Platform switching configuration

and peri-implant soft and hard tissue response

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Inhaltsverzeichnis

Abkürzungsverzeichnis

Seite

AA % **25; 29**
collagen content

ALP **26**
alkaline phosphatase

BMP-2 **26**
bone morphogenetic protein-2

BOP **29**
Bleeding on probing

BSP **26**
biglycan, bone sialoprotein

CC **28**
connective component of biologic width

CD-3 **25**
antigen for characterize Linf T

CT **15**
connective tissue

ED1 **26**
Anti-cd68 antibody

IAJ **15; 28; 31; 35; 36**
implant abutment junction

ICT **20; 25; 28; 29; 34; 35**
infiltrated connective tissue

IL-1β **26**
interleukin 1-beta

JE **28; 29; 34**
junction ephitelium

MVD **25; 29**
microvascular density

OC osteocalcin	**26**
OP osteopontin	**26**
OPG osteoprotegerin	**26**
PC prosthetic component	**28**
PD probing depth	**29**
PMNL polymorph nuclear leukocytes	**17**
PMNS polymorphonucleates	**17**
RANKL receptor activator of nuclear factor kappa-B ligand	**26**
SD standard deviation	**29**
TNF-α tumor necrosis factor alpha	**26; 30; 38**
TRAP artrate-resistant acid phosphatase	**25**
VEGF vascular endothelial growth factor	**26**
vWF von Willebrand factor	**26**

1. Deutsche Zusammenfassung

1.1 Einleitung

Dentale Implantate stellen eine kombiniert chirurgisch-prothetische Methode zum Ersatz von fehlenden Zähnen dar. Herkömmlicherweise bestehen diese aus dem Implantat und einer dem Durchmesser des Implantates entsprechenden Aufbaukomponente. Longitudinalstudien haben gezeigt, dass es nach Implantatinsertion zur Ausprägung der sogenannten biologischen Breite mit 1-2mm periimplantärem Knochenverlust kommt.

Kürzlich veröffentlichte Studien zeigten, dass ein Missverhältnis zwischen Implantat und Aufbau eine bessere Stabilität des periimplantären Knochenniveaus gewähren. Dennoch bleibt das eher unkonventionelle Konzept dieses sog. „platform switchings" histologisch fragwürdig und steht unter dem Verdacht, die bakterielle Invasion in den periimplantären Spalt zu begünstigen.

Gleichermaßen enthalten alle Daten, welche die Knochenniveauschwankungen um Implantate mit „platform switching" beschreiben – obwohl diese geringer ausfallen als bei herkömmlich versorgten Implantaten – eine große Schwankungsbreite.

Dies könnte bedeuten, dass eine individuelle Knochenstruktur die Dimension der „biologischen Breite" und darüber hinaus die Veränderungen im Knochenniveau bedingt.

Aus diesem Grund war das Ziel dieser Arbeit, die folgenden Fragen histologisch zu ergründen:

1. Wie kann eine Hart- und Weichgewebsadaptation an eine unkonventionelle Implantat-Abutment-Konfiguration positive klinische Ergebnisse erklären?
2. Kann eine durch „platform switching" auftretende Veränderung mittel-und langfristig zu einer negativen Entzündungsreaktion führen?
3. Ein weiteres Ziel der Untersuchung war es, in einem klinischen Ansatz herauszufinden, ob sich unterschiedliche histologische Knochenstrukturen auf Veränderungen des periimplantären Knochenniveaus auswirken.

1.2 Material und Methoden

Um diese Hypothesen zu untersuchen, wurden drei Studien durchgeführt:

1. Eine Tierstudie (Minipig), um die Struktur der biologischen Breite um herkömmlich und um mittels „platform switching" versorgte Implantaten histologisch zu untersuchen.
2. Histologische und immunhistochemische Untersuchungen an menschlichem Gewebe zur Beschreibung der Entzündungsreaktion nach Implantatbelastung an herkömmlich und mittels „platform switching" versorgten Implantaten.

3. Vergleichende klinische Longitudinalstudie zur radiographischen Veränderung des Knochenniveaus bei konventionell und mit „platform switching“ versorten Implantaten.

1.3 Zusammenfassung der Ergebnisse

1. Im Vergleich zum herkömmlich versorgten Implantat haben Situationen mit „platform switching“ einen geringeren Einfluss auf die Länge der epithelialen Komponente der biologischen Breite, während der Bindegewebsanteil nachgewiesenermaßen über der Implantatplattform und in direktem Kontakt mit den prothetischen Komponenten ansetzte.
2. Es konnte kein statistisch signifikanter Unterschied bei beiden Hauptgruppen in Bezug auf Entzündungsreaktion, Gefäßdichte und Kollagengehalt gefunden werden. In allen Gruppen zeigten die meisten Proben mit gut erhaltenem Epithel eine kleine, lokale Entzündungsreaktion in Verbindung mit wenig organisierten Kollagenfasern und erhöhter Vaskularisation.
3. Nach Standardisierung des periimplantären Knochen-Remodellingsteilweise ist die amerik. Version verwandt worden, also remodeling, teilweise die britische Version, also remodelling. Bitte einheitlch konnte auf eine geringe Korrelation zwischen Knochenniveauveränderung und dem Nachweis von an anabolen Biomarkern, aber einen indirekten Zusammenhang zwischen Veränderung des Knochenniveaus und katabolen Biomarkern geschlossen werden.

1.4 Schlussfolgerung:

Aus histologischer Sicht bietet das Verbindungsdesign des „plattform switchings“ dem Eindringen von Bakterien und nachfolgender Ausbreitung einer Entzündungsreaktion kein günstiges Umfeld. Gleichermaßen bewirkt die Ausbildung der biologischen Breite das Ausbleiben eines Knochenverlusts und könnte somit die herkömmliche inflammatorische Reaktion an modifizerten Implant-Abutment Verbindungen erklären. Dennoch zeigten die Ergebnisse der klinisch-histologischen Studie, dass das periimplantäre Knochen-Remodelling von der individuellen Knochenstruktur des Patienten abhängt.

2. Abstract

2.1 Introduction

Oral implants are a surgical/prosthetic integrated method to restore missing teeth. Their original configuration provide for matching diameter implant platform and prosthetic components (prosthetic components diameter = implant platform diameter). Longitudinal studies have demonstrated that the matching diameter fixture and prosthetic components configuration leads to a formation of a so called “biologic width” with 1-2 mm of peri-implant bone resorption.

Recently published studies have shown that prosthetic components smaller in diameter compared to the implant platform (prosthetic components diameter < implant platform) allow better bone level maintenance. However, the diameter mismatching configuration of the platform switching concept still remains histologically debatable and might suggest to be prone to a bacterial invasion, because this configuration moves the infected site away from the sensitive environment (bone).

At the same time, all data expressing bone level changes around platform switched implants, although more positive (0.5mm on average) compared to traditionally restored implants (1.5mm on average), present very often high variability. It might suggest that an individual bone pattern could influence the dimension of biologic width re-establishment and, thus, bone level changes in the long run.

Therefore, the aim of this thesis was to verify histologically:

1. How hard and soft tissue adaptation to the platform switching configuration can explain the positive clinical results.
2. The diameter mismatching configuration of platform switched implants could lead to a negative inflammatory response in the middle/short term.
3. An additional aim was to test clinically if an individual bone pattern (structure, “bone quality”) could affect peri-implant bone level changes.

2.2 Materials and Methods

To test these hypotheses, 3 different studies were performed:

1. Animal (minipigs) study to compare the structure of biologic width around implants restored using traditional approach and platform switching histologically.

2. Histological and immunohistochemical studies in human specimens analyzing soft tissue inflammatory reactions after loading around implants restored using traditional approach and platform switching
3. Clinical study comparing radiologic bone level changes with histological and immunohistochemical aspects of bone alterations longitudinally after loading around implants restored using traditional approach and platform switching.

2.3 Results

The most important results were:

1. Compared to traditionally restored implant, the platform switching configuration may have a minor impact on the length of the epithelial component of the biologic width, while the connective tissue compartment was demonstrated to be seated over the implant platform and in direct contact with prosthetic components.
2. No significant difference was found between platform switching and traditional matching diameter configurations in terms of inflammatory infiltrate, micro-vascular density and collagen content. In all groups, most samples with a well-preserved junctional epithelium showed a small and localized inflammatory infiltrate associated with not-well-oriented collagen fibers and an increased vascularization.
3. After statistical leveling (standardization) of peri-implant bone remodeling values, a borderline direct correlation between peri-implant bone changes and levels of anabolic biomarkers and a borderline indirect correlation between bone changes and levels of catabolic biomarkers was found.

2.4 Conclusion

From a histologic point of view, the particular design of platform switched implants do not offer a favorable environment for bacterial colonization and subsequent inflammatory infiltration. At the same time, the medialization of biologic width seems to prevent bone downgrowth and could explain the positive soft tissue inflammatory response to this diameter mismatching implant/abutment configuration.

However, histologic *in vivo* study demonstrated that peri-implant bone remodeling might be influenced by the “individual bone resorption pattern” of each patient.

3. Cumulative Study Overview

3.1 Introduction

Oral implants are a surgical/prosthetic integrated method to restore missing teeth. In the late 1960s and early 1970s, criteria for the predictable integration of endosseous dental implants were proposed. Fundamental experimental studies conducted by Brånemark et al. (1977) and Schroeder et al. (1981) demonstrated that titanium implants regularly healed with a direct bone-to-implant contact, so called “osseointegration” or “functional ankylosis” (Albrektsson et al., 1991).

Many clinical studies have demonstrated in recent years that implant integration can be achieved and maintained in various areas of the mouth on long term basis. In these studies two basic approaches to the placement of dental implants emerged: submerged two-stage as described by, De Bruyn et al., 2013 and non-submerged or one-stage as reported from Weber et al., 1992. In the submerged approach, the implant is placed at or below the bone crest level underneath the soft tissues and allowed to heal typically for 3 to 6 months. A second stage surgery is then required to uncover the implant with a secondary prosthetic component placed on the top of the implant. The restoration is then located on the abutment. This procedure results in 2 gaps, one located at the crestal level and one slightly above the soft tissue margin. In the non-submerged approach, the implants itself extend beyond the alveolar crest and there is only one microgap, below or on the gingival margin (Fig 1).

Fig 1.

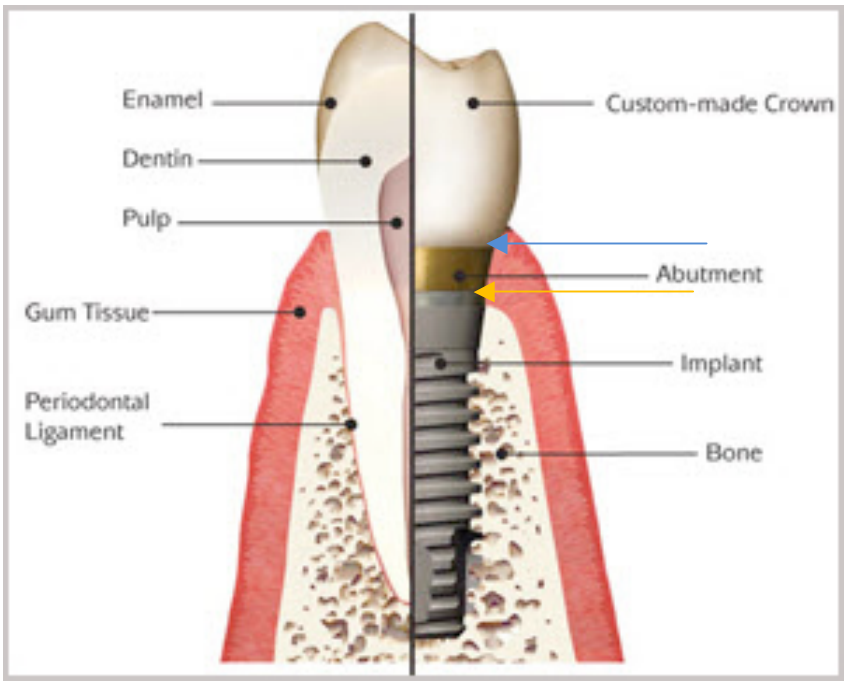


Fig 1: A two-stage submerged dental implant compared to a normal tooth. Gaps at the implant/abutment interface (orange arrow) and at abutment/crown interface (blue arrow) can be present (http://www.sweden-martina.com)

Surgical placement of two-piece implants, using a submerged, non-loaded healing protocol resulted in crestal bone levels 1.5 to 2 mm apical to the abutment/implant junction (IAJ), after 1 year of loading (Hermann et al., 2001; Manz, 2000). Several factors may affect this post-restorative biologic process. Although position of the implant platform (Grunder et al., 2005), biomechanical stress (Isidor, 2007) or framework misfit (Assuncao et al., 2011) were controversially supposed to be related to this process, peri-implant bone resorption seems to be the “physiological” response to bacterial invasion of the implant/abutment interface (Broggini et al., 2006). From an etiopathogenetic point of view, the bacteric contamination at the IAJ produces, in fact, a variable amount of bone resorption, leading to a so called “biologic width re-establishment” (Fig. 2), similar to the one described around teeth by Gargiulo (1961), (see Piattelli et al., 2011).

Fig. 2.

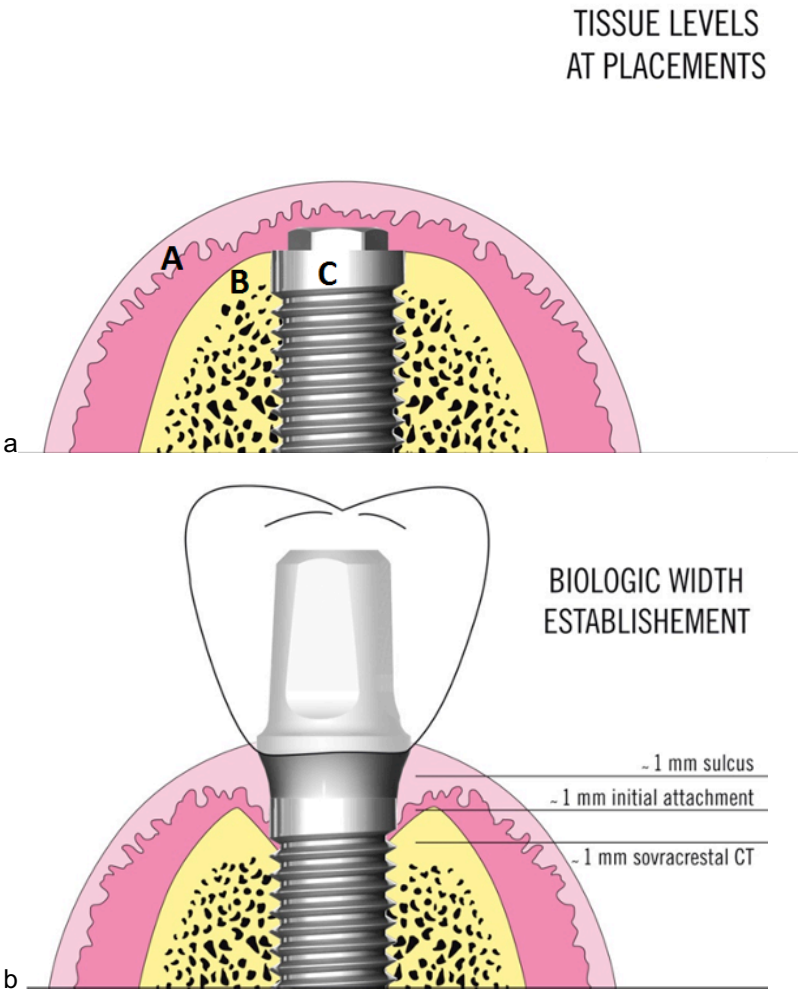


Fig. 2: Hard tissue level at the time of implant placement (a). Formation of the biologic width with different soft tissues layers, following abutment connection (b).A: soft tissues, B: bone, C: implant (from Canullo et al., 2011)

Focusing on the interaction between soft and hard tissues and bacteria, several investigators have suggested that crestal bone remodeling could be the result of localized inflammation within the soft tissue located close to the implant-abutment connection due either to the soft tissue's re-establishing the biologic width or to the presence of a septic reservoir at the implant-abutment interface. (Ericsson et al., 1995; Jensen et al., 1997; King et al., 2002)

Several studies in human and animal models have examined and described the anatomy of the biologic width. It is now accepted that the biologic seal around oral implants consists

of two principal layers, regardless of the surgical protocol that was used (one- or two-stage): the epithelial attachment and the underlying connective tissue barrier.

The epithelial component of the implant–mucosa interface has been demonstrated to form a cuff–like barrier which adheres to the surface of titanium abutments (Abrahamsson et al., 1998a). Histological studies suggest that peri-implant epithelium is directly attached to the titanium via hemidesmosomes (Lindhe et al., 2000). The morphology and structure of the connective tissue barrier has also been investigated in animals (Cochran et al., 1997). The connective tissue immediately next to the implant surface is characterized by an absence of blood vessels and the presence of abundant fibroblasts, interposed between thin collagen fibers. The connective tissue away from the implant contains more abundant fibers, which may run in a variety of directions and appears to be functionally organized. Therefore this implant/soft tissue interface may be interpreted as a scar-like response to implant surgery, formed to keep bone protected from the contaminated intra-oral environment.

After the placement of an abutment (both in single and two stage implant surgical protocols), the connective tissue plays a key role in soft tissue healing and, therefore, in the histomorphogenesis of the biologic width (Rompen et al., 2006).

On the natural tooth, dento-alveolar collagen fibers are firmly inserted into cementum and bone. They are perpendicularly or obliquely oriented to the tooth surface, serving as a barrier to epithelial migration and bacterial invasion (Piattelli et al., 2011). In contrast, there is no cementum on implant surfaces: the orientation of the connective fibers in the supracrestal soft tissue compartment is parallel to the implant surface, providing no effective connection to the implant (Berghlund et al., 1991). As the connective tissue attachment is considered of paramount importance in supporting the epithelium and blocking its apical migration, its absence around implants represents a weak area in the peri-implant defense mechanism: tearing the connective tissue/implant interface could induce, due to lack of soft tissue stability, apical migration of the junctional epithelium. From a clinical point of view, this could lead to gingival recessions or pocket formation and bone resorption.

The morphogenesis of biologic width (Piattelli et al., 2011), as previously mentioned, is basically the same in the two different clinical situations routinely adopted: single stage implant surgery and second stage surgery for exposure of a previously placed implant (Berghlund et al., 2007).

According to Berglund et al. (2007) and Tomasi et al. (2013), immediately following second surgery, a blood clot fills the space between the mucosa and the implant and the platelets release chemotactic and growth factors. After 4-7 days, the blood clot is infiltrated by several polymorph nuclear leukocytes (PMNL) entangled in a dense fibrin network; this starts the formation of an initial seal at this early stage of healing. However, the protective function of soft tissues is still incomplete and therefore, during the first week after single stage implant surgery, bacteria are allowed to accumulate around the abutment-implant connection: the result is an inflammatory response in the surrounding tissues. Bacteria may cause peri-implant tissues damage directly (by releasing exotoxins and endotoxins) and indirectly (by activating systemic and local immune responses through PMNs and macrophages).

Approximately two weeks later, initial epithelial growth can be observed. These cells extend from the basal epithelium toward the smooth surface abutment, which is already contaminated. The smooth surface does not offer a stable attachment and causes initial apical migration.

After two weeks, according to one widely used restorative protocol, the healing abutment is removed and implant level impression is made. There is histologic evidence that this procedure also produces an additional apical migration of the epithelium.

At the 3rd and 4th week, following the combined effects of bacteria and immune response, bone resorption can be observed. Bone remodels in an apical direction and is replaced by a circumferential band of connective tissue with abundant inflammatory cells (Abrahamsson et al., 1998b). At this stage, additional insertions and removals of healing abutments for prosthetic procedures typically occur.

At the 5th and 6th weeks, connective tissue results attached to a horizontal surface (the first thread of the Branemark type implant). Ingrowth (maturation and growing) of the connective tissue on to the rough surface inhibits epithelial downgrowth and permits its attachment to the lateral surface of the implant (Rompen et al., 2006).

At the 8th-12th week, when the abutment and crown are placed onto the implant, morphogenesis of the biologic width is concluded. Definitive establishment of the biologic width takes the form of a band of 1.5 mm supra-alveolar connective tissue that provides support and nutrition to the epithelium above. The connective tissue cells are dispersed in a dense extra-cellular matrix. Connection of this tissue to the implant surface depends upon the extra-cellular matrix. Fibroblasts and the extracellular matrix tend to interdigitate into the rough surfaces of the implant (Rompen et al., 2006).

According to the literature, connective tissue fibers run parallel to the implant surface in the most coronal portion. In the most apical region, the fibers tend to be arranged in oblique or perpendicular directions (Piattelli et al., 1997, 2003). Phase-contrast microscopy revealed that the collagen bundles were not randomly oriented, but rather organized into three major systems: longitudinal, circular and oblique oriented fibers (Schierano et al., 2002). According to these studies, it can be concluded that re-establishment of the biologic width is responsible for early crestal bone resorption around endosseous dental implants. Controversially, any change in the macro design of the prosthetic restoration could influence peri-implant soft and hard tissue re-arrangement.

However, the unavoidability of this peri-implant bone remodeling was put under question by a study from Lazzara & Porter (2006), where it was shown that non-matching diameter abutment restoration could lead to a more favorable soft and hard tissue re-arrangement. During the past decade, wide-diameter implants (5.0 and 6.0 mm) were available, partly as "rescue" implants for failed standard 4.1 mm diameter implants, but also intentionally used in wide edentulous ridges. Originally, these larger diameter implants were restored with standard dimension abutments (having the same connection as the original 4.1mm diameter implants); the net result was that a circumferential horizontal difference could be observed between the implant seating surface and the seating surface of the restorative component. In this way, the outer edge of the implant-abutment interface was horizontally repositioned inward (towards the screw) and away from the outer edge of the implant platform. This prosthetic arrangement was defined as "platform switching " (Fig. 3).

Fig 3.

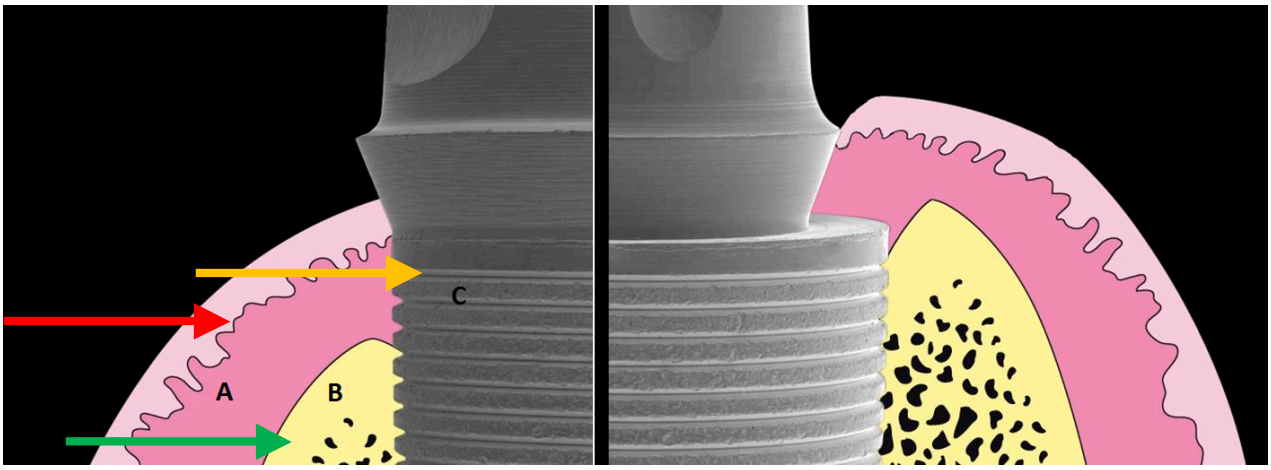


Fig 3: Soft tissue (A, red arrow) and bone (B, green arrow) remodeling according to traditional restoration: matching diameter abutment, (left) or “platform switching”:

mismatching diameter abutment (right). (C: Implant, yellow arrow) (from Canullo et al., 2011)

This long follow-up study (Lazzara and Porter, 2006) demonstrated with radiographic follow-up that wide-diameter dental implants restored with this "platform switching" technique resulted in a smaller than expected vertical change in crestal bone height around implants compared to traditionally restored implants. This study introduced the concept and described, in a non-analytic fashion, the clinical rationale and radiographic findings for this technique, retrospectively.

Several theories were adopted to explain the positive behavior of platform switching concept. Both histomorphometric studies and three-dimensional finite element models have showed the potential role of platform switching configuration to limit the peri-implant marginal bone resorption, optimizing spaces for the biological width components (Degidi et al., 2008), medializing implant abutment microgap and inflammatory cell infiltrate (Luongo et al., 2008), and shifting the area of maximum biomechanical stress towards the central axis of the implant (Maeda et al., 2007; Chang et al., 2010).

Prospective controlled clinical trials confirmed reduced bone remodeling values around implants restored with this prosthetic innovative concept compared to standard approach (Vela-Nebot et al., 2006; Cappiello et al., 2008).

Horizontal inward repositioning (medialization) of the implant-abutment interface could lead to two different results:

1) The overall effect of the inflammatory cell infiltrate (ICT) on the surrounding tissue may be reduced and an inflammatory infiltrate in the connective tissue was described to be localized over the entire surface of the implant platform and approximately 0.35 mm coronal to the implant-abutment junction (Fig 4a). This has been reported along healing abutments. A possible reason for bone preservation around a platform-switched implant, in fact, is supposed to be related to the inward (medial) shift of the inflammatory connective tissue zone at the implant-abutment junction (Fig 4b). Medialization of the biologic width is thought to reduce its injurious effect on alveolar bone adjacent to endosseous implants (Luongo et al., 2009).

Fig 4.

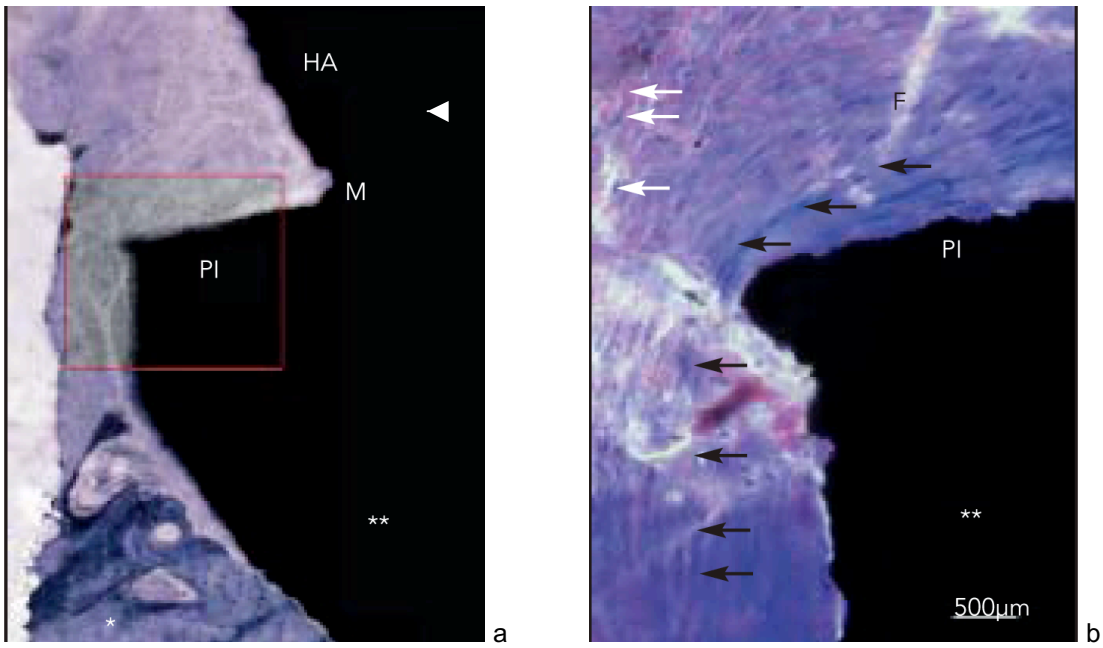


Fig 4a: Histologic view of the platform area. The collagen fibers of the connective tissue appear to be coronal to the platform (PI); HA = healing abutment; M = microgap; asterisks = bone; double asterisks = implant; acid fuchsine and toluidin blue staining, magnification 30xFig 4b: Higher magnification (100x) of the platform area: collagen fibers run toward the healing abutment (black arrows). Collagen fibers running circularly around the implant (white arrows). (from Luongo et al., 2010)

2) The platform surface not covered by the abutment increases the surface on which connective tissue can stabilize. In fact, it was observed that the horizontal mismatch promotes the presence of perpendicular fibers to the abutment and prevents apical down-growth of the junctional epithelium (Vela-Nebot et al., 2012)

However, in several studies analyzing platform switching, high variance of peri-implant bone level changes presented might suggest that the positive outcomes are the result not only of the mentioned prosthetic concept but they could be also related to an individual bone response. At the same time, since several implant systems with different implant/abutment mismatchings were involved in the previously mentioned studies, the high variance of the reported bone level changes might suggest also that there are biologic rules behind “platform switching” concept.

Following this hypothesis, own recent work has shown that bone loss seems to be related to implant/abutment mismatching in an inverse linear relationship (Canullo et al., 2010).

While a variety of clinical studies reported favorable outcomes with respect to preservation of crestal bone (for review see Atieh et al., 2010; Annibali et al., 2012; Al-Nsour et al., 2012; Cumbo et al., 2013), histological evidence relative to platform switching remains sparse and controversial. In fact, only two case-reports with human histology confirmed minimal crestal bone loss after a short period of loading (1 to 6 months) (Degidi et al., 2008; Luongo et al., 2009).

Several other histologic studies on animal models have been published. For example, in a study by Cochran et al. (2009), 60 implants with non-matching platform designs were placed in submerged or non-submerged modalities, and compared with traditional implants. After 6 months, crestal bone loss was significantly less important (five- to six-fold) at or in or around those sites with non-matched implant/abutment junctions placed at the bone crest when compared to matched implant/abutment components. Similar conclusions were reported by Weng et al. (2008).

On the contrary, Becker et al. (2007, 2009) did not find any statistically significant difference in buccal and palatal crestal resorption when comparing traditionally restored implants with those restored under a platform-switching concept after 4 to 24 weeks. Absence of statistically significant difference between matching diameter and platform switching restorations were found also in the study by Baffone et al. (2012):, matching diameter implants were compared to platform switched implants with 0.25mm mismatching in a study using dog model. Histological analysis failed to show also differences in peri-implant bucco-lingual tissue dimensions.

The controversial aspects of the results mentioned so far might be explained by the fact that different study designs were adopted. For example, in the study of Becker et al. (2007, 2009), the authors used implants inserted supracrestally: this approach, obviously, minimizes the advantages of platform switching. In the study of Baffone et al. (2012) different planes for histological analysis were used. For example, the bucco-lingual bone dimension was analyzed: being narrower than mesio-distal aspect, it could be more prone to amplify the resorptive effect of flap elevation and osteotomy site preparation.

Positive clinical outcomes of platform switching were confirmed by the last systematic review with meta-analysis (Athie et al., 2010; Annibali et al., 2012; Al-Nsour et al., 2012; Cumbo et al., 2013). The authors confirmed that this prosthetic approach appeared to be useful in limiting bone resorption. Nevertheless, these data should be interpreted

cautiously as significant heterogeneity and possible publication bias were noted. Finally they concluded that further research is needed to identify the factors most associated with successful outcomes

3.2 Aims

In spite of the good clinical results, however, the biological basis of this prosthetic concept still remains debatable and several comments could be raised. Despite the promising bone level maintenance of platform switching restorations in the long run, the diameter mismatching configuration of the platform switching concept might suggest to be prone to a bacterial invasion, because of the horizontal gap between implant collar and prosthesis (please see Fig 1).

At the same time, all data expressing bone level changes around platform switched implants in the mentioned studies are referred as mean values, very often with high standard deviation. It might suggest that an individual resorption bone pattern could influence the dimension of biologic width re-establishment and, thus, bone level changes in the long run.

Therefore, the aim of this thesis was to histologically verify

- how hard and soft tissue adaptation to the diameter mismatching configuration can explain the positive clinical results,
- how the mentioned diameter mismatching configuration of platform switched implants could lead to a negative inflammatory response in the middle/short term.

At the same time, additional aim was to test clinically if the presence of an individual bone pattern (structure, “bone quality”) could affect peri-implant bone level changes.

For this reason, three different studies were performed.

1. Animal (minipig) study aim to compare the structure of biologic width around implants restored using traditional approach and platform switching histologically (Farronato et al., 2012)
2. Histologic study in human specimens analyzing soft tissue inflammatory reaction longitudinally after loading around implants restored using traditional approach and platform switching (Canullo et al., 2010)

3. Clinical study comparing histologic aspect of bone and radiologic bone level changes longitudinally after loading around implants restored using traditional approach and platform switching (Canullo et al., 2011).

3.3 Materials and Methods

Experimental studies protocols were as following:

Study 1: The animals, 5 minipigs, were treated and housed according to law regulations in force in Italy (D.L. 116/92) and in the European Community (2007/526/CE 18 June 2007) at the laboratories of the Section of Agriculture Animal Husbandry Department of Animal Science and the Faculty of Veterinary Medicine, University of Milan, Italy. After total anesthesia, they received three implants each (Global, Sweden & Martina, Due Carrare, Italy) yielding a rough surface (ZirTis; zirconium sandblasted acid etched). Implants were inserted in native bone mesial and distal to the canine tooth with a 0.25mm implant/abutment mismatch and were placed flush (T0), 1mm below (T-1) and 1mm above (T+1) the alveolar bony crest, and as a control, one conventionally restored implant placed at the bone level. The implants were randomly inserted flapless into the mandible. Four months after implant insertion, the animals were sacrificed, and undecalcified block sections were obtained and used for histological analyses. In fact, sections were stained with a modified Goldner Trichromic staining combined with the count of osteoclasts following TRAP staining.

Study 2: In 14 patients, a total of 37 implants (Global, Sweden & Martina, Due Carrare, Italy) yielding a rough surface (ZirTis; zirconium sandblasted acid etched) were restored using abutments with the following mismatches: 0 mm (control group), 0.25 mm (test group1), 0.5 mm (test group2) and 0.85 mm (test group3). Four years after, loading all sites were clinically healthy, and soft tissue samples were harvested. Biopsies were processed for traditional histology and immunohistochemical analysis. Samples were processed to evaluate the inflammatory infiltrate area [inflamed connective tissue (ICT) using traditional Hematossilin-Eosin staining], the microvascular density (MVD using CD-3 immunostaining) and the collagen content (AA% using Sirius Red staining).

Study 3: Ten patients (24 implants) were randomly assigned to receive implants with different platform diameters (3.8, 4.3, 4.8, or 5.5 mm), all of which were restored with standard 3.8-mm-diameter abutments. Biopsy specimens were obtained prior to implant placement, and histologic and immunohistochemical analyses were performed. Immunohistochemical investigations were performed to identify anabolic markers (alkaline phosphatase [ALP], biglycan, bone sialoprotein [BSP], collagen type I, osteocalcin [OC], osteopontin [OP], osteoprotegerin [OPG], and runx2); catabolic markers (ED1, cathepsin K, interleukin 1-beta [IL-1β], receptor activator of nuclear factor kappa-B ligand [RANKL],

and tumor necrosis factor alpha [TNF-α]); the growth factors bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF); and vessels (von Willebrand factor [vWF]).

At the same time, standardized radiographs with templates were made at each site after implant placement and at 36 months after prosthetic loading and bone levels were determined.

The Pearson correlation test was used to detect eventual correlation between bone patterns (semi-quantitative immunohistochemically detected bone-biomarkers) and marginal bone loss. To prevent bias resulting from the different restorative concepts, the marginal bone loss data were standardized using the mean bone remodeling values within each group.

3.4 Results

At the end of the studies, the following results were obtained:

Study 1: The mean values for peri-implant bone resorption were 1.09±0.59mm (control), 0.51 (±0.27mm, T0), 1.50 (±0.46mm, T+1) and 1.29 (± 0.21mm, T-1), respectively. Statistically significant differences ($p < 0.05$) were found among test (T0, T-1) and the control sites. Control implants presented an average biologic width length of 3.2mm (±0.34), with a connective tissue adaptation compartment of 1.29mm (±0.54) and an epithelial attachment of 1.91mm (±0.72). T0, T+1 and T-1 implants presented with a mean biologic width of 2.05 mm (±1.21), 2.87mm (±1.36), 2.84mm (±0.91), respectively with a connective tissue adaptation compartment of 1.21mm (±0.97), 1.21mm (±0.65) and 1.50mm (±0.70) and an epithelial attachment of 0.84mm (±0.93), 1.66mm (±0.88) and 1.35mm (±0.44), respectively.

Differences between the configurations were mainly associated with the length of the epithelial attachment. The epithelial attachment was significantly longer in the control than in test sites ($p=0.014$). Focusing on the connective component of the biologic width, Control and test groups showed the same length, however in platform switching configuration, it was shown at the level of the implant abutment junction while in the matching diameter configuration, it was located below that reference (Figs. 5a and 5b).

Fig. 5

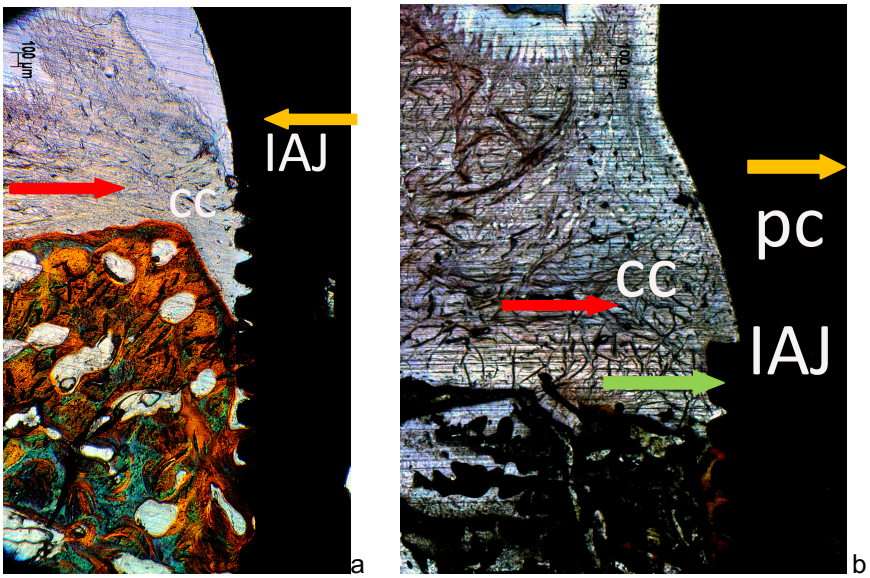
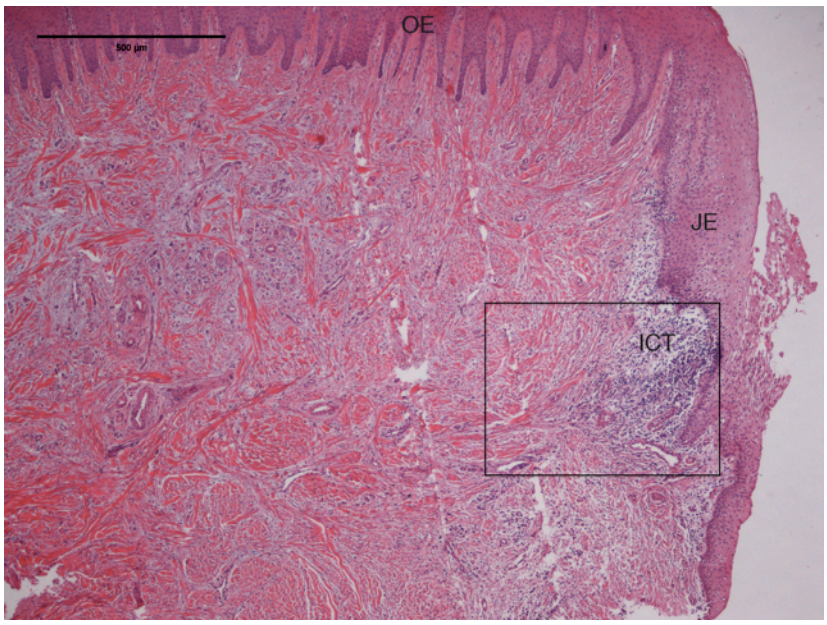


Fig 5:
a: Matching diameter restoration: massive bone level change. Connective component of biologic width (cc) is below the Implant/abutment junction (IAJ).
b: Platform switching restoration: minimal bone level change. Connective component of biologic width (cc) adjacent the Implant/abutment junction (IAJ) and prosthetic component (pc).
Trichrome Van Gieson staining. 30x magnification (from Farronato et al. 2012)

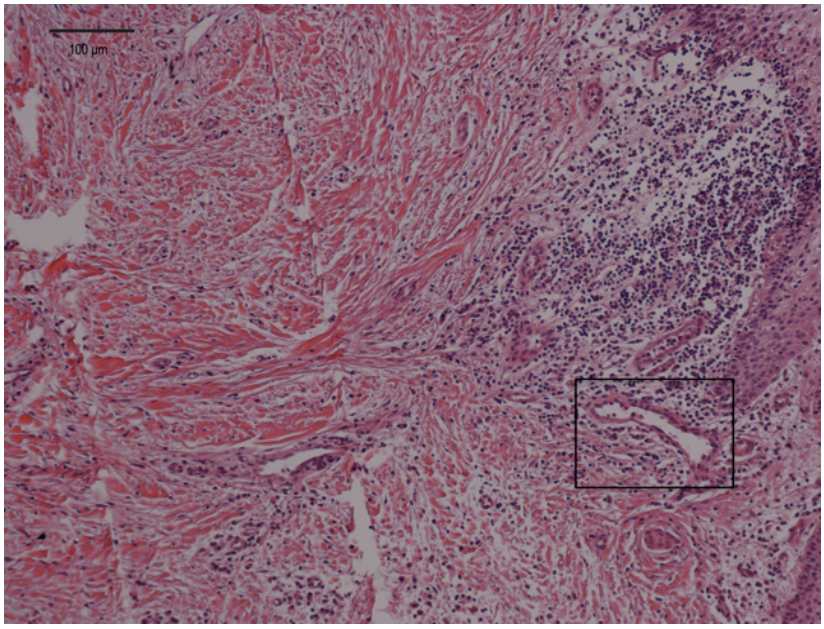
Study 2: At histological evaluation, all samples presented a well-organized connective tissue underneath the oral epithelium. In most samples of all groups, a small localized inflammatory infiltrated associated with not-well-oriented collagen fibers (Fig 6). All samples showed microvessels mainly distributed underneath the oral epithelium and the vascular density decreased in the deep connective tissue.

Fig 6.

a



b



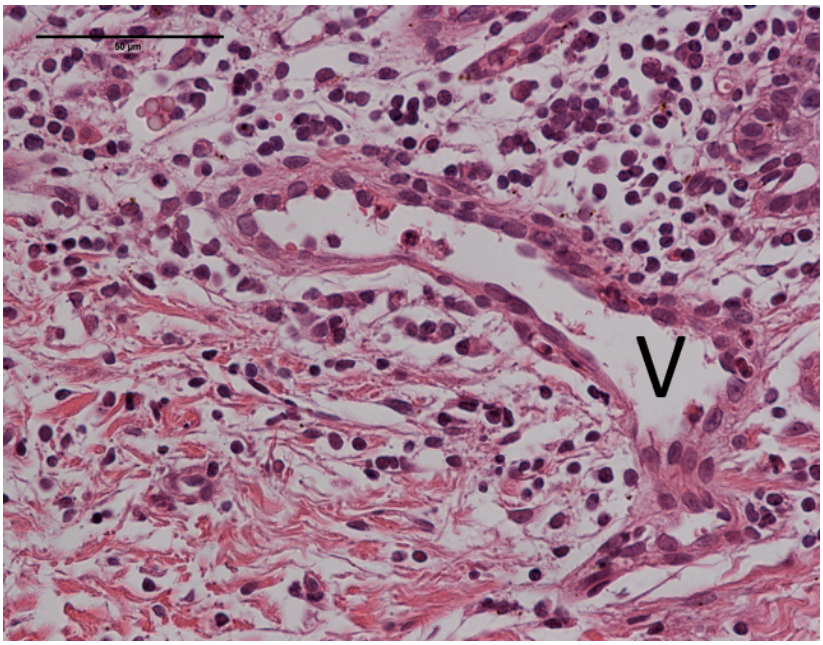
c 

Fig. 6a: Sample of test group1 (implant diameter 4.3 mm), localized area of infiltrated connective tissue (ICT) underlies the junctional epithelium (JE) with healthy and well organized connective tissue, Haematoxylin eosin staining, magnification x40.
b: Higher magnification from Fig. 6a. Lymphocytes underlay the JE, Haematoxylin eosin staining,, magnification x100.
c Higher magnification of fig. 6b representing a large diameter vessel (v) with T lymphocytes (violet spots), Haematoxylin eosin staining, magnification: x200. (from Canullo et al. 2011)

At the evaluation with polarized light, the collagen fibers under the oral epithelium were thick and closely packed and appeared well oriented in a perpendicular structure of bundles. In correspondence of JE where the ICT was localized, the collagen fibers were arranged in a thin, loose and disorganized structure, and also unstained areas appeared.

At the analyses, no significant difference was found between groups in terms of ICT, MVD and AA% (p: 40.05). No significant correlation between the ICT, MVD, AA% and the clinical variables (BOP and PD) was found.

Study 3: Mean bone resorption was 1.358 mm for non–platform-switched implants; mean resorption was 0.832, 0.486, and 0.375 mm for implant platforms of 4.3, 4.8, and 5.5 mm, respectively. with a common process of normalization (by subtracting the global mean from each individual measure and then dividing the difference by the global SD) bone change assessments of the present study were standardized. With respect to individual standardized bone resorption, a resorption trend was demonstrated in most patients. After standardization of peri-implant bone remodeling values, a borderline direct correlation

between peri-implant bone changes and levels of biglycans was found. At the same time a borderline indirect correlation between bone changes and levels of tumor necrosis factor-α was found (Figs. 7a and b).

Fig. 7

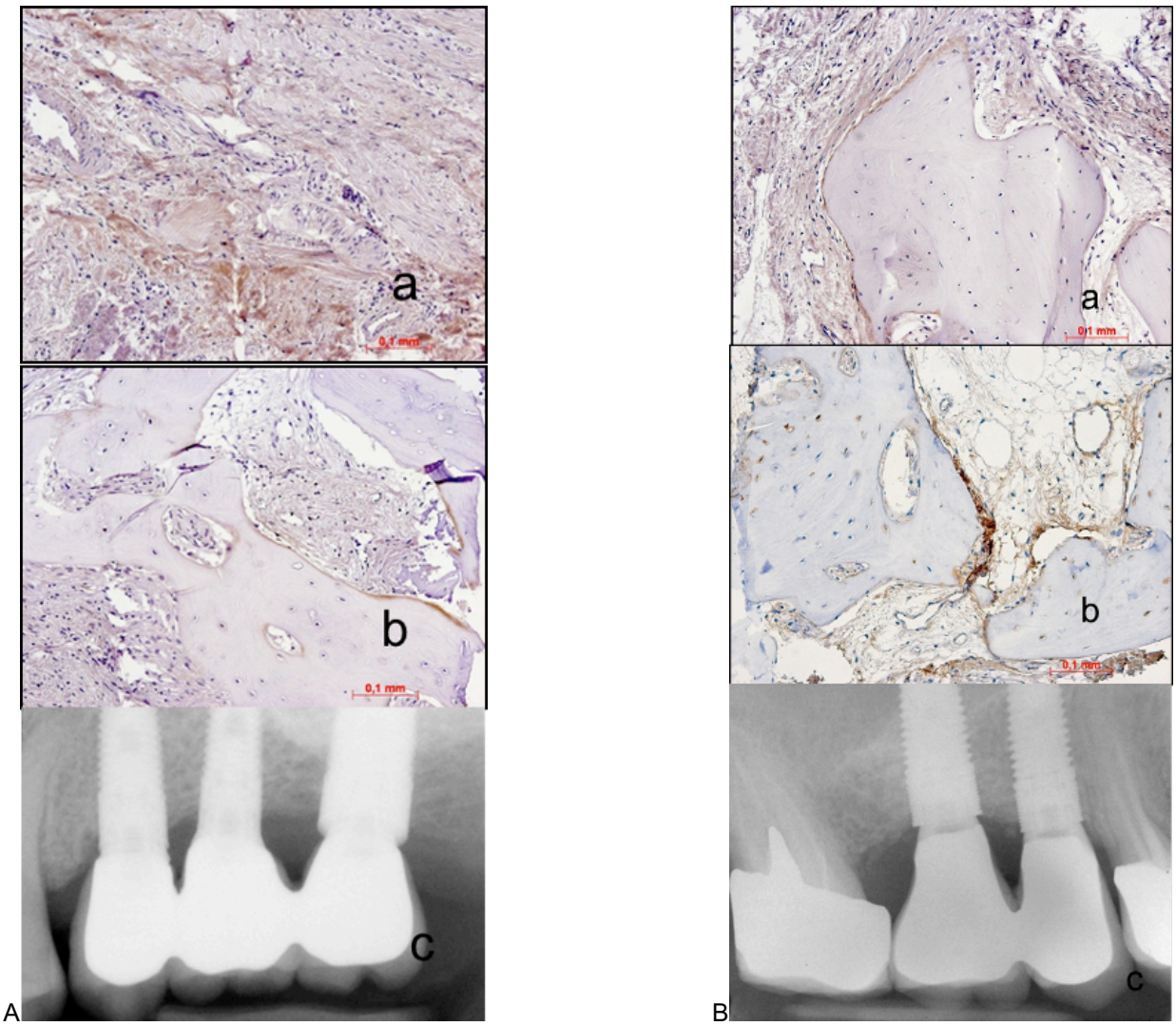


Fig 7: A: Connective tissue with weak biglycan staining (violet spots), a) and stronger TNF-α (Tumor necrosis factor-α,blue spots, b), in patient showing high resorptive trend (radiographic analysis, c).
B: Connective tissue with strong biglycan staining (violet spots), a) and weak to moderate TNF-α (blue spots, b) in patient showing low resorptive trend (radiographic analysis, c).
(from Canullo et al., 2011)

3.5 Discussion

The present thesis was aimed to verify the adaptation(clear definition, should also be included intro introduction) and the inflammatory response of soft tissues around implants restored using platform switching histologically. An additional aim was to test the clinical presence of an individual capability of each patient to respond to bacterial contamination with bone resorption, so called “individual bone resorption pattern”.

Final outcomes allowed to confirm the presence of a connective component laid over the mismatching. At the same time, histological proof demonstrated same (quality and quantity) inflammatory response around traditionally restored and platform switched implants. Existence of individual bone pattern was ratified by immunohistochemistry.

In order to understand how platform switching minimizes bone remodeling, the first step was to analyze the arrangement of the soft tissues around platform switched implants.

In the first study considered for this thesis (Farronato et al., 2011), histologic analysis showed different arrangement of biologic width around traditionally restored or platform switched implants: if the implants are positioned at the level of the alveolar bony crest, the platform switching concept may have a minor impact on the length of the epithelial attachment (0.84 vs. 1.91 mm), while the connective tissue adaptation compartment remains relatively unaffected. This first data might explain better esthetic outcomes reported in the literature (Cappiello et al., 2008; Vigolo et al., 2009; Canullo et al., 2009). Changing observation point and focusing just on the connective component, however, the most clinically relevant data of this study can be highlighted: position of the connective component, in fact, is dramatically different in test and control group. Using IAJ (Implant Abutment Junction) as reference, histologic data confirmed that, while traditionally restored implants present connective component below the IAJ, platform switching implants allow a more coronal positioning of connective tissues. In fact, this histologic structure, while control group connective tissue is adapted below the IAJ, the platform switching connective tissue is medialized to the abutment, especially over the implant platform not occupied.

Because connective tissue behavior is the main factor in establishment of the biologic width, this may help to explain why a reduced amount of bone loss has been observed more frequently around platform-switched implants: it might seem that more efficient organization of soft tissues provides greater protection to underlying alveolar bone (Farronato et al., 2012).

Horizontal inward repositioning (medialization) of the implant-abutment interface, in fact, seems to lead to two different results:

1) The overall effect of the inflammatory cell infiltrate on the surrounding tissue may be reduced as described by Luongo et al. (2008) and earlier by Ericson et al. (1995)

An inflammatory connective tissue infiltrate was described to be localized over the entire surface of the implant platform and approximately 0.35 mm coronal to the implant-abutment junction This has been reported along healing abutments. A possible reason for bone preservation around a platform-switched implant is supposed to be related to the inward (medial) shift of the inflammatory connective tissue zone at the implant-abutment junction. This is thought to reduce its injurious effect on alveolar bone adjacent to endosseous implants (Luongo et al., 2008).

2) The platform surface not covered by the abutment increases the surface on which connective tissue can stabilize. In fact, it was observed that the horizontal mismatch promotes the presence of perpendicular fibers to the abutment and prevents apical down-growth of the junctional epithelium.(Luongo et al., 2008; Weng et al., 2008).

Platform switching seems to shift the inflammatory cell infiltrate inward (medial) and away from the adjacent crestal bone. The net effect is a reduction in the amount of crestal bone loss around a platform switched implant.

However, although platform switching presents encouraging results in terms of bone preservation, according to the histo-morphogenesis of traditionally restored implants (Berglundh et al., 2007; Tomasi et al., 2013), when platform switching implants are exposed to the oral environment, bacteria colonize the microgap between implant and abutment

Within the first week, implant exposure to the oral cavity promotes peri-implant inflammation; at two weeks, initial epithelial growth is found (Schierano et al., 2002). These results are amplified by prosthetic procedures, during which implant abutment is disconnected several times: at the time of impression, of provisional abutment insertion and at the time of definitive abutment placement (Abrahamsson et al., 1998).

These clinical traditional procedures could in fact jeopardize hard tissue stability due to the unconventional biologic width disposition: according to Berglundh et al. (2007) continuous dis/reconnections of implant-abutment were demonstrated to results in soft tissue disruption, allowing for epithelial downgrowth even in the traditionally restored implants. This shortcoming could result even amplified in platform switching configuration by the fact connective tissue is located just over the platform, directly adhering to the abutment.

Obviously, results of the present study were obtained in an animal model, for this reason linear values of the peri-implant soft tissues should be considered with caution and not compared to human values. However, the proportional distribution of the peri-implant tissues in the current study may provide reference values applicable to humans.

All these data can be used to better analyze hard and soft tissue reactions to platform switched implants, may yield additional information to clinicians to optimize implant placement, manipulate soft tissue and achieve better aesthetic results.

From a clinical point of view, compared to traditional platform switching clinical behavior (with several abutment dis/reconnections), using an immediately definitive abutment ("one abutment-one time" concept, without traumatizing connective tissues once abutment is positioned) seems to be an additional strategy to further minimize peri-implant crestal bone resorption as demonstrated clinical studies (Canullo et al., 2010; Degidi et al., 2012).

Once histologic findings regarding the platform switching concept explain how the biologic width has an impact on the distribution and stabilization of the peri-implant soft and hard tissues, inflammatory response to this non-standard configuration remained to be clarified,

From a biologic perspective, the rationale for preservation of peri-implant bone level has been related to the overall effect of the abutment Inflammatory Connective Tissue (ICT) on the surrounding tissue. The effect of platform switching on the ICT is possibly due to the reduced perimeter of the implant-abutment junction towards the central axis (Luongo et al., 2008), which potentially decreased the biologic/bacteriologic deleterious effects in the adjacent peri implant soft and hard tissues. In addition, the increased amount of implant surface made available for soft tissue attachment may lead to a longer and denser barrier between any potential septic reservoir and crestal bone.

However, the most common comment to platform switching configurations that could be raised is that mismatching could create a favorable environment for bacterial selection, leading, in the short-medium term, to peri-implant tissue inflammatory conditions: in fact, bacteric contamination of the horizontal neck/abutment gap is supposed to easily reach the bone due to the implant/crown configuration.

To test the biologic rational and reject the above comment, the same protocol adopted for the previously mentioned study (Canullo et al., 2010) was used again and soft tissue samples were taken 36 months after prosthetic loading to detect eventual differences in inflammatory response between platform switched implants, traditionally restored implants and adjacent natural teeth (Canullo et al., 2011).

Histology confirmed that all sites were healthy and demonstrated localized regions rich in lymphocytes below the JE; only a few scattered inflammatory cells (lymphocytes and macrophages) appeared in the connective tissue located more distant from the implant surface.

No significant difference in the ICT size was found between the experimental groups ($p = 0.30$). These observations on inflammatory status are consistent with previous studies that reported on healthy peri-implant soft tissues. Collagen fiber content was similar in the four groups. The fiber network resembled the distribution of inflammatory infiltrate: at the periphery of the specimens, connective tissue was healthy and mature with collagen contents comparable to those of normal peri-implant mucosa In proximity of the ICT, collagen fibers were thin, loose and disorganized. Similarly, in all groups the microvascular density increased along with the ICT, thus reflecting clinically healthy peri-implant tissues.

The lack of significant histological differences between test and control sites may confirm the hypothesis that the radiographic benefit at crestal bone levels arise from an internal shift of the IAJ and a subsequent horizontal distribution of biologic width in the mismatched implants, rather than from an augmented seal of connective tissue (Becker et al., 2007). Indeed, the radiographic results of a previous study (Canullo et al., 2010) showed crestal bone loss larger in the controls than in the test specimens. This alteration was more evident in the first nine months post-rehabilitation. Two years after, the Authors ascertained stabilization of bone remodeling as expected by the characteristics of mature tissues reported in the present histologic investigation. It might be supposed that in the early phases following prosthetic rehabilitations, tissues tend to re-establish the normal biologic width with subsequent resorption of marginal bone. This event was more severe in controls than in test groups. After reaching a sound architecture, the resorbing mechanism may stop, thus allowing soft tissues to mature and recover normal anatomy.

Clinical data on hard tissue level change (Athieh et al., 2010; Annibali et al., 2011) described only the mean behavior (peri-implant bone loss) of platform switched implants. However, several papers have reported that post-restorative peri-implant bone resorption is not static but subject to inter-individual variation (from implant to implant and from patient to patient). This assumption seems to be corroborated by data from our own preliminary study (Canullo et al., 2012). It was reported that inter-individual variability and individual homogeneity, suggested that individual factors could affect peri-implant bone resorption.

From the analysis of the data reported in these three studies, some conclusions could be drawn.

Junctional epithelium is attached to the smooth lateral surfaces of implants. This attachment usually occupies a position apical to the implant-abutment interface. The microgap offers an ideal environment for bacterial colonization and, moreover, abutment may be prone to micro- movement between implants and abutments.

If this environment is mechanically disturbed by prosthetic manipulations, further bacterial colonization of the micro-gap takes place, causing apical migration of the attachment and increased bone resorption.

It may be supposed that in the platform switched restoration, connective tissue occupies the area surrounding the horizontal portions of the platform, and the junctional epithelium extends along the abutment and stops at the IAJ (Implant Abutment Junction) (Farronato et al., 2012).

From a histological point of view, the particular connection design of platform switched implants do not offer a favorable environment for bacterial colonization and subsequent inflammatory infiltration. This may, in part, ensure a long term healthy state of the peri-implant soft tissue (Canullo et al., 2011). The unconventional configuration of mismatched implants allows the biologic width connective compartment stabilization on the implant platform not occupied by the abutment (mismatching). At the same time, the medialization of biologic width seems to prevent bone downgrowth and could explain the “conventional” soft tissue inflammatory response to this “unconventional” implant/abutment configuration.

However, histologic *in vivo* study demonstrated that peri-implant bone remodeling might be influenced by a so called “individual bone pattern” (Canullo et al., 2012).

3.6 Figures List

Figure 7A : Connective tissue in patient showing high resorptive trend

a : with weak biglycan staining; b : stronger TNF-α; c : radiographic analysis

Figure 7B : Connective tissue in patient showing low resorptive trend

a) with strong biglycan staining; b: weak to moderate TNF-α; c: radiographic analysis

Source : Canullo et al., 2011

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5. Offprints

Publication 1

Title : Soft tissues around long-term platform switching implant restorations: a histological human evaluation. Preliminary results.

Authors : Canullo L, Pellegrini G, Allievi C, Trombelli L, Annibali S, Dellavia

Publication : Journal of Clinical Periodontology 2011; 38: 86-94

Publication 2

Title : Individual Bone Pattern Influence on peri-implant Bone Loss. Preliminary report from a 3-year randomized clinical and histological trial in patients treated by implants restored with matching diameter abutment or platform-switching concept.

Authors: Canullo L, Götz W, Iannello G.

Publication : The International Journal of Oral and Maxillofacial Implants 2011; 26: 618-630

Publication 3

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