INICELL® Series

This series explains the benefits of the INICELL surface of the Thommen Medical implant system in a simple way.

Part 1: Starting point: Why do dental implants need to be firmly retained in the jaw?

Very high forces are transmitted via the teeth when chewing. These forces are generated by the chewing muscles and transmitted to the teeth by the periodontium. The teeth need to be adequately retained in the osseous jaw for this. With natural teeth, collagen fibers (Sharpey's fibers) fulfill this role and convert the masticatory force on the teeth into tensile stress in the jawbone which acts as a growth stimulus. This mechanism stimulates growth and ensures that the bone regenerates in response to loading. The greater the tensile stress on the bone, the more bone will be formed. Conversely, bone is broken down if subjected to lower tensile forces.

Reference
Huja SS, Fernandez SA, Hill KJ, Li Y. Remodeling dynamics in the alveolar process in skeletally mature dogs. Anat Rec A Discov Mol Cell Evol Biol. 2006 Dec;288(12):1243-9

Part 2: How is good retention of dental implants achieved?

When inserting an implant, retention in the jawbone is crucial. Since the Sharpey's fibers can no longer do this, the implants must be retained directly in the bone (Fig. 1). This interface, the bone-implant interface, is critical in determining whether the tooth replacement will last for the rest of the patient's life.

Complication-free healing of the implant and optimal long-term integration (osseointegration) in the surrounding bone are prerequisites for good retention.

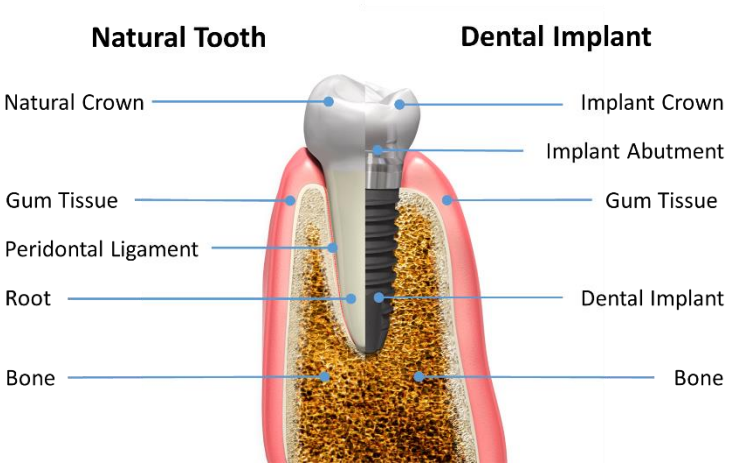


*Figure 1: The difference between collagen fibers and implant retention in bone as a schematic diagram**

Inserting an implant creates a wound in the jawbone into which blood flows, initiating the healing process. The surface of the implant is thereby brought into contact with blood and it's components including platelets, plasma proteins and fibrin. The plasma proteins undergo aggregation while the fibrin polymerizes. The intrinsic coagulation cascade results in a blood clot, which serves as a starting point for formation of the extracellular matrix and, at the same time, attracts bone-forming cells. The initial wound-healing process is the same for all tissues in the skeletal system and forms the basis for complete osseous integration of a dental implant.

The extracellular matrix is replaced later by bone which directly surrounds the implant and, thus, ensures transmission of force from the implant to the jawbone. A successful start to the healing phase is crucial for long-term retention. Retention of the implant, measured as holding force, is proportional to its contact surface with the surrounding bone. Therefore, all measures promote formation of bone and also long-term retention.

Reference
Listgarten MA. Soft and hard tissue response to endosseous dental implants. Anat Rec. 1996 Jun;245(2):410-25.

Part 3: What is conducive to good retention?

How well an implant is retained in the bone depends on two factors: the patient and their reaction to the implant and also the implant itself. In terms of the patient, factors such as healing and osseointegration play a significant role. Poor quality of the bone, e.g. due to severe osteoporosis, immunosuppression and smoking can have a negative impact. In addition, medications that have a direct or indirect impact on wound healing, coagulation or bone metabolism can compromise retention. These include high-dose bisphosphonates – e.g. for treatment of bone metastases – which compromise healing or which can result in loosening of the implant that has undergone osseointegration.

A dentist can influence very few patient factors. Therefore, patient selection is critical for stable and long-term implant retention. In patients with multiple risk factors, alternative treatment should be considered.

Dental implants, just like other implants, are foreign material that can trigger a reaction in the surrounding tissue. The type and severity depend on the properties of the implant material. These are differentiated into immunological reactions, e.g. in chromium-nickel allergies, from cell reactions to direct contact with the material surface.

While immunological reactions are known and are not really an issue with modern implant material, direct cell reactions are less well-researched. We have only known for a few years that the surface topography impacts the adhesion and alignment of cells in the surrounding tissue. Smooth surfaces, e.g. polished stainless steel, can result in the formation of a fibrous capsule. Whereas rough titanium surfaces enable direct contact with the bone (Fig. 2)

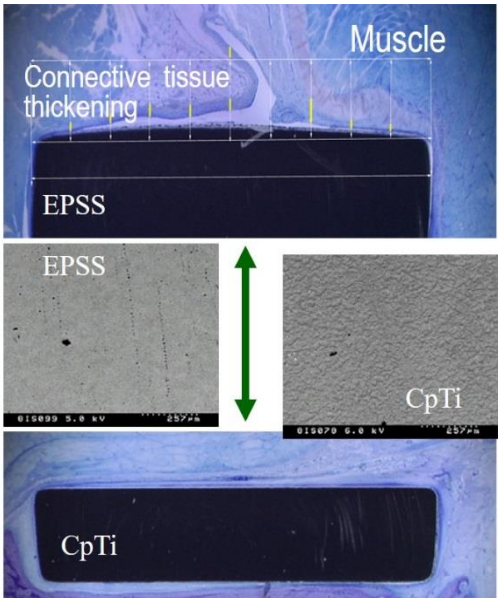


*Figure 2: Differing tissue reactions to a variety of materials and their surface geometry (EPSS electropolished stainless steel, CP titanium). Courtesy: Geoff Richards**

This knowledge is used specifically in implant development to improve osseointegration.

Reference

Alghamdi HS. Methods to Improve Osseointegration of Dental Implants in Low Quality (Type-IV) Bone: An Overview. J Funct Biomater. 2018 Jan 13;9(1).

Part 4: How can retention of dental implants be improved?

Coated implants can promote osseointegration. Laboratory experiments demonstrated, e.g. improved healing of implants coated with hydroxylapatite.

Healing and retention of implants in the bone can be supported by other biological factors. Thus, administration of growth factors such as bone morphogenic protein (BMP) results in a transient increase in osteogenesis around the implant. Coating with medications for osteoporosis, or also administering them systemically, inhibits bone resorption.

In both cases, an additional active substance must be applied which makes treatment more difficult. In addition, there may be stricter requirements (combinations of drug and medical device). The control of bioavailability over time increases the complexity of this approach which is why extensive studies are required. Furthermore, side effects such as bone formation at undesired sites cannot be completely excluded.

Reference
Pilipchuk SP, Plonka AB, Monje A, Taut AD, Lanis A, Kang B, Giannobile WV. Tissue engineering for bone regeneration and osseointegration in the oral cavity. Dent Mater. 2015 Apr;31(4):317-38.

Part 5: What is INICELL® – how it differs from conventional Systems?

INICELL® is the patented surface from Thommen Medical. This is chemically modified so that it becomes superhydrophilic, i.e. can be wetted extremely easily. This also improves the direct cell reaction at the bone-implant interface. INICELL® does not need other active substances such as growth factors or medications for osteoporosis. The tissue reaction required for healing remains local at the site of implantation. Systemic effects or side effects at other sites in the body are unlikely and were also not reported in studies.

The implant surface is modified in a conditioning process

on the sterile implant. As the surface is treated under sterile conditions, the problem that implants with a biologically active coating have is eliminated: the potential reduction in the effect of the coating caused by the sterilization process.

directly before insertion into the bone. This eliminates a reduction in the effect as a result of longer storage of the implant.

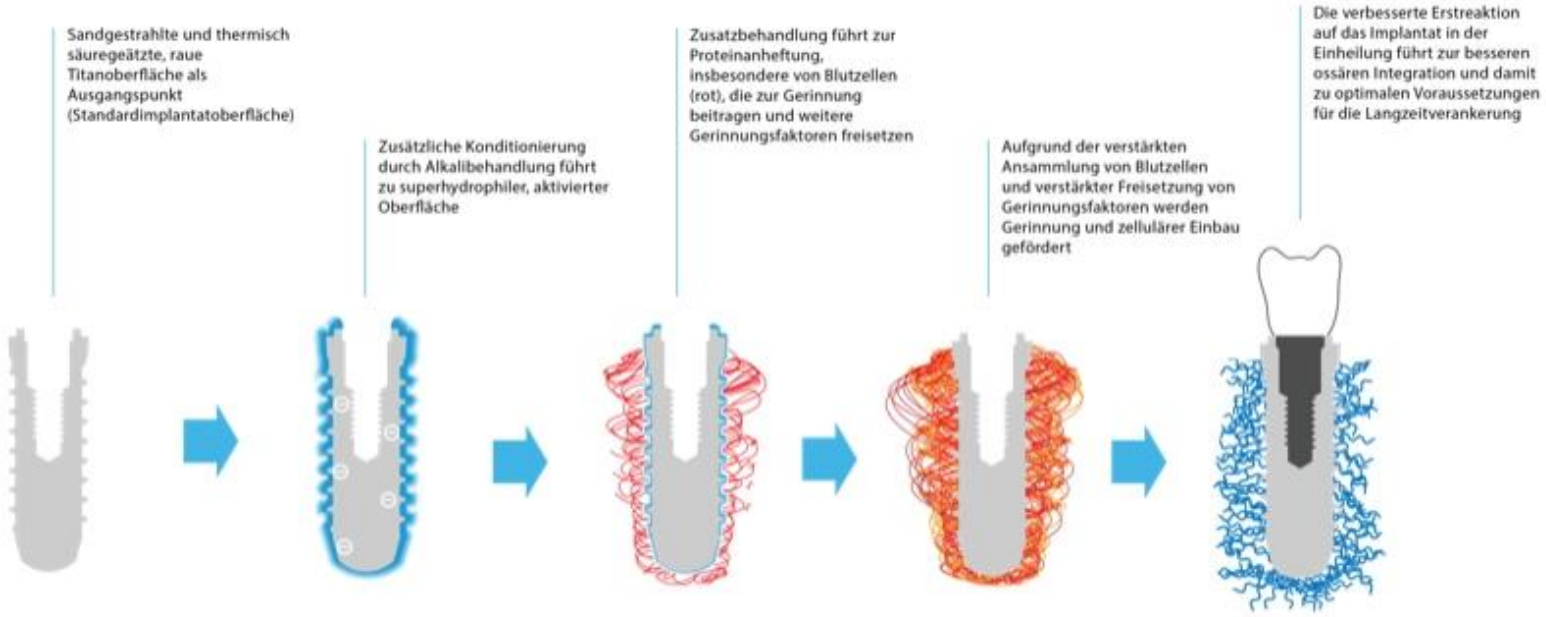
INICELL® does not require an additional coating (e.g. hydroxylapatite) with the result that there is no danger of abrasion on insertion.

→ The three most important sources of error for a reduced effect of coated implants (storage, sterilization, abrasion) are completely eliminated with INICELL®.

Reference
Tugulu S, Löwe K, Scharnweber D, Schlottig F. Preparation of superhydrophilic microrough titanium implant surfaces by alkali treatment. J Mater Sci Mater Med. 2010 Oct;21(10):2751-63. doi: 10.1007/s10856-010-4138-x. Epub 2010 Aug 20.

Part 6: How does INICELL® work?

Mechanism of action



Sandblasted and thermal acid-etched, rough titanium surface as a starting point (standard implant surface)	Additional conditioning through alkali treatment results in a superhydrophilic, activated surface	Additional treatment results in protein adhesion, especially of blood cells (red), which contribute to coagulation and also release other coagulation factors	The increased concentration of blood cells and enhanced release of coagulation factors promotes coagulation and cellular incorporation	The improved initial reaction to the implant during the healing phase results in improved osseointegration and, thus, optimal conditions for long-term retention.

Figure 3: Schematic diagram of the mechanism of action. Conditioning in the second step creates a hydrophilic surface, activates coagulation and subsequent wound healing and, thus, better and faster healing with subsequent direct bone contact (red structure corresponds to the fibrin network from wound healing; blue structure to the subsequent osseous contact

Application

INICELL® represents the further development of the clinically validated, sandblasted and thermal acid-etched Thommen surface. This is currently considered to be the best surface topography for fast and reliable healing of implants (Fig. 4). The rough surface, especially the micropores, allows for direct bone contact to the implant and, thus, good retention in the bone.

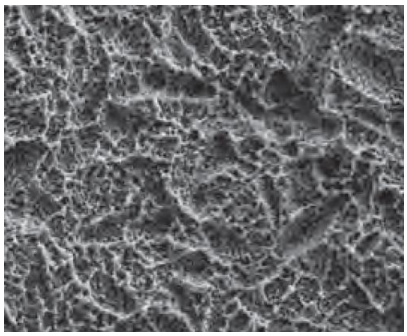
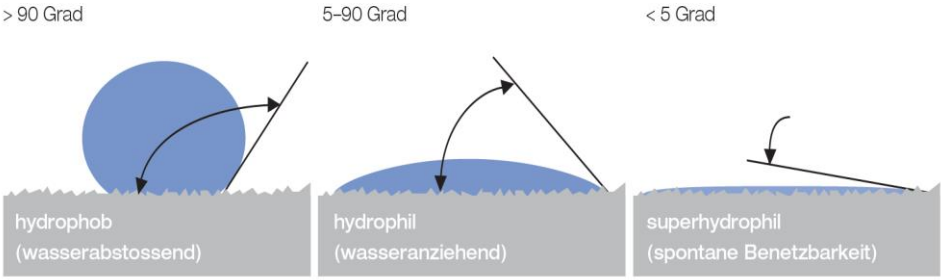


Figure 4: Electron microscopy image of a sandblasted and acid-etched surface

The hygroscopic (superhydrophilic) surface results in direct cell contact and subsequent blood coagulation as the starting point of healing directly on the implant. INICELL® produces increased surface energy and, thus, results in better wetting (Fig. 5).



Hydrophobic (water repellent)	Hydrophilic (attracted to water)	Superhydrophilc (spontaneous wettability)

Figure 5: Schematic diagram and classification of the water contact angle on microrough surfaces

The superhydrophilic surface is created by the alkali treatment using the unique APLIQUIQ® system. This conditioning directly before implantation is performed by contact of the implant with the specific conditioning agent as per the manufacturer's instructions (Fig. 6). The APLIQUIQ® set required for this is supplied in sterile packaging and can, thus, be used in the operating room just before the operation. As there is very little preparation time, the impact on the surgical procedure and time plan is minimal.

Figure 6: Conditioning with the patented APLIQUIQ® system as per the manufacturer's instructions: Bring into contact, shake 5x and remove (exact instructions in manufacturer's brochure)

The alkali treatment makes the surface superhydrophilic and activated. This modification promotes wound healing in peri-implant tissue as it results in a thicker blood clot that contains more platelets and fibrin fibers. Furthermore, more factors that favor healing and retention of implants are released into the tissue. Released *matrix metalloproteinases* (MMPs) rapidly convert fibrin tissue into bone during endochondral ossification. The *vascular endothelial growth factor* (VEGF) that is also released contributes to this.

Thanks to INICELL®, the foundation for long-term successful prosthesis retention is laid. With good bone substance, the implant can be subjected to stress loading after just three weeks.

References

Milleret V1, Tugulu S, Schlottig F, Hall H.Alkali treatment of microrough titanium surfaces affects macrophage/monocyte adhesion, platelet activation and architecture of blood clot formation. Eur Cell Mater. 2011 May 15;21:430-44.

Tugulu S, Löwe K, Scharnweber D, Schlottig F. Preparation of superhydrophilic microrough titanium implant surfaces by alkali treatment. J Mater Sci Mater Med. 2010 Oct;21(10):2751-63. doi: 10.1007/s10856-010-4138-x. Epub 2010 Aug 20.

Part 7: What evidence is there for the efficacy of INICELL®?

The efficacy of INICELL® has been confirmed in several experiments Here is a selection of these:

In contrast to untreated titanium surfaces, INICELL® increases the adhesion of platelets to the implant which results in a larger blood clot and increased release of coagulation-activating factors (MMPs, VEGF). The in vitro study was carried out in laboratories at the ETH Zurich (1).

In contrast to untreated titanium surfaces, INICELL® stimulates increased proliferation of human mesenchymal stem cells, increased formation and conversion of the extracellular matrix and increased release of matrix fragments and factors that promote vascularization (VEGF). The in vitro study was carried out in laboratories at the ETH Zurich (2).

References

Burkhardt MA, Gerber I, Moshfegh C, Lucas MS, Waser J, Emmert MY, Hoerstrup SP, Schlottig F, Vogel V. Clot-entrapped blood cells in synergy with human mesenchymal stem cells create a pro-angiogenic healing response. Biomater Sci. 2017 Sep 26;5(10):2009-2023.

Burkhardt MA, Waser J, Milleret V, Gerber I, Emmert MY, Foolen J, Hoerstrup SP, Schlottig F, Vogel V. Synergistic interactions of blood-borne immune cells, fibroblasts and extracellular matrix drive repair in an in vitro peri-implant wound healing model. Sci Rep. 2016 Feb 17;6:21071. doi: 10.1038/srep21071.

Part 8 How does INICELL® work in patients?

In patients with INICELL®, functional loading after 6 weeks results in higher primary stability compared to patients who were only able to subject a conventional system to stress loading after 15 weeks. This is achieved by the buccal bone-implant contact surface that is up to 40 percent higher. Furthermore, there was less bone loss around the implant 3 months after implantation in patients in the INICELL® group compared to the control group. The study on patients was carried out on 15 implants in each group and the primary stability was determined in vivo by means of resonance frequency analysis (1).

Patients with poor bone substance benefit especially from earlier loading of the conditioned dental implant with INICELL®. This was proven in a human study in which a predefined value of 70 percent had to be achieved in the implant stability quotient 21 days after implantation. This was determined by means of resonance frequency analysis. The predefined value was achieved in all patients as early as 3 weeks after implantation with the result that complete construction with prosthetics was subsequently carried out. The subsequent measurements after 3 and 6 months demonstrated that the implant had grown fully into the bone – also without additional bone filling. None of the implants failed during the period of observation. The study authors concluded that conditioning the implants with INICELL® results in reliable and predictable healing, allowing functional loading from the third week after implantation. (2)

The failure rate shortly after implantation (early failure rate) is also statistically lower when using INICELL® than without. This resulted in a retrospective analysis of more than 1000 implants per group. By the end of the entire observation period of 6 years, no further implant losses were observed. Thus, the long-term failure rate of conditioned implants with INICELL® is below the average failure rate in a large Swedish implant registry and performs even better than any of the implants in this registry (3).

References

1. *Makowiecki A, Botzenhart U, Seeliger J, Heinemann F, Biocev P, Dominiak M. A comparative study of the effectiveness of early and delayed loading of short tissue-level dental implants with hydrophilic surfaces placed in the posterior section of the mandible-A preliminary study. Ann Anat. 2017 Jul;212:61-68.*
2. *Hicklin SP, Schneebeli E, Chappuis V, Janner SF, Buser D, Brägger U. Early loading of titanium dental implants with an intra-operatively conditioned hydrophilic implant surface after 21 days of healing. Clin Oral Implants Res. 2016 Jul;27(7):875-83.*
3. *Le Gac O and Grunder U. Six-Year Survival and Early Failure Rate of 2918 Implants with Hydrophobic and Hydrophilic Enossal Surfaces. Dent. J. 2015, 3(1), 15-23*