap filling (Cameron et al., 1976; Sandborn et al., 1989; Futami et al., 2000). As mentioned above, good implant stability tends to minimize distortional strains in the regenerating tissue facilitating osteogenesis and bone ingrowth. On the contrary, motion or poor implant stability which result in tensile and shear motions stimulate fibrous tissue formation (Carter and Giori, 1991). A high-quality bone seems to be important for the initial stability of

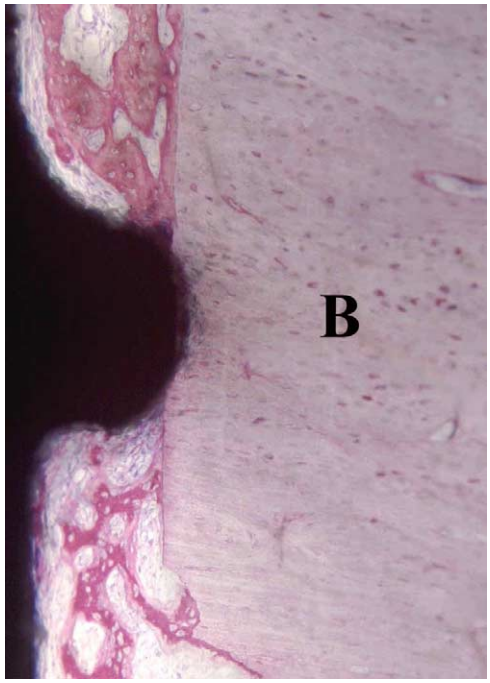

Fig. 3. Screw implant inserted in sheep femur 14 days after implantation. Ground section observed at light microscope. A thread of implant screw interlocking with the host bone (B) ensures a mechanical anchorage of the implant clinically called 'primary implant stability'. Where the thread is in close contact with the host bone no newly formed bone is seen, whereas in the gap between the implant body and the host bone new bone trabeculae support the biological fixation of the implant.

implant devices (Wittenberg et al., 1991) as bone changes in structural and mechanical properties due to bone rarefaction and micro architectural alterations are responsible of reduced mechanical stability of implants. For this reason, osteoporotic tissue might not provide the firm primary stabilization required for long-term clinical success.

4. Early bone response to implant

The integration of an implant into bone, namely 'osseointegration', has been widely studied in literature and has long been considered the pre-requisite for implant loading (Puleo and Nanci, 1999). However, to better understand the complex biological processes of new bone formation around the implant until its final osseointegration, it is useful to point out what happens in the peri-implant space when an implant is inserted into a pre-drilled bone cavity. The principle mechanisms underlying the osseointegration process around implants are very similar to those occurring during bone fracture repair and involve a cascade of various cellular and extracellular events (Fini et al., 2004). The initial host response after implantation is characterized by an inflammatory reaction elicited mainly by the inevitable surgical trauma and modified by the presence of the implant. The implant bone cavity must be considered as a common bone wound where injuries to pre-existing bone, presumably the consequence of heating, are located within 100 μm (Futami et al., 2000) or even beyond 500 μm (Listgarten, 1996). The host tissue response to the implant is a physiological consequence of the local surgical trauma, macroscopic transport processes, and molecular reactions at the material-tissue interface (Kasemo and Lausmaa, 1991). Immediately after the surgical damage the walls of bone are rapidly covered with blood, so that this is the first tissue coming into contact with the implant surface after the implant is positioned in the bone cavity (Davies, 1996; Park and Davies, 2000). Inflammatory cells, initially polymorphonuclear granulocytes, and later monocytes, emigrate from post-capillary venules and migrate into the tissue surrounding the implant. After the blood comes into contact with the implant surface, proteins are adsorbed from blood and tissue fluids. From the implant side an oxidation of metallic implants has been described both in vitro and in vivo (Sundgren et al., 1986; Ask et al., 1989). Different methods of sterilization can determine an oxidation thickness of titanium implant surfaces (Lausmaa et al., 1988) but the surface of any material can also change over time when implanted in the living body (Nanci et al., 1998). Several of the inflammatory cells detected at the interface respond after stimulation by a secretion of proteins with effects on inflammation, bone healing and immune reactions (Thomsen and Ericson, 1991). These products may also alter the structure and physiochemical properties of the implant surface (Thomsen and Ericson, 1991). Continuous electrochemical events at the tissue-implant interface are related to a release of metal ions into tissue (Williams, 1982; Puleo and Nanci, 1999). These ions may be localized in the peri-implant tissues or other organs (Bianco et al., 1997; Woodman et al., 1984; Urban et al., 2000), in the patient's serum (Jacobs et al., 1998) and urine (Woodman et al., 1984). Moreover, clinical investigations reported hypersensitivity and allergic reactions to Ti in some patients (Peters et al., 1984; Lalor et al., 1991). An excessive metal ion release has been shown 'in vitro' to inhibit cell function and apatite formation (Blumenthal and Postner,1984; Blumenthal and Cosma, 1989). Small titanium particles of unloaded implants have also been found inside the peri-implant medullary spaces or in newly formed bone trabeculae of animals 3 months after surgery and may increase Ti dispersion in blood vessels, on account of the high vascularisation of medullary tissues (Martini et al., 2003). Franchi et al. (2004a) demonstrated that some Ti particles detached from the implant surface as a consequence of the friction between the implant surface and host bone cavity during implant insertion.

The early host tissue response involves the deposition from osteogenic cells of a non-collagenous matrix layer on the implant surface, similar to the bone cement lines and laminae limitans (Linder, 1985; Albrektsson and Hansson, 1986; Davies et al., 1990; Nanci et al., 1994; Murai et al., 1996; Davies, 1996; Meyer, 2004). Morphological studies reported a heterogeneity of the implant-bone interface but the early calcified afibrillar layer looks similar in all implants despite the different type of materials implanted (Puleo and Nanci, 1999). It appears as individual globular accretions that fuse to form a continuous layer 0,5 μm thick, rich in calcium, phosphorus, osteopontin and bone sialoprotein (Shen et al., 1993; Peel, 1995). These proteins regulate cell adhesion and binding of minerals (Butler and Ritchie, 1995; Gorsky, 1998). Davies (1996) suggested that less differentiated cells in the osteogenic lineage, or perhaps mesenchymal cells, migrating to colonize the implant surface as the earliest events leading to new bone formation on the implant surface. The interaction of red blood cells, fibrin and platelets with the implant surface may modulate the migration, differentiation and activity of osteogenic cells during peri-implant healing (Park and Davies, 2000; Davies, 2003). These events are very early biological processes as in vivo study (Meyer, 2004) demonstrated that, osteoblasts attach on the implant surface from day one of implant insertion. Murai et al. (1996) showed a thin layer (20–50 nm) of flat cells and slight mineralized area at the bone-implant interface. This cellular adhesion was confirmed by the presence of fibronectin and fibronectin receptor at the cell surface (Rosengren et al., 1996).

As just mentioned, the bone implant cavity surgically created is compared to a bone wound, with heating injuries, including death of osteocytes, extending 100–500 μm into the host bone (Listgarten, 1996; Futami et al., 2000). In bone physiology the newly formed bone is laid down on the reabsorbed surface of the old bone after osteoclastic activity

(Davies, 1996) and cement lines are morphological structures which demarcate the area where bone reabsorption was completed and bone formation initiated (Pritchard, 1972; Parfitt, 1983). The width of cement lines has been variously reported as ranging from 0,2 to 5 μm (Philipson, 1965; Villanueva et al., 1986). Cement lines contain 'ground substance' like sulphated polysaccharide complexes (Frasca, 1981) and osteopontin (McKee and Nanci, 1993) which is implicated in osteoblasts attachment (Butler, 1989). Davies (1996) observed that the interfacial structure achieved in vitro between bone and implant is equivalent to the cement line structure observed at the remodelling sites in natural bone tissue. When the implant is positioned firmly fixed into the host bone cavity (primary stability) the early deposition of a cement line from the damaged host bone and a similar mineralized layer on the implant surface can be seen. These double similar events suggest that the implant surface may be positively recognizable from the osteogenic cells as a biomimetic scaffold which may favour early peri-implant osteogenesis.

5. Biological implant fixation

A few days after implantation osteoblasts begin to deposit collagen matrix directly on the early formed cement line/lamina limitans layer described on the implant surface (Linder, 1985; Albrektsson and Hansson, 1986; Davies et al., 1990; Nanci et al., 1994; Murai et al., 1996; Davies, 1996; Puleo and Nanci, 1999) (Fig. 4). Recently Meyer et al. (2004) indicated that even osteoblasts in direct contact with the implant surface of both loaded and unloaded implants inserted in mandible of minipigs are able to produce fibronectin, fibronectin receptor and osteonectin on the implant surface.

Early bone formation in the peri-implant environment is the result of an appositional process on the cement line/lamina limitans holding onto the solid surface of the implant. The osteoblasts cannot always migrate so rapidly to avoid being completely enveloped by the mineralizing front of calicifying matrix and thus they become clustered as osteocytes in bone lacunae (Fig. 5). This type of mineralization may be compared to the so called 'static osteogenesis' described in the building of the first trabecular bony framework (Ferretti et al., 2002). In this study the osteoblasts may be considered 'stationary osteoblasts' which transform into osteocytes, clustered within confluent lacunae, in the same place where they differentiate.

The early deposition of new calcified matrix on the implant surface is followed by the arrangement of the woven bone and bone trabeculae developing in tridimensional directions and delimiting marrow spaces (Franchi et al., 2004b). This tissue consists of woven bone, cancellous bone or trabecular bone and is particularly suitable for the implant healing process as it shows a very active wide surface area, contiguous with marrow spaces including

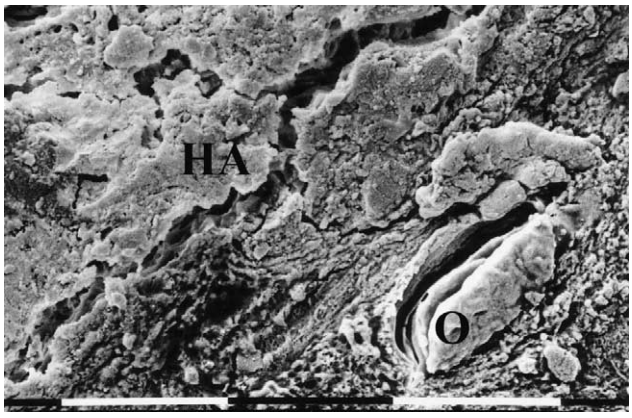

Fig. 4. Scanning electron microscopy of an HA-coated titanium dental implant from human. On the bottom right side, around an osteocyte (O) next to the implant surface, collagen fibrils of a newly formed bone (see enlargement of this picture in Fig. 5) in close contact with the HA surface (HA) are seen. Bar = 10 μm.

many vessels and mesenchymal cells (Franchi et al., 2004a,b) (Fig. 3). Marrow tissue of this bone containing a rich vasculature supports mononuclear precursors of osteoclasts so bone trabeculae remodels faster than cortical bone (Davies, 2003). Firstly, rapid woven bone formation occurs on implants to restore continuity, even though its mechanical competence is lower than that of lamellar bone on account of the random orientation of its collagen fibers (Probst and Spiegel, 1997). There is evidence of woven bone during embryonal skeleton development and rapid growth stages when it is then replaced with the lamellar bone in the normal skeleton on completion of bone growth. Woven bone is, in fact, composed of coarse loosely-packed collagen fibers of varying size, distributed without any ordered spatial arrangement, and containing more sulphated glycosaminoglycans, thus contrasting with the regularity and mineralization of lamellar bone (Chappard et al., 1999).

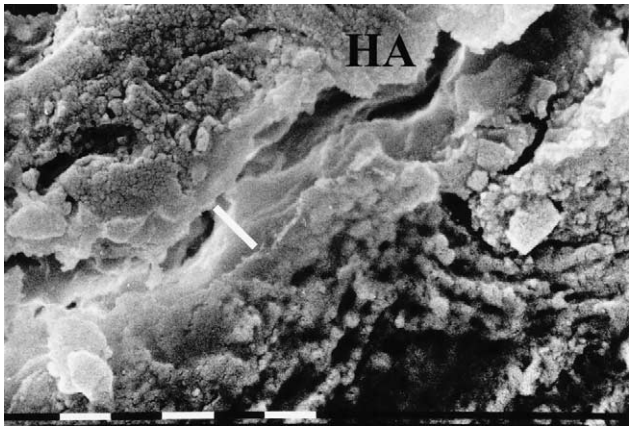

Fig. 5. Enlargement of picture 4. An afibrillar layer of calcified material is present (\) between the newly formed peri-implant bone including calcified collagen fibrils in the lower right side of the picture and the HA implant surface (HA). Bar = 1 μm.

Secondly, woven bone is progressively remodeled and substituted by lamellar bone and may reach a high degree of mineralization (Chappard et al., 1999). Three-months post-implantation, a mixed bone texture (woven and lamellar matrix) has been found around different types of Ti implants (Chappard et al., 1999; Giavaresi et al., 2003b).

The early peri-implant trabecular bone ensures tissue anchorage that corresponds to biological fixation of the implant. This is quite different from the mechanical implant stability easily obtained during the implant insertion. In the presence of newly formed peri-implant trabecular bone on the implant surface the removal torque values of implants with different surfaces are much higher than the insertion torques recorded during insertion of the same implants (Buser et al., 1998). The trabecular bone is the healing calcified tissue which can fill the gap between implant and bone more rapidly, and offer a mechanical resistance to loading thanks to its three-dimensional structure (a network of bone trabeculae arranged in arches). Peri-implant osteogenesis consists in woven bone and trabecular bone formation which proceeds in two different directions: from the host bone towards the implant surface (*distance osteogenesis*) and from the implant toward the healing bone (*contact osteogenesis*) (Davies, 1998; 2003) (Fig. 6). This last bone formation is 30% faster than the former and is prevalently observed in rough implant surfaces (Puleo and Nanci, 1999). Contact osteogenesis may better contribute to the development of biological implant fixation as new bone directly forms on the implant surface. As on his surface no bone was present when the implant was inserted, this osteogenic process is also called *de novo* bone formation (Davies, 2003).

Host bone chips, produced by the burr action, have been observed just enveloped in woven and trabecular bone suggesting that they may improve and guide peri-implant osteogenesis acting as osteoconductive and osteoinductive biological material (Franchi et al., 2004a, 2005-in press).

A decreased number and/or activity of cells of the osteogenic lineage (mesenchymal staminal cells, osteoblasts) an increase in osteoclast activity, an imbalance between anabolic and catabolic local factors acting on bone formation and remodelling, an abnormal bone cell reactivity in proliferation rate and systemic activity to systemic and local stimuli and mechanical stress and an impaired vascularization (Fini et al., 2004; Augat et al., 2005) have been implicated as major determinants of an increased failure risk of implantation surgery in aged and osteoporotic patients (Augat et al., 2005).

Vascularization is of critical importance for the osteogenetic process (Augat et al., 1999; Carano and Filfaroff, 2003). The process of tissue differentiation is strictly dependent on tissue vascularity and ossification is closely related to the revascularization of the differentiating tissue (Carter and Giori, 1991). Angiogenesis, the formation of new vessels from pre-existing vasculature, is impaired

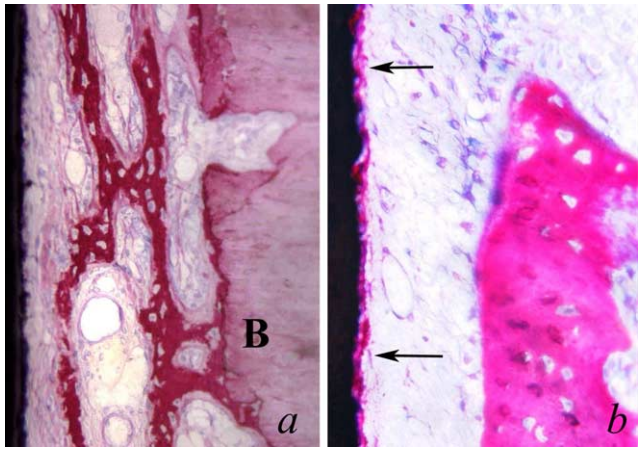

Fig. 6. Titanium dental implant inserted in sheep femur 14 days after surgery. Ground section observed at light microscope. (a) The gap between the implant surface and the host bone (B) is filled by newly formed trabeculae developing from the host bone towards the implant surface (distance osteogenesis). The newly formed network of bone trabeculae ensures the biological fixation of the implant and surrounds marrow spaces containing many mesenchymal cells and wide blood vessels. (b) The sandblasted surface of the implant is widely covered by a thin layer of calcified and osteoid tissue deposited by osteoblats directly on the implant surface (contact osteogenesis) (arrows). On the right, newly formed bone with rounded osteocytes in large lacunae is present. Many blood vessels and mesenchymal cells fill the spaces where no calcified tissue is present.

with aging (Augat et al., 1999; Martinez et al., 2002; Shimada et al., 2004; Bach et al., 2005). It is now universally recognised that osteoporosis and aging are associated with a spontaneous increase in pro-inflammatory cytokines including TNFα, Fas ligand, IL-6, IL-1, PGE2 (Garcia-Moreno et al., 2004; Raisz and Rodan, 1998; Villareal and Morley, 1994), whereas levels of bone-forming factors (IGF-1, TGF-β1) are decreased in osteoporotic patients (Raisz and Rodan, 1998). A decreased capacity of osteoblasts isolated from osteoporotic bone to proliferate in response to systemic or locally released osteotropic factors has been observed (parathyroid hormone, growth hormone, calcitonin, TGF-β1, IGF-1, PDGF (Pfeilschifter et al., 1993; Wong et al., 1994). These changes have been observed in different in vivo studies performed on pathological animal models by the decrease of trabecular bone volume and other static and dynamic histomorphometric parameters as well as of bone-to-implant contact around implants (Fini et al., 1997; 2001; 2004; Rocca et al., 2001; Giavaresi et al., 2001; Nicoli Aldini et al., 2002, 2004) (Fig. 7).

6. Influence of loading on peri-implant osteogenesis

Primary stability and postponement loading (3–6 months after surgery) have long been considered necessary for the osseointegration of endosseous dental implants (Chiapasco, 2004; Nedir et al., 2004). Implant stability at

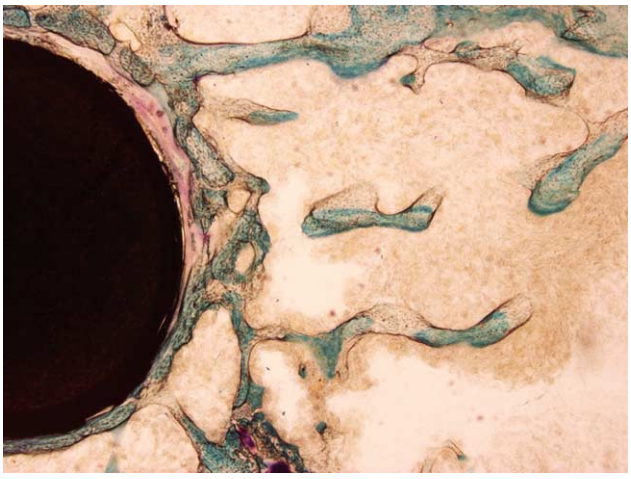

Fig. 7. Transversal section of a titanium implant 1 month after implantation in distal femur of ovariectomized osteoporotic rats. Trabecular bone rarefaction and interposition of fibrous tissue at the bone-implant interface. Staining with acid fuchsin and fast green.

the time of insertion and during peri-implant healing is critical to clinical success (Horwitz et al., 2003; Romanos, 2004; Degidi and Piattelli, 2005) as biomechanics are strictly related to osteogenesis at the implant-bone interface. An excessive loading of the implant may determine a high interfacial micromotion during bone healing which damages the fibrin network and new vasculature of early bone healing (Szmukler et al., 1998; Puleo and Nanci, 1999; Degidi and Piattelli, 2005). This implies implant mobility with a progressive marginal bone loss and final implant failure. The weak points may be located at the afibrillar layer on the implant surface which lacks substantial tensile or shear strength (Puleo and Nanci, 1999) probably due to the absence of collagen, the elastic component of bone.

For a long time it was assumed that premature loading limited peri-implant osteogenesis inducing a peri-implant fibrous tissue formation, and osseointegration was the necessary condition for applying a prosthesis with functional loading to the implants (Branemark et al., 1977; 1985). However, physiological loading using low forces can promote early peri-implant osteogenesis (Carter, 1987; Piattelli et al., 1993; Simmons et al., 1999; 2001a; Meyer et al., 2004; Romanos, 2004) and peri-implant tissue formation is related to the local mechanical environment at the interface bone-implant (Szmuckler-Moncher et al., 1998; Pilliar, 1991). As immediate implant loading can shorten treatment time to the satisfaction of patients, clinicians have studied guidelines for immediate and early implant loading (Mish, 2004). A 1-year follow-up study on the outcome of immediate and early loaded implants (from 0 to 11 days after surgery) in selected patients showed results comparable to those achieved with a delayed implant loading (Luogo et al., 2005). A survival rate of 96.7% of immediately loaded transmucosal single implants in mandible was reported after a 1-year study (Cornelini et al., 2004). Early loading (2 weeks after implantation) of sandblasted and acid-etched implants in posterior mandible showed a survival of 100% (Salvi et al., 2004). A long-term clinical survival study (7-year follow-up) of 93 immediately loaded dental implants demonstrated a clinical success of 93.5%, primary stability and quality of bone being fundamental to allow immediate loading (Degidi and Piattelli, 2005). Payne et al. (2003) suggest that functional loading of endosseous dental implants with mandibular overdentures is possible as early as 2 weeks after surgery. In immediate loading implants Horwitz et al. (2003), suggest that insertion torque is correlated to primary implant stability measured by resonance frequency analysis, and suggest that primary stability may be influenced mainly by implant diameter and not by implant length, location or bone level.

Simmons et al. (2001b) suggest that the undisturbed osseointegration process is the result of a proper implant macro-design which prevents peak strains at the interfacial layer, as physiological bone loading (500–3000 micro-strains) develops mature bone formation whereas higher peaks strains produce immature bone mineral formation and fibroblastic cell pattern (Meyer et al., 2004).

7. Bone remodelling after osseointegration

Like normal and physiological bone adaptation in the skeleton, wound maturation around implants via modelling and remodelling mechanisms, expected to be the two primary mechanisms by which bone at the interface can adapt to mechanical loading, are thought to be responsible for reshaping or consolidation of bone at the implant site (Brunski, 1991). Mature adult bone is continuously being turned over, so that the net activity of bone resorbing cells equals the net activity of bone forming cells. Remodeling comprises the process of bone resorption followed by bone formation and provides a mechanism for self repair and adaptation to stress. Generally, the remodelling process starts as a consequence of a fatigue damage to bone and involves four different processes: osteoclasts activation, bone resorption, osteoblasts activation, and finally mineralization of new bony tissue (Kanis, 1997). The first three processes represent the modelling phase which is mainly influenced by biomechanical stability of an implant in its healing site (Brunski, 1991). The peri-implant healing may be compared to a wound tissue repair process: the gap between implant and host bone cavity is immediately filled by a blood clot early substituted by a trabecular bone which then remodels into a mature lamellar bone. This final condition shows the mature bone in direct contact with most of the implant surface, and is called implant osseointegration (Branemark et al., 1977; 1985; Adell et al., 1981; Nevins and Langer, 1993). Mature bone with bone lamellae arranged in osteons is a vital tissue with the physiological turnover of bone tissue.

For this reason, and considering the occlusal loading forces applied to endosseous dental implants it is reasonable that bone in contact with the implant surface may undergo morphological remodelling. In fact, during the remodelling of the peri-implant bone, new osteons circled around the implant with their long axes parallel to the implant surface and perpendicular to the long axis of the implants. The remodelled bone can extend up to 1 mm from the implant surface (Roberts, 1988) and for this reason this calcified tissue belongs to the bone/implant interface (Brunski, 1991) (Fig. 8). The turnover of peri-implant mature bone in osseointegrated implants is confirmed by the presence of medullary or marrow spaces containing osteoclasts, osteoblasts, mesenchymal cells and lymphatic/blood vessels next to the implant surface (Fig. 9). It is likely that the small areas of marrow tissue still detectable 90 days after implantation around unloaded implants may support and favour the biological turnover of the bone at the interface with the implant (Franchi et al., 2004a,b).

Bone remodelling is a complex process involving not only interactions between cells of the osteoblastic lineage and bone matrix proteins, but also a variety of systemic and local regulatory factors (Dempster, 1995). The cells of bone coordinate their proliferation and activities by the expression and response to hormones (PTH), and cytokines (IGFs, TGF-β1, FGF, BMP, EGF, PDGF, etc.) (Dempster, 1995; Augat et al., 2005). Moreover, bone cells and, in particular osteocytes, are sensitive to mechanical loading and respond to it by proliferation, matrix synthesis and modulation of cytokine, NO, PGE2 and other growth factor expression (Rubin et al., 1992; Klein-Nulend et al., 2002). The capacity not only to express bone stimulating factors, but also the cell capacity to react to these factors, may alter with increasing age and hormonal changes (Augat et al., 2005). The capacity of osteoblasts to proliferate in response to systemic or locally released osteotropic factors was decreased when stimulating osteoblasts from 61- to 70 year-old donors with parathyroid hormone, growth hormone and calcitonin, TGF-β1, IGF-I, PDGF (Pfeilschifter et al., 1993). A decreased response to PTH in osteoporotic and older patients compared to younger subjects was also found for the cAMP response (Wong et al., 1994). All these aspects may lead to the imbalance between bone resorption and bone formation and a consequent decrease in implant osseointegration and thus mechanical stability.

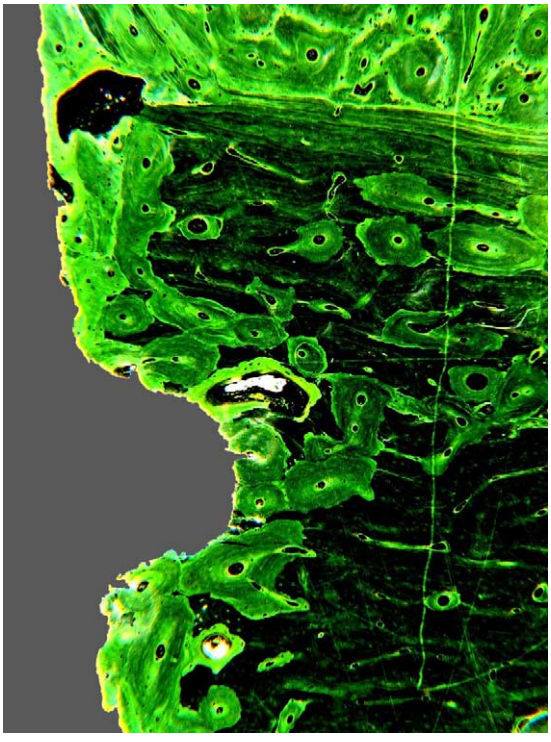

Fig. 8. Sandblasted titanium dental implant inserted in sheep femur and observed at light microscopy 90 days after surgery. The negative effect of the picture (the implant=I is on the left) was obtained using an image-processing programme. The imaging-effect better shows the newly formed osteons which circle around the implant with their long axes parallel to the implant surface and perpendicular to the long axis of the implant, and extend far from the implant surface demonstrating that a remodelling of the host bone has just occurred.

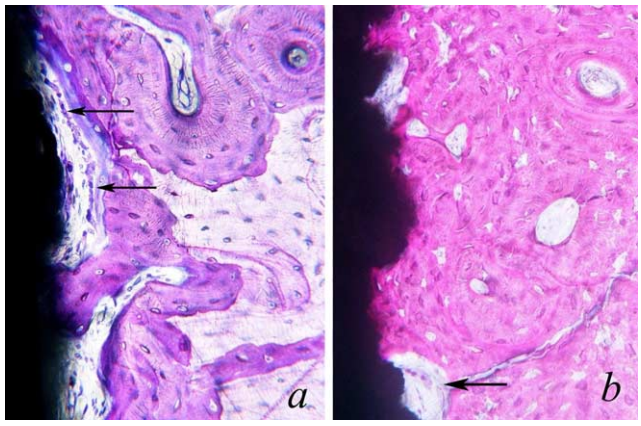

Fig. 9. Titanium plasma-sprayed (TPS) implant inserted in sheep femur 90 days after implantation. (a) In some areas at the implant-bone interface the newly formed bone indicates that a bone remodelling of the peri-implant mature bone has just occurred (the recently new formed bone is more stained), while osteoid tissue produced by osteoblasts (arrows) shows that a new osteogenesis is underway. (b) In the lower part of the picture a marrow space at the implant surface contains an osteoclast (arrow) presumably involved in resorption of peri-implant lamellar bone.

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