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Open Access Review Article

# **Contemporary Trends in Dental Implants**

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#### **Abstract**

A high number of patients have one or more missing tooth and it is estimated that one in four world subjects over the age of 74 have lost all their natural teeth. Many options exist to replace missing teeth but dental implants have become one of the most used biomaterial to replace one (or more) missing tooth over the last decades. Therefore, the use of dental implants is also a common practice. Although research on dental implant designs, materials and techniques has increased in the past few years and is expected to expand in the future, there is still a lot of work involved in the use of better biomaterials, implant design, surface modification and functionalization of surfaces to improve the long-term outcomes of the treatment. This paper provides a brief history and evolution of dental implants. It also describes the types of implants that have been developed, and the parameters that are presently used in the design of dental implants. Finally, it describes the trends that are employed to improve dental implant surfaces, and current technologies used for the analysis and design of the implants.

Keywords: Dental implants, History, Design, Surfaces, Osseointegration, Biopolymers.

### Introduction

In our society of appearance, teeth must be white and the dentition harmonious. Teeth participate primarily as one of the main attributes of smile. When decayed, grey or blackish, they can scare and must be hidden. Today, patients are still suffering from this evil of another age confining to archaism. Total edentulism is the ultimate degree of the parodontal disease and is still observed nowadays1. A poorly treated decay, a genetic alteration of enamel or dentine (e.g., amelogenesis or dentinogenesis imperfecta) and a trauma are sufficient to lose a tooth. Fortunately, in most cases, a solution exists for a tooth replacement such as bridge, dental implant, pivot tooth or denture. The solution depends of the local conditions of the dental status and also of the financial aspect of the treatment. Uncemented endosseous implants have become a most valuable alternative to dental prostheses supported by remaining teeth or adjacent oral soft tissues. The method started in the late sixties. During the last decades, metallic implants have become the most frequently used treatment. Titanium is one of the most commonly used biomaterial in oral and maxillo-facial surgery. Excellent clinical results have been obtained with threaded titanium implants by pioneer workers<sup>2-4</sup>. After more than four decades, dental implantology is now a well-recognized therapeutic advance in the treatment of partial or complete teeth loss<sup>5</sup>. The technique is reliable and suppresses the use of fixed or removable dentures, which invariably alter the supportive adjacent teeth after a short or medium period. The sustainability of dental implantology is primarily based on the overall analysis of the patient's clinical situation (periodontal

condition, occlusion, available bone volume, general health condition) and the appropriate adaptation of surgicalprosthetic options. The threaded implants currently available meet strict criteria of manufacturing and surgical procedures for their bone fixation and adaptability are now done according to specific prosthetic concepts. The pre-implant bone site is the most important point to consider in its ability to favor the implant osseointegration (i.e., primary bone anchorage of this metallic biomaterial) and its long-term stability. However, a reduced bone volume (constantly observed in the edentulous patient) impairs the placement of implants<sup>1</sup>; this has led to develop bone grafting techniques and the use of synthetic biomaterials6. Statistics provided by the American Association of Oral and Maxillofacial Surgeons show that 69% of adults ages 35 to 44 have lost at least one permanent tooth to an accident, gum disease, a failed root canal or tooth decay. Furthermore, by age 74, 26% of adults have lost all of their permanent teeth7. Therefore, the use of dental implants reveals that about 100,000-300,000 dental implants are placed per year, which approximates the numbers of artificial hip and knee joints placed per year8. Research on dental implant designs, materials and techniques has increased in the past few years and is expected to expand in the future<sup>9</sup> due to the recent growth of the global market for dental implants and the rising in the demand for cosmetic dentistry.

# **Historical Overview**

The history of dental implants can be traced back to ancient Egypt, where carved seashells and/or stones were placed into human jaw bone to replace missing teeth. Other documented

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examples of early implants are those fabricated from noble metals and shaped to recreate natural roots<sup>10</sup>. Dental implants have a history of several centuries starting with the early civilizations more than 2,000 years ago in South and North America and regions of the Middle Asia and Mediterranean. Archeological findings have indicated that these civilizations replaced missing teeth using carved stone, shells, bones and gold<sup>11</sup>. Around 1930s, archaeological excavations in Honduras revealed that the Mayan civilization had the earliest known examples of dental implants, dating from about 600 AD, when a fragment of mandible with implants was found. The specimen had three pieces of shells carved into tooth shapes placed into the sockets of three missing lower incisor teeth. Later on, it was also observed that there was compact bone formation around two of the implants<sup>12,13</sup>. In the middle Ages, dental implantation was performed by using allografts and xenografts. However, this practice didn't become very popular, since it was identified as the reason for infectious diseases and even deaths<sup>12,14</sup>. Modern dental implant history starts during World War II when in the years of service in the army, Dr. Norman Goldberg thought about dental restoration using metals that were used to replace other parts of the body. Later on in 1948, in association with Dr. Aaron Gershkoff, they produced the first successful sub-periosteal implant<sup>13</sup>. This success formed the foundation of implant dentistry in which they were pioneers in teaching techniques in dental schools and dental societies around the world<sup>13</sup>. One of the most important developments in dental implantology occurred in 1957, when a Swedish orthopedic surgeon by the name of Per-Ingvar Branemark began studying bone healing and regeneration and discovered that bone could grow in proximity with the titanium (Ti), and that it could effectively be adhered to the metal without being rejected 15. Therefore, Brånemark called this phenomenon 'osseointegration', and he carried out many further studies using both animal and human subjects. In 1965, he placed the first Ti dental implants into a 34-year-old human patient with missing teeth due to severe chin and jaw deformities. Branemark inserted four Ti fixtures into the patient's mandible, and several months later he used the fixtures as the foundation for a fixed set of prosthetic teeth4. The dental implants served for more than 40 years, until the end of the patient's life. Branemark published many studies on the use of Ti implants, and between 1978 and 1981, he cofounded a company for the development and marketing of dental implants. Branemark's discovery had such a profound impact in dentistry that to the present day, over 7 million Branemark System implants have now been placed and hundreds of other companies produce dental implants<sup>15,16</sup>. In May of 1982, Branemark presented the results of his 15 years of human and animal research at the Toronto Conference on Osseointegration in Clinical Dentistry, and shortly after the conference, researchers from the United States were trained in Branemark's methods in Sweden. In 1982, the US Food and Drug Administration approved the use of Ti dental implants, and in 1983, Dr. Matts Andersson developed the Procera (Nobel Biocare, Zurich, Switzerland) computer-aided design and computer-aided manufacturing method of high precision, repeatable manufacturing of dental crowns. Recent progress in the past century has focused on materials and techniques to improve quality and anchorage<sup>17</sup> and after the mid-1980s, other important developments in dental implantology have been focused in the esthetic restorations. The development of modern ceramics started in 1992; and from that time on, dental implant companies, have incorporated ceramic surface treatments and ceramic-like elements to implants with the purpose of further enhancing osseointegration<sup>18</sup>. Today, approximately 450,000 osseointegrated dental implants are being placed every year, with an expectation of 95% success rate (in the case of single tooth replacement with an implant supported crown), with minimum risks and associated complications  $^{12}$ .

# **The Dental Implants**

The vast majority of implants that have been placed in patients all over the world in 2015 have a similar shape: a hollow supporting screw that receives, in a second time, a supraprosthetic device. There are numerous variations in the overall shape of the implants (e.g., a rounded or pointed apex; more or less spaced threads, cylindrical or conical body) (Figure 1). The surface quality of an oral implant is one of the essential features for a successful early clinical outcome. The manufacturers have developed a number of specific processes to improve the rate of osseo-integration and the long-term biomechanical anchorage of the implant on the bone matrix. Implants with a rough surface have a better osseo-integration, evaluated by histomorphometric parameters, than the original machined titanium implant of Nobel Biocare, which had a smooth surface<sup>19</sup>. Roughness results in a better interlocking between the implant and bone on growth by increasing the developed surface at the micrometer scale. However, an excess of roughness, especially in the upper threads can increase peri-implantitis as well as ionic leakage<sup>20</sup>. It is generally accepted that a moderate roughness of 1-2 $\mu m$  is the most suitable condition<sup>21,22</sup>. Several methods have been proposed by the manufacturers to produce a rough surface on a dental implant<sup>23</sup>.

## Titanium plasma-spraying

The method uses a plasma torch under argon (hot titanium powder is explosive in the air) to project titanium particles onto the surface of the implant. They fuse and constitute a layer more or less uniform. However, some inconveniences have been described with filaments of metals, an increased risk of wear debris and the leakage of metal ions<sup>24</sup>.

### Particle blasting and acid etching

Blasting the implant surface with hard ceramic particles (corundum) at high velocity causes numerous impacts and tears at the material surface creating irregularities. However, the surface is made by defects with acute angles and can retain impacted foreign particles. For these reasons, an additional acid treatment using strong acids such as HF, HCl and HNO<sub>3</sub> is usually done after the blasting step. This produces a very typical rough surface with the appearance of waves and valleys, a condition that favor osseo-integration<sup>25</sup>. Other treatments can also induce surface irregularities such as sodium fluoride since titanium can be attacked by halogens.

## Anodization of the implant surface

Anodization can produce micro or nano-textured rough surfaces. This causes an increase in the passivation layer of titanium oxide associated with pores<sup>26</sup>.

# **Coatings**

Several coating methods have been also proposed to modify the roughness and improve cell attachment<sup>27</sup>. Hydroxy-apatite can be deposed by plasma-spraying but the layer tends to delaminate, leading to implant failure in mid-term studies<sup>28</sup>. These implants are nowadays abandoned. Similar problems were also encountered with coatings made of other orthophosphate calcium salts. Biomimetic calcium phosphate have also been electro-deposited or created by immersion in synthetic body fluids (gel-sol technique) <sup>29</sup>.Whatever the mechanisms used to induce a surface roughness, this favors fibronectin deposition, cell attachment and spreading as evidenced by in vitro and in vivo studies<sup>30,31</sup>.

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### Placement methods

The placement of a dental implant can be done under local or general anaesthesia; the local anaesthesia being the most commonly used in daily practice. The implantation protocols are totally painless regardless of the maxillary or mandibular location. Occurrence of intra-operative pain is the result of incomplete anaesthesia or an iatrogenic act. Although occurring in the oral cavity which contains many of saprophytic bacteria, the asepsis protocol must be strict and similar to the general rules of surgery with the use of sterile implant packages and sterile drapes to cover the patient, CT scans are necessary to ensure a correct implant placement in bone at distance from nerves or vessels which would be a source of complication. The principle for an implant placement is based on the use of calibrated drills with increasing size until the width of the implant is obtained. Depending of the bone density, drilling is more or less intensive. This step ends with a control of locking the implant on the bone with a torque wrench. Indeed, a residual mobility will not permit the stability of the implant and it will be necessary to remove it. At the end of surgery, two possibilities exist: (i) Bury the implant on bone for several months under the sutured gingiva. Proponents of this method consider that such a quiescent condition is more favorable without mechanical stress, risk of infection or epithelial invasion. (ii) Other authors prefer to immediately place the implant collar inside the oral environment by fixing a cover screw at the top of the implant until the impression procedure. Overall, there is no consensus on the superiority of either of these two methods. As mentioned above, the concept of osseo-integration is defined by the tolerance into the living bone of a foreign and inert body (the titanium implant) which will provide a sustainable

and stable bone anchor. An X-ray follow-up must confirm the absence of peri-implant osteolysis (appearing as a radiolucent edging around the implant). Osteolysis is also associated with a painful inflammatory reaction and implant mobility. This situation requires removal of the implant as soon as possible to limit the expansion of the peri-implant osteolysis of the alveolar bone. As previously mentioned, the surgical protocol is now no more strictly based on the Branemark's concepts pro-posed thirty years ago. The timing for loading the implant has raised a considerable amount of articles and can be done in several ways. It has been advocated that after implant placement, the surgical site should be left undisturbed for 4 to 5 months to allow a good wound healing between the implant and the bone. This period is in accordance with bone cell physiology: osteoblasts elaborate woven bone rapidly to ensure the primary bone anchorage and this bone (being of poor quality) is secondarily remodelled and replaced by lamellar bone which possesses a better quality. More recently, other authors have proposed the concept of immediate loading of the implant to support provisional fixed crowns or prosthesis32,33. Immediate loading is the placement of a temporary prosthesis on the implants just after the implant placement. The benefit of this protocol is to immediately correct the tooth loss and to favor maturation of the gingival tissues at the implant's base. The obvious disadvantage of this procedure is that loaded implants are exposed to the chewing force immediately after implantation, a situation that may delay osseo-integration. This protocol is not the subject of a consensus and the exact definition of immediate loading may vary from same-day implant loading to a shortly-delayed loading (usually three days to one week), making published results difficult to compare.



Figure 1: Different types of dental implants proposed by several companies

# **Implant Requirements and Design**

Since the use of dental implants has a long history, there are many factors that have been recognized as critical for the successful performance of the implants<sup>9</sup>. One of the most important factors is biocompatibility; which not only involves compatibility of the material with the tissue but its ability to perform a specific function. Therefore, this property is not dependent just on the physical, chemical and mechanical properties of the material, but also by the application in which

the material is used. In the case of dental implants, the biocompatibility of materials is evaluated by studying the direct interactions between the implant and the tissues, which is a measurement of the degree of osseointegration<sup>34</sup>. In order to improve osseointegration; therefore long-term success of the implants, the following variables are critical and should be considered in the design of dental implants include biomaterials composition, implant width length and geometry, biomechanical factors, surface characteristics, medical status of the patient, bone quality and surgical technique<sup>35</sup>.

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## 1. Biomaterials

The biomaterials used for manufacturing dental implants include metals, ceramics, carbons, polymers, and combinations of these. Polymers are softer and more flexible than the other classes of biomaterials. They also present with low mechanical strength, which makes them prone to mechanical fractures during function under high loading forces. Polymeric materials were reported to have very little application in implant dentistry and were only used to fabricate shockabsorbing components placed between the implant and the suprastructure<sup>35</sup>. Ti, including alloy Ti-6Al-4V (Ti-6 aluminum-4 vanadium), is the first modern material used for dental implants, and it is still one of the most used in contemporary dental implants. Commercially pure Ti is a light metal with excellent biocompatibility, relatively high stiffness and high resistance to corrosion. However, when exposed to air, a surface oxide is formed and this layer of oxide determines the biological response. This oxide layer is a dynamic interface that acts as platform for the apposition of bone matrix<sup>35</sup>. Other metals have been used for osseointegration, including zirconium, gold and Ti-aluminumvanadium alloys. These alloys may strengthen the implant but have been shown to have relatively poor bone-to-implant contact. Bioceramics such as hydroxyapatite are also used although their low strength, because biocompatibility, and capacity to integrate with hard tissue and living bone8. Besides their brittle nature, hydroxyapatite, tricalcium phosphate, and aluminum oxide ceramics are currently used as plasma-sprayed coatings onto a metallic core. This results in union of the implant with the host tissue<sup>35</sup>.

### 2. Implant design

A wide variety of different sizes and shapes of implants have evolved to fit current surgical concepts and improve patient treatment. Continuous research has revealed that subtle changes in shape, length, and width of the implants could influence success rates<sup>36</sup>.

# Length

Implant length and diameter have an influence on the stress distribution at the bone-implant interface, as well as on success rates<sup>37</sup>. Implant length is the dimension from the platform to the apex of implant9. Implant length varies from 6-20 millimeters. The most common length employed is between 8-15 millimeters<sup>36</sup>. Research in implant dentistry has shown that longer implants guarantee better success rates and prognosis; and that shorter implants have statistically lower success rates due to reduced stability, which can be explained in terms of less bone to implant contact and smaller implant surface<sup>36</sup>. However, short or narrow implants are preferred for the prosthetic solution of the extremely resorbed alveolar bone areas<sup>38</sup>.

# Diameter

The diameter of the implant is measured from the widest point of a thread to the opposite point on the implant and typically ranges from 3 to 7 mm; although narrower diameter implants can be used in small spaces. For clinical applications, physicians select implant diameter depending on the patient's bone quantity and quality to yield optimal stability and to prohibit over-instrumentation. For example, wider implants allow for interaction with a larger amount of bone. Ivanoff et al<sup>39</sup> concluded from animal studies that larger diameter implants are more stable in removal torque tests, and that they may be more useful in the clinical setting since there is a larger contact area with cortical bone. In addition, it has been shown in mechanical simulations that larger diameter implants can resist larger vertical loads<sup>40</sup>. Using FEA, it was determined that the implant diameter was much more

important in stress dissipation than implant length, especially in cortical bone<sup>41</sup>, though other groups have reported that the length of the implant was more important in controlling stress distribution in the cancellous bone<sup>42</sup>. Based off of the literature, implant lengths ranging from 8 mm to 12 mm are used clinically.

### Geometry

One of the main concerns in terms of design is the shape of the implant, since the geometry affects the interaction between the bone and implant, the surface area, the distribution of forces to the bone and the stability of the implant. Therefore, commercial dental implants are classified into different groups according to their shape. The main types of implants are cylindrical, conical, stepped, screw-shaped, and hollow cylindrical. Several studies revealed that conical implant surfaces or surfaces with geometric discontinuities resulted in higher stresses than smoother shapes such as cylindrical or screw-shaped. For this reason, the cylindrical screw threaded implants are the most commonly used<sup>9,10</sup>.

### Threads

As mentioned before, threads are incorporated into implants in order to improve initial stability, enlarge implant surface area, distribute stress favorably while minimizing the amount of extreme adverse stresses to the bone-implant interface. The thread profile is characterized by the depth, pitch (number of threads per unit length), flank angle, the top radius of curvature, and the straight part at the bottom of the thread1. Different modifications in thread patterns such as microthreads near the neck of the implant, macrothreads on the mid-body, and variety of altered pitch threads have been employed to accentuate the effect of threads and induce a desired biomechanical behavior 34,43.

### 3. Biomechanical factors

Dental implants are primarily anchored in bone by means of mechanical interlocking1; therefore, implant stability is considered to play a fundamental role in successful osseointegration. It has been found an implant failure rate of 32% for implants with inadequate initial stability. As mentioned above, major contributors to dental implant stability are the design parameters such as length, diameter, geometry and threads have important effects on biomechanical stability, load transfer mechanisms and either success or failure of implants. Other factors that affect the stability are the material properties and the quality and quantity of surrounding bone. Masticatory forces acting on dental implants can also result in undesirable stress within the surrounding jawbone, and this can cause bone rejection and eventual failure of the implant8. Moreover, bone resorption can be activated by surgical trauma or bacterial infection, as well as by the design parameters used<sup>42,43</sup>.

# 4. Surface characteristics

When a material is placed in the body, there will be a biological response that will be mediated by the interaction of the implant through its surface. Micro-level features are included to impart osseointegration or direct bone to implant contact at the micro level<sup>44</sup>. At the points of contact between cells and biomaterials there is an exchange of information leading to activation of specific genes and remodeling. The first step in this response involves the adsorption of specific proteins, lipids, sugar, and ions that can activate cells mechanisms to induce either acceptance or rejection of the implant by determining which and how many cells populate the surface<sup>45,46</sup>.

Therefore, a high percentage of bone-implant contact is necessary to create sufficient anchorage of the implant, which

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is a determinant factor in osseointegration. Two of the most important factors that affect the quality and speed of osseointegration are the physical and chemical nature of the surface of the implant. These properties also have an effect on the maintenance of soft tissue and surrounding bone around the implant. In order to increase the success rate of dental implants, research has focused on the control of surface properties such as morphology, topography, roughness, chemical composition, surface energy, residual stress, the existence of impurities, thickness of Ti oxide film, and the presence of metallic and nonmetallic compounds on the surface. These properties profoundly influence the osseous and tissue response to the implant by either increasing or decreasing healing times and osseointegration37. Research has shown that osteoblastic cells adhere more quickly to rough surfaces than to smooth surfaces 1. This property can also produce orientation and guide locomotion of specific cell types and has the ability to directly affect cell shape and function<sup>47</sup>. There are two broad types of chemical alterations: 1) addition of inorgainic phases (e.g., hydroxyapatite or calcium phosphates) and 2) addition of organic phases (growth factors). In both cases, the goal is to impart direct bone to implant contact. The addition of inorganic phases such as calcium phosphates imparts osteoconductive properties to the implant<sup>48,49</sup>. Coating Ti implants with calcium phosphates increases the speed at which bone formation occurs and also serves to span a gap between bone and the implant<sup>50,51</sup>. Ti implants are typically coated with hydroxyapatite using plasmaspraying to form an inorganic film. Though this coating serves to increase osteoinduction, the bond between the film is a limiting factor in the efficacy of inorganic coatings; the micronsized film can delaminate or loosen and release large particles, causing implant failure 18. Secondly, the addition of organic molecules or bioactive molecules also influences the surrounding cells. For those reasons most commercial dental implants have a microroughened surface (0.5-1µm) obtained by techniques such as grit-blasting and/or acid-etching54. Although many studies have demonstrated the importance of roughness in osseointegration, there is no standard for the roughness of dental implants1. However, many animal studies support that bone ingrowth into macro rough surfaces (2-3μm) enhances the interfacial and shear strengths. Surface roughness can also induce orientation and guide locomotion of cells and has the ability to directly affect cell shape and function<sup>52,53</sup>.

# **Contraindications**

They are now well identified and classified. General contraindications are psychiatric disorders, severe cardiovascular troubles, hematological malignancies and ongoing therapeutic trials. A special attention is given to patients receiving intravenous amino-bisphosphonates for a malignant disease. Due to the high risk of inducing an osteonecrosis of the jaw, scientific societies and health agencies consider that dental implants are prohibited in these particular cases. However, bisphosphonate treatment for other metabolic bone disease such as osteoporosis is not a contraindication and recommendations should be care-fully followed. Local contraindications are represented by an absent oral hygiene, a massive bone loss and occlusal disorders. Smoking is a discussed contraindication: it has been shown that a significantly higher percentage of implant failures may occur in smokers (particularly at the maxilla) 54-56 but smoking do not preclude implant placement; smokers should be informed that they are more at risk for peri-implantitis.

# **Limits and Complications of Dental Implants**

The limits of implantology derive from careful analysis of the contraindications but nowadays, there are fewer and fewer

taboos. As an example, a limited bone volume is typical of the evolution and adaptation of the therapeutic strategies. At the beginning of implantology, a minimum of bone volume was required for the placement of the fixtures. The development of new grafting techniques was proposed to overcome the problem of bone insufficiency. During the 1990s, filling or apposition grafts were extensively developed at the maxilla or the mandible after having harvested a bone autograft at the skull or iliac bone. The history of sinus lift is characteristic of the huge amount of progress made with bone grafts. In this technique, a bone autograft is added between the jaw and the olfactory epithelium covering the maxillary sinus (Schneider's membrane). After healing, an increased bone volume is obtained allowing the placement of the implants after 6 to 9 months. The use of biomaterials as bone substitute has led to the development of this protocol by eliminating the first surgical time (harvesting of the autograft). This led to a more easy and reliable technique ensuring a high level of success and a better anchorage of the implant with prosthetic devices. At that time, the most recommendable biomaterial to use for making a sinus lift is beta tricalcium phosphate ( $\beta$ -TCP), which is gradually resorbed and induces bone osteoconduction. In the past, implant placement was a source of infectious complications and had a reputation of an ill-fitting. Since 3-4 decades, implant outfits are the rule, explaining the interest of dentists and maxillo-facial surgeons for these techniques. The present complications are mainly infectious. After nearly four decades of implant practice, it is possible to observe a bone lesion, termed peri-implantitis, which can threaten the implant holding. This leads to a peri-implant osteolysis associated with an inflammation of soft tissues. Bone loss occurs around the implant as a saucer defect and its progression is non-linear and accelerated by risk factors (tobacco, poor oral hygiene). Removal of the implant before the bone loss is too pronounced may represent a preventive and conservative action to protect the bone volume. Fractures of the prosthetic elements are not rare and can be easily corrected. However, it should be noted that iatrogenic complications are not uncommon. They can be due to a surgical fault, after a poor X-ray analysis, a defective positioning of the implant, the fracture of an instrument, the compression or section of the inferior alveolar nerve, the migration of an implant in the maxillary sinus or the lack of a global therapeutic evaluation. These cases usually have medico-legal consequences. The lifetime of dental implants is exceedingly high, generally in the order of two decades if the protocols are correctly followed. The percentage of complications (loss of implants) remains low because, usually less than 5% in the first 5 years for the majority of authors<sup>57</sup>.

## **Conclusion**

At the end of the 20th century, a major advance in the treatment of tooth loss is represented by the discovery of dental implants. Although implantology has not the same importance that other surgical techniques concerned with lifethreatening diseases, the correction of a dental deficit influences the physiological and psychological condition of the patients and improves their quality of life. Rigorous manufacturing processes, the recognition of an operative consensus and the numerous prosthetic adaptations available have really accomplished a technological revolution. The technique remains; however, poorly known among all the other organ grafts but its therapeutic value is now well admitted.

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