# The role of metallic nano- and microparticles in peri-implantitis

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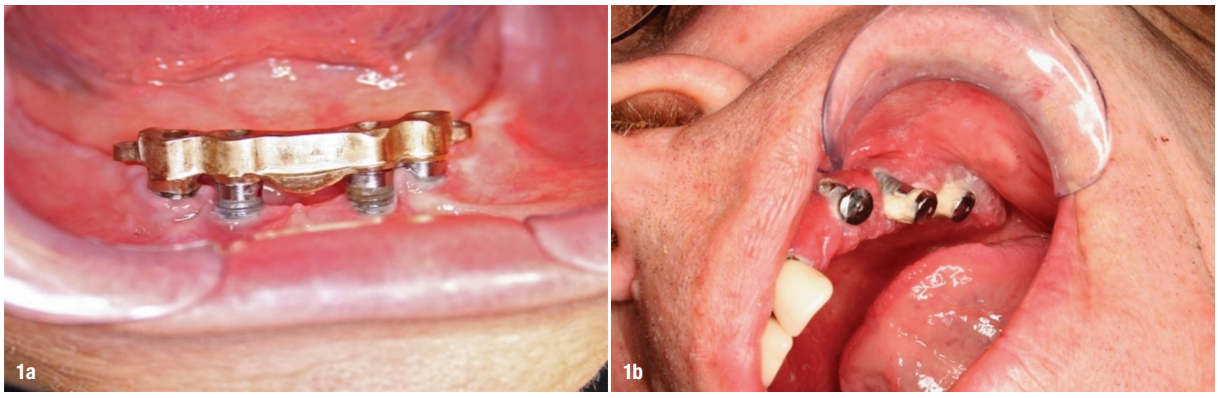
**Dental implantology** has become a fundamental component of oral rehabilitation and is closely associated with prosthetic therapy. The aim of both implantology and prosthetics is to replace a lost natural tooth and to achieve *restitutio ad integrum*. To attain this goal, attempts have been made with different materials and techniques for many centuries. In the last few decades, metal implants in particular have established themselves extremely successfully as an alternative to purely prosthetic therapies; however, the extent to which these may have a negative impact on the organism and the reasons for which they can lead to inflammatory reactions must be examined more closely.[1,2]

In the middle of the twentieth century, Brånemark's Gothenburg research group first researched the biocompatibility of different materials with bone and has since triggered an uninterrupted upswing in dental implantology. It was found that implants made of pure titanium have the ability to heal in the bone without any signs of inflammation or rejection. Brånemark defined this process as osseointegration, which includes all elements of biocompatibility, a bio-inert material and bioactivity.[1,3] The term "biocompatibility" defines materials that have no negative effects on living organisms. This is extremely important with implants, as they remain in the living tissue for a long time. Implant materials must also be bio-inert, which means that no toxic substances may be released from them over time. Bioactivity involves the creation of a chemical bond between the implant and the surrounding tissue.[1,3] Since Brånemark was able to demonstrate these properties of pure titanium, it is now the material of first choice for implants. An alternative to pure titanium is zirconium dioxide, which also has very good biocompatible properties. In addition, in medicine, other metals, metal alloys, polymers and ceramics are used as biocompatible materials.[1,3] Bone deposition on the titanium implant surface, important for osseointegration, was also confirmed in many studies. Primary stability is achieved through mechanical blocking.

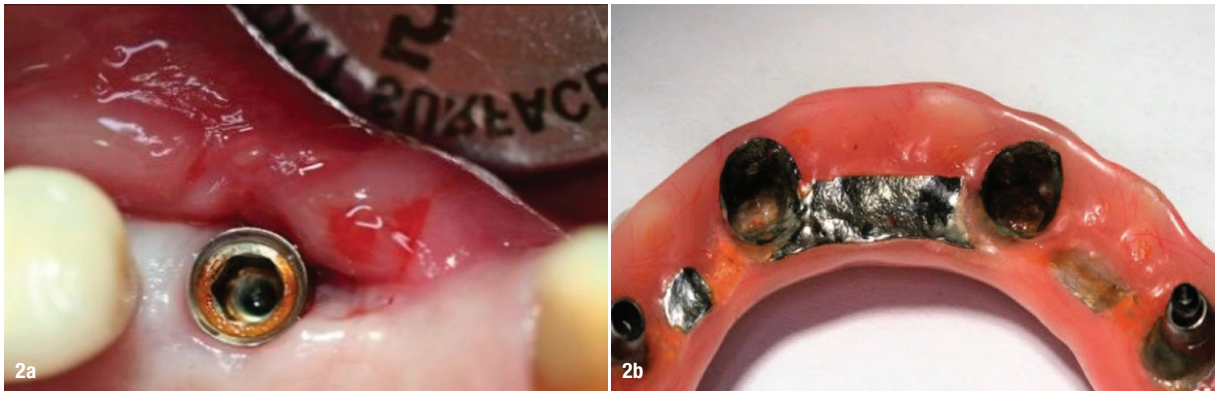
While natural teeth develop simultaneously with periodontal tissue to form a functional unit, endosteal implants, being artificial, are made of inorganic material, for which no artificial periodontium has yet been found. This constitutes a weak point regarding later peri-implant inflammation.[4,5] The morphological differences between a natural tooth and a titanium implant cause implants to be more prone to inflammation.[32] Overall, metals have good mechanical properties, but their susceptibility to corrosion and their possible release of metal ions and consequently the sensitisation of the organism represent disadvantages. Therefore, collar-shaped stable soft tissue around the implant protruding into the oral cavity is essential for long-term success of an implant, including the prosthetic restoration. The healing processes after implantation can only start from a vital bone.[6,7]

## Periodontitis and peri-implantitis

Biofilm is mandatory for the development of periodontitis. The bacteria from this infiltrate the periodontal tissue, resulting in inflammatory reactions and subsequent irreversible tissue damage. Risk factors such as nicotine and




**Figs. 1a & b:** Clinical peri-implantitis.



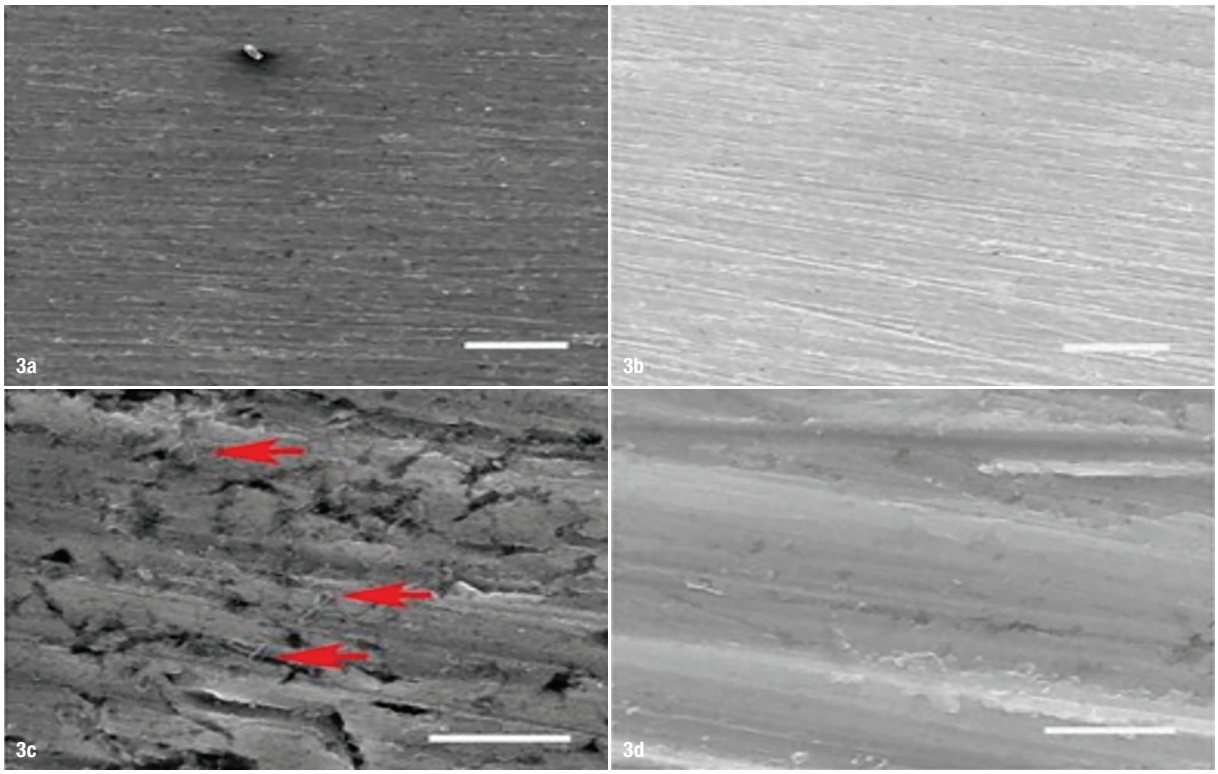
**Figs. 2a & b:** Corrosion on implants and the superstructure. Corrosion of the implant–abutment connection **(a)**. Corrosion of the overdenture prosthesis **(b)**.[33]

alcohol abuse, as well as systemic disease (e.g. diabetes mellitus) or even stress, amplify the bacteria migration into the tissue.[6] Peri-implantitis is progressive peri-implant bone loss with simultaneously inflammable and inflamed soft tissue. Bacterial infection and biomechanical overload are considered to be its triggers. Clinically and radiographically recognisable destruction is the result, since the bone is more easily exposed to the inflammatory infiltrate without a protective periodontal ligament. Since peri-implantitis is clinically and microbiologically similar to chronic marginal periodontitis, it is concluded that plaque can cause peri-implant disease. However, it still remains to be clarified whether a predisposition to periodontal disease also favours peri-implant inflammation. Nevertheless, it is recommended that alternative therapies to intraosseous implants should be preferred in patients with an increased susceptibility to periodontal disease.[6,8,9–14] At the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, peri-implantitis was defined as "a plaque-associated pathological condition occurring in tissues around dental implants, characterised by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone". This definition does not take factors such as metal particles or the cytotoxicity of metals into consideration.

Clinical cases of pronounced peri-implantitis are documented in Figures 1a & b. The purulent secretion from the peri-implant pockets is noticeable. The soft-tissue cuff is no longer present, and the loss of bone can be guessed. There is scientific consensus that periodontitis or peri-implantitis is caused by excessive bacterial colonisation of the gingiva caused by inadequate dental and oral hygiene. It has been shown that progressive periodontitis occurs more often in families. Although its origin is multifactorial, genetic predisposition is important because some genes have been isolated as risk factors, including the interleukin 1 gene, proteinase 3 and cathepsin.[15,16] Nanoparticles that gain access to the bone compartment during implantation through the surgical instruments themselves and through the implant insertion are increasingly being researched as a cause and a trigger of peri-implantitis. However, there is still no clearly defined standard or protocol for the treatment of peri-implantitis. Owing to the very high recurrence rate of peri-implantitis after one year despite therapeutic intervention (surgical or non-surgical), the question now arises of whether metal abrasion particles from the implant surfaces maintain peri-implantitis. No studies have compared non-surgical measures with surgical measures.[2,17,18]

## Nanoparticles

In the last 20 years, nanotechnology has experienced a great boom. Particles below 100 nm are referred to as nanoparticles. They are produced industrially, but also occur naturally (for example viruses and in volcanic ash and forest fires). They are characterised by their extremely large surface in relation to their low mass. Nanoparticles are mainly made from silicates and various metal oxides, including titanium and aluminium oxides. They can be found, for example, in candies and in many skin care products, especially sunscreens. Titanium dioxide particles and zinc oxide are used as stabilisers. It was found that orally ingested titanium dioxide particles are deposited in the intestine and in other tissue (peritoneal tissue, liver, spleen, kidney and heart) without being excreted, causing epithelial disorders, and chronic damage of the intestinal cells can be triggered. In the case of intact skin, evidence of titanium dioxide can only be detected in the top layer of the epidermal layer.[19] Nanoparticles are also used in medicine. Owing to its higher efficiency and accuracy, nanoparticle-based fluorescent marking is indispensable in diagnostics and imaging. The use of nanoparticles in pharmaceuticals has shown that they have better bioavailability and effectiveness, fewer side effects and, above all, reduced organ toxicity.[20] Because of these positive and negative aspects, the question arises as to whether nano- or microparticles from implants or metallic instruments lead to an increased risk of peri-implantitis during implantation. Very little is known about the risks and translocation of titanium dioxide nanoparticles from implants or metallic instruments. The existing literature from 2010 onwards should be examined for references

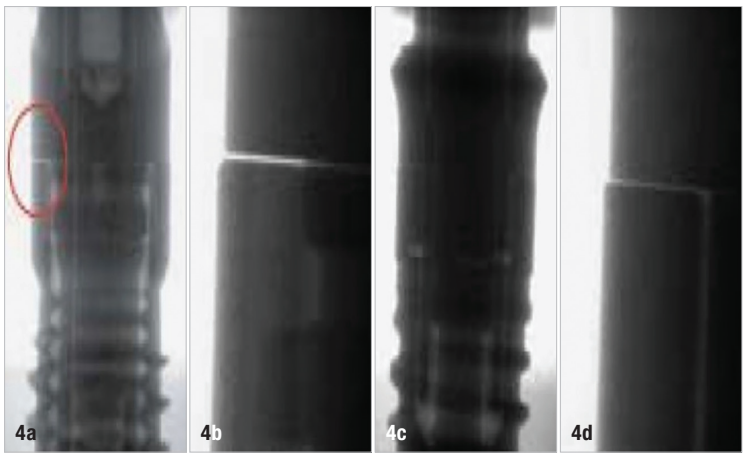



**Figs. 3a–d:** SEM images of the effect of *Streptococcus sanguinis* on the titanium surface. Titanium surface in artificial saliva enriched with *S. sanguinis*. Scale: 100 µm **(a)** and without *S. sanguinis*. Scale: 100 µm **(b)**. Enlarged view of Figure 4a (the arrows show *S. sanguinis*). Scale: 10 µm **(c)**. Enlarged view of Figure 4c. Scale: 5 µm.[24] **(d)**.

to this, because the aspects of particle formation during implantation have been investigated in more detail only in the recent last few years.

## Titanium properties

The grey colour of titanium is caused by the oxide layer that forms on the surface immediately after the metal comes into contact with oxygen and is 2–5 nm thick. This normally very dense and chemically stable oxide layer gives titanium its biocompatibility and mediates osseointegration by allowing cellular adhesion molecules to accumulate. In some cases, however, different types of corrosion can be observed clinically: pitting, crevice and stress corrosion, and erosion (Figs. 2a & b).[7,21,22] Pitting corrosion occurs primarily and predominantly at the connection point between the implant and the abutment, which can cause crevice corrosion. As a result, a concentration of chloride ions is created, which lowers the pH in the immediate vicinity of the implant. Thus, the oxide layer on the titanium implant dissolves irreparably and cannot renew itself due to *Streptococcus sanguinis*. These bacteria form a barrier to oxygen through a biofilm formed around the implant; owing to the lack of oxygen, titanium ions and particles are released from the complex titanium structure. On the one hand, this inflames the tissue, and on the other hand, the titanium implant continues to corrode. The saliva, which can act as an electrolyte, also contributes to the permanent damage to the oxide layer because the corrosion is supported by electrochemical processes in the mouth.[23,24] The extent of damage to the implant surface, which is significant, is shown in Figures 3a–d.[24] In addition, Nakagawa et al. found in a further study that pure titanium and titanium alloys corrode faster owing to the influence of fluorides at a low oxygen content, whereas without fluoride they showed a higher corrosion resistance at the same oxygen concentration.[25] For this, the fluoride concentration in commercially available toothpastes was considered, which turned out to be too high and does not protect the metals from corrosion damage.[25]




**Figs. 4a–d:** Detailed images of two implant–abutment connections under masticatory load.[31]

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## Metal abrasion during insertion and its consequences

The original implant surface and shape can be modified by the insertion procedure. A very deep insertion causes greater damage to the bone and implant than a less forced insertion. By torsion and friction of the implant on the bone, titanium particles are released from the surface structure of the implant into the already damaged bone tissue. The size of the released titanium particles varies between 10 nm and 20 µm. At the sharp edges of the implant, the entire oxide layer is partially lost as a result of the insertion. The loss of the oxide layer also depends on the type of implant.[26–28] Martini et al. showed that implants coated with fluoro-hydroxyapatite were less susceptible to abrasion during insertion than plasma-coated implants. Titanium particles released by plasma-coated implants were found at a distance of 200–250 µm from the implant surface and prevented neo-osteogenesis. A deformation of the implant thread can be seen in the area of the bone, especially in the form of microfractures. Titanium abrasion can be found both in the peri-implant mucosa and in the newly formed bone. Titanium particles have even been detected in organs further away: the liver, kidneys, lungs and heart.[29,30] In addition to the implant insertion, the high mechanical loads on the connection between the implant and the abutment are another factor that contributes to the release of metallic particles. Complete implant failure can also occur as a result. In addition, micro-gaps can form at the implant–abutment connection, where titanium and metal particles can also loosen. Microleakage, material wear, material fatigue and screw loosening are other possible consequences that can result from the micro-gaps. Microleakage is particularly evident in hexagonal connections with a loose fit (Figs. 4a–d) through which—in addition to metal abrasion and material damage—liquids and bacteria gain entry to the interior of the implant and cause internal corrosion of the implant. The microgap movements can be reduced by a conical connection between the implant and the abutment.[31]

## Conclusion

At the beginning of the implantology era, the focus was on the euphoria about solving the problem of osseointegration, but in recent years, the question of the reasons for a shortened lifetime of implants has moved increasingly into focus. Peri-implantitis, which sometimes turns out to be therapy-resistant, was seen as a further indication that, in addition to a *lege artis* insertion, factors that lay the foundation for peri-implantitis during insertion can be responsible for achieving osseointegration. Nano- and microscale titanium and zirconium dioxide particles detach themselves from both the instruments and the implants during insertion and the surgical, prosthetic and aftercare phases. They can be detected in bone and other tissue and have only recently been shown to be cytotoxic. According to the current research, the release of these particles cannot yet be prevented regardless of the implant surface. The metal and titanium ions and particles dispersed into the peri-implant hard and soft tissue trigger cellular reactions that can be compared to aseptic chronic inflammation. This can lead to therapy-resistant peri-implantitis and thus to failed osseointegration.

Although these clinically and radiographically visible peri-implant changes are very similar to periodontitis, peri-implantitis is not always bacterial. For this reason, the classic treatment concept for periodontitis cannot generally be transferred to peri-implantitis. A concept for the treatment of peri-implantitis that is not caused by bacteria is not yet available. Particle-induced peri-implantitis is often accompanied by osteolysis, which is clearly not considered to be bacterial. In such cases, explantation with thorough lavage of the bone cavity is necessary. Further investigations are required to determine whether and to what extent bone regeneration measures need to be taken. Overall, however, the prevailing opinion is that metallic nano- and microparticles are of no importance in dental implantology. For this reason, the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions defined peri-implantitis without including factors such as metal particles and their cytotoxicity. However, it is expressly advised that further research regarding metallic nanoparticles is absolutely necessary owing to their potential danger.

Author details

Literature

## about the author

**Dr Ioannis Papadimitriou** specialised in oral surgery and holds an MSc in oral implantology and periodontics from the German Association of Oral Implantology and the Steinbeis University in Berlin in Germany. He is a senior physician at the department of oral and maxillofacial surgery at the St Lukas hospital in Solingen in Germany.

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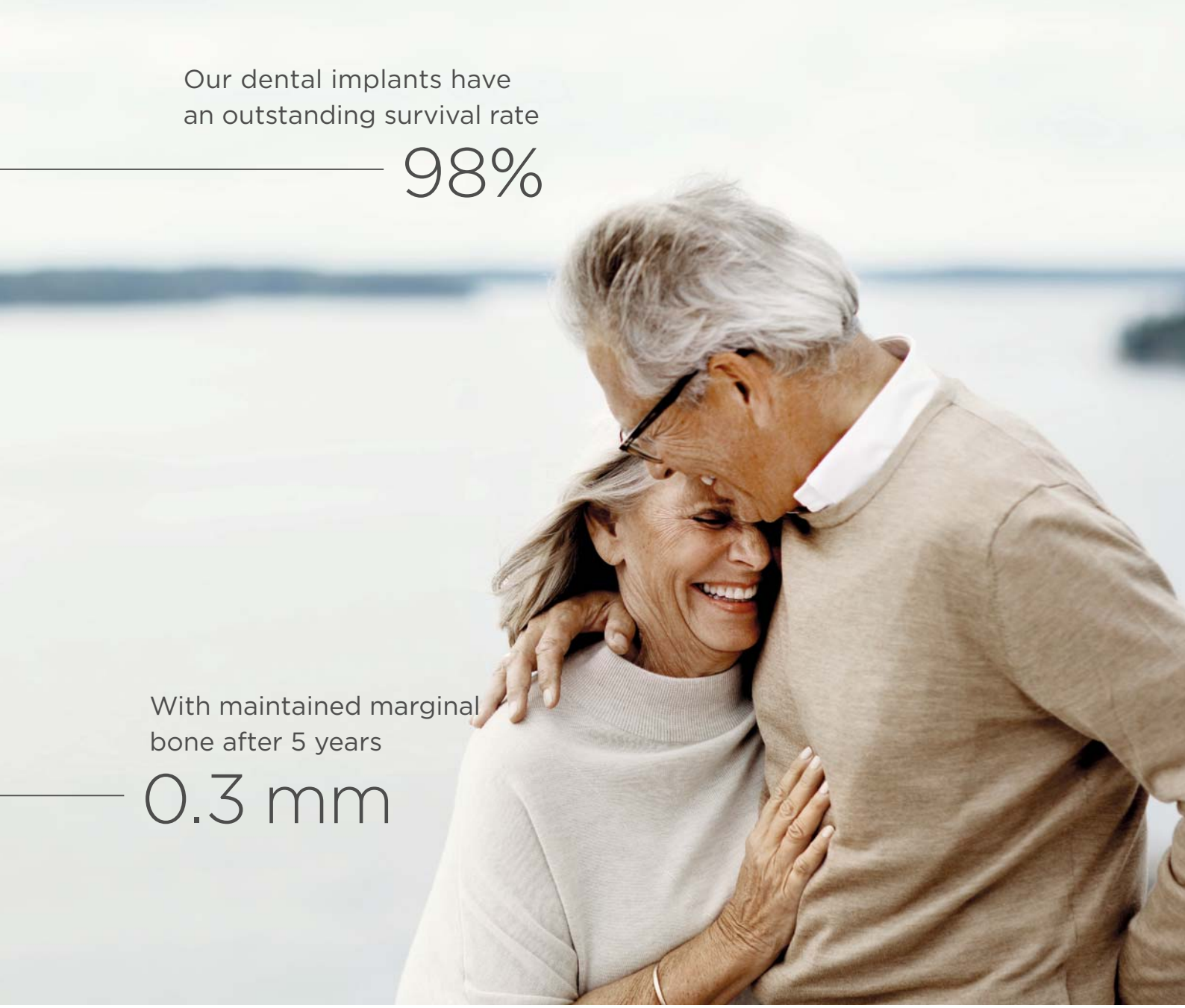

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