The development and future of dental implants
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Since 1970s, a lot of effort has been devoted toward the development of dental implants. Dental implants are nowadays an indispensable part of clinical dentistry. The global dental implant market is expected to reach $13 billion in 2023. Although, the survival rate of dental implants has been reported above 90%, compromised bone conditions promote implant failure and endanger the current high success rates. The main concern is related to the aging population. Diabetes, osteoporosis, obesity and use of drugs are all medical conditions, which can hamper bone healing around dental implants. In view of this, research toward developing better methods of enhancing implant osseointegration have to be continued, especially in the presence of impaired bone condition. In this paper, the current changes and their future perspective are discussed.

Keywords: Implant, Bioactive, Osseointegration, Titanium, Biocompatibility

INTRODUCTION

The problems related to the loss of teeth have bothered mankind for centuries. Since ancient times attempts have been made to replace a missing tooth with an implant. Initially, an anatomical replica of the natural tooth was prepared, employing a wide variety of material including ivory, bone, metals, and precious stones. The famous surgeon Ambrosius Paré (1517–1590) even used freshly extracted non-curious teeth.

The history of the present dental implantology starts at the turn of the 19th century. In 1891, Znamenski and Hillischer implanted teeth made of porcelain and gutta percha. Payne used gold plated tin capsules filled with gutta percha and Greenfield inserted endosseous implants consisting of hollow latticed iridio-platinum cylinders. At the top of each cylinder was a grooved disk in which an artificial tooth was cemented. The operative procedure was performed with a cylindrically shaped trephine. A circular socket was prepared in the jaw, leaving intact a core of bone over which the cylinder was placed. Greenfield supposed that the core of bone, left in the implant site, induced the deposition of new bone. He reported considerable success.

The next 20 years brought little innovation to the field of implantology and it was not, until the late 1930’s and 1940’s that new results were published. The Strock brothers experimented with endosteal vitallium screw implants and introduced the endodontic implant. Despite some early failures they reported that vitallium was very well tolerated by bone. Also, during this time, a spiral shaped subperiostal implant was developed.

The period of 1950–1970 was characterized by a burst of new developments, especially modifications of designs described earlier. A new concept was the introduction of the blade vents by Linkow and the ceramic bone screw by Sandhaus. The blade vent implant was inserted in a groove which was prepared in the alveolar bone if the lower as well as upper jaw. The implants developed by Sandhaus were made of aluminium oxide. Sandhaus claimed that this material was less irritating to the tissues than the commonly used metal alloys.

After 1970, more interest was devoted to unravel the factors that determine clinical success or failure of dental implants. It was attempted to explain the implant outcome on basis of the results of clinical studies. However, due to a lack of standardization in the evaluation criteria and because only one type of implant was considered in most of these studies, it appeared very difficult to indicate a specific guide-line for the realization of high success rates. An exception was the statistical evaluation of clinically applied implants by Cranin et al. Cranin evaluated all the endosteal implants inserted by the Brookdale hospital group since 1966. The criteria used to evaluate the success rates were even more stringent than the criteria used for the assessment of periodontal disease. Implants were considered successful when they showed no or less than 1 mm cervical bone loss. Such stringent criteria were accepted since bone loss of more than 1 mm could cause exposure of the implant infrastructure which was compared with the furcation involvement in periodontal disease.

In addition to these clinical evaluations, histological examinations were performed to examine dental implants. Close adaptation of the bone and attachment of the gingival epithelium as well as fibrous encapsulation and epithelial downgrowth were reported. It became clear from these studies that the penetration of the oral mucosa is the critical item in oral implantology and that gingival health and long-term implant functioning could

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be maintained by a tight implant-bone contact without intervening connective tissue layer. As a consequence of these findings, Brånemark introduced at the end of the 1970’s threaded screw implants manufactured from pure (99.7%) titanium\textsuperscript{11-13}. The basis for the use of titanium in implants was its high corrosion resistance, thanks to the presence of a very inert and tenacious passivation film of titanium-oxide (TiO\textsubscript{2}) covering the metal surface. Brånemark observed that this TiO\textsubscript{2} layer could achieve a direct bone-implant contact provided that a careful surgical technique was applied, which was obtained by the combination of the screw design, a strict drilling protocol for implant installation into the alveolar bone and the requirement to follow a course at the Brånemark clinic in Göteborg, Sweden.

On basis of the early attempts and the breakthrough of Brånemark, we have witnessed in the past 30 years significant advances in the development of dental implantology. Dental implants are nowadays an indispensable part of clinical dentistry. The global dental implant market is growing steadily and is expected to grow to about $13.01 billion by the year 2023. Although, the survival rate of dental implants over a 10-year observation has been reported to be higher than 90%\textsuperscript{14}, this forms also a challenge for the future. This concern is related to the aging of the population. Worldwide the number of elderly people increases dramatically. Accordingly, more than 20\% of the European and 30\% of the USA population have been estimated to be older than 65 years in 2030\textsuperscript{15}. Aging is associated with the increased loss of teeth, but elderly people are also more exposed to factors that compromise their physical health. Diabetes, osteoporosis, obesity and use of drugs are all medical conditions, which can hamper bone regeneration around dental implants. Consequently, this can promote implant failure and endanger the current high success rates.

In view of the above mentioned there is a clear need for the continuing evolution of modern dental implants, which finally has to result in dental implants that can actively stimulate bone formation. In this paper the developments and their future perspective will be discussed, which includes progress made in the development of surgical techniques, implant design as well as material and implant surface properties. At first, a short description of implant-bone healing will be given.

**OSSEOINTEGRATION:**

**THE SUCCESS KEY OF DENTAL IMPLANTS**

The term “osseointegration” was first introduced by Brånemark to describe the histological evidences suggesting successful outcome of dental implants after placement in the jaw bone\textsuperscript{16}. An osseointegrated dental implant reflects the biological and mechanical fixation of implant fixture into jaw bone under normal clinical function.

The process of implant osseointegration in a healthy condition is complex and takes several weeks of healing. Immediately after implantation, the reactions of inflammatory cells as well as bone cells take place at the bone-implant interface. These events are followed by the process of bone regeneration, which is regulated by several biological factors in the implant vicinity\textsuperscript{17,18}. Thereafter, bone mineralization (remodeling) occurs at the contact and distance sites of dental implants.

An optimal bone mineralization insures high quality of bone-to-implant contact (BIC) and will provide dental implants with long-term biomechanical stability\textsuperscript{19}. Thus, decreased quality of bone in an impaired condition can be considered as a possible risk factor for implant failure. This can be hypothetically related to various factors that compromise the osteogenic capacity of bone around implants\textsuperscript{20}. It is evident that attempts should be continued toward developing better methods of enhancement of implants osseointegration, especially in the presence of an impaired bone condition. Consequently, the maximizing of BIC is still the main goal of preclinical research to enhance osseointegration through developments in dental implant design, surface characterization, and methods of implant placement.

**THE DEVELOPMENT IN DESIGNS OF DENTAL IMPLANTS**

Nowadays, several developments in dental implants design have occurred. Most of the commercially available designs of dental implants are threaded with cylindrical or conical (root) shapes (Fig. 1). The shape of a dental implant primarily affects its biomechanical fixation and function in the bone tissue. Certainly, implant diameter and length as well as thread pitch, shape, and depth, are the main parameters under focus of researchers. Implant threads increase the surface area for direct bone-implant integration\textsuperscript{21}. Also, implant thread design can significantly enhance long-term stability of a dental implant\textsuperscript{22}.

Also, implant surface macroporosity (a pore size of 150–300 μm) can favor the osseointegration process\textsuperscript{23,24}. Various methods have been used to create porosity onto an implant surface. In recent years, researchers developed tantalum-based, highly porous-surfaced implants with a trabecular bone-like surface topography (Trabecular Metal Zimmer®, Dental Implant System Parsippany, NJ, USA), which is described to improve the bone ingrowth and bone ongrowth properties of dental implants by increasing the surface-interface with bone tissue\textsuperscript{25,26}. Nevertheless, long-term clinical studies are needed to confirm the possible potential of such highly porous dental implants in compromised bone conditions.

Despite an important role of biomechanics in the establishment of osseointegration, implant-design concepts are not expected to promote advantageous functions by specific control of bone cells and tissues interactions at the implant interfaces. In view of this, commercially pure titanium, known for its high degree of biocompatibility and good mechanical properties, remains the preferred biomaterial for the manufacturing
of dental implants. Modifications by alloying titanium with other metals, like zirconium and resulting in mechanically stronger implants, seem more driven to allow the use of smaller diameter and shorter implants than by improving the implant-bone response. A similar comment can be made about the use of zirconia, as implant material. The major consideration for the choice of this ceramic material is esthetics and not bone biology.

**IMPLANTATION PROTOCOLS AND DRILLING TECHNIQUES**

Traditionally, the placement of dental implants is performed with a consecutive series of surgical drills (based on the manufacturer’s instructions) to prepare implant bed fit exactly the implant. However, several implantation protocols have been proposed to increase implant stability, especially in limited bone quality.

Also, new drilling techniques have been suggested without removing additional bone. For example, an osteotome spreader has been introduced to compress the bone tissue laterally and apically. Additionally, the undersized drilling protocol has been studied extensively and proposed for implant placement in low quality (Type-IV) bone. In this procedure, by using a final drill diameter smaller than the implant diameter, bone is compressed laterally along the implant sides. The undersized drilling has demonstrated higher insertion torque values, and then showed increased implant stability.

The development in surgical techniques showed several advantages for the process of bone healing and remodeling around implants. For example, researchers noticed that osteogenic bone fragments became translocated and interspersed along the surface of an implant when using the undersized drilling technique, with evident signs of contribution of these bone particles to stimulate peri-implant bone healing and remodeling.

Still, more research is necessary to further evaluate the biological mechanisms underlining the favorable results of the undersized drilling technique and to explore its beneficial role in the process of new bone formation in impaired bone conditions.

**THE DEVELOPMENT IN SURFACE MODIFICATIONS AND COATINGS**

Implant surface modification is considered as an important approach to favor osseointegration. Implant surface modification can accelerate the interactions with biological fluids and cells to promote peri-implant bone regeneration. In the past two decades, various surface modification approaches have been proposed and studied to improve implant osseointegration.

**Micro-roughness of the implant surface**

Micro-roughness is the most common surface modification as applied to the modern dental implants. It plays a significant role in anchoring cells and connecting to surrounding tissues, thereby favoring peri-implant osteogenesis. Different physicochemical methods have been developed to modify the implant surface roughness, e.g. grit-blasting, acid etching, or combinations. Grit-blasting is commonly performed by using silica, hydroxyapatite, alumina or TiO₂ particles, and is followed by acid-etching to homogenize the micro-profile of the implant surface and to remove the residual blasting particles. Hydrofluoric, nitric, sulfuric acid or combinations are the chemical agents used for acid-etching.

**Nano-texturing of the implant surface**

Recently, the modification of the implant surface at the nanoscale level has been also introduced, which is based on the assumption that mimicry of the nanopattern of bone structures might increase the surface energy, and hence improve matrix protein adsorption, bone cell migration and proliferation, and finally enhance osseointegration. However, further investigations are needed to explore the capacity of nanometer scale surface topographies to enhance the osteogenicity of titanium implants.
Calcium phosphate (CaP)-based implant coatings

The deposition of CaP coatings onto the implant surface has received significant attention because of their chemical similarity to the natural bone mineral. For such surface coatings, several biochemical deposition techniques have been explored\(^\text{35-37}\). CaP-based implant coatings show the ability to directly bond to bone tissue and increase the biochemical interlocking between bone and surface materials\(^\text{38}\).

Extracellular matrix (ECM)-based implant coatings

The deposition of ECM proteins onto the implant surface has also attracted more attention in the recent years. Coating surfaces with ECM proteins is expected to enhance osseointegration through accelerating the process of bone regeneration at the implant interface\(^\text{39}\). In addition, recent investigations reported that both surface coating materials (CaP and ECM) play a synergetic role in controlling the cellular/molecular events related to bone-implant interactions\(^\text{55}\).

Drug-based implant coatings

Additionally, the development of new coatings strategies involves drug-loading ability onto the implant surface, which can be effective to target bone disorders around dental implants. For example, bisphosphonates\(^\text{39}\), strontium ranelate\(^\text{40}\), and statins\(^\text{41}\) are the drugs of choice used to promote implant osseointegration in osteoporotic bone. Technically, these drugs are incorporated onto the surface of an implant using different deposition methods.

In a recent meta-analysis\(^\text{42}\), all preclinical studies were investigated on the possible benefit of anti-osteoporotic drugs on implant osseointegration. Although poor reporting was assessed in the included studies, results showed a positive effect of anti-osteoporotic drugs on implant osseointegration, i.e. implants coated with drugs showed a higher value of BIC\% compared to implants without the use of anti-osteoporotic drugs. However, further preclinical trials on this area of research are warranted.

From the aforementioned, it appears that there are many methods to modify the surface characteristics of dental implants by means of physical, chemical, or therapeutical methods. Still, the mechanism of bone response to anyone of these surface modifications has not been fully characterized. Consequently, more preclinical research is still necessary in order to achieve the desired biological responses to dental implants, especially in compromised conditions.

PRECLINICAL MODELS FOR TESTING OSSEOINTEGRATION

For testing the osseointegration of newly developed implant designs and surface modifications, animal experiments are required. Several preclinical models\(^\text{43}\) are commonly used to study implant osseointegration. Also, specific animal models are needed resembling the medical conditions, in which the relevant biological response to biomaterials can be tested prior to clinical use. For instance, models reproducing diabetic and osteoporotic conditions are useful to help understand the influence of such pathogenesis on implant osseointegration. In addition, inducing human-like diseases in animal models has been proposed using different methods. These models would allow to mimic the complexity in bone-implant interactions due to the impairment in wound healing that accompany medical conditions in humans\(^\text{44,45}\). Indeed, dental implants research using compromised animal models will further gain importance in future.

Irrespective to the animal models, several outcomes related to implant osseointegration can be measured. Mainly, histomorphometrical and radiographical examinations as well as biomechanical testing are commonly applied to evaluate bone-to-implant healing. Moreover, fluorescence analysis provides dynamic measurements of the bone healing around implant surfaces. Finally, for an accurate judgment of the obtained results regarding peri-implant osteogenesis, an in vivo experimental setup should be well designed and statistical analysis should be well conducted. A carefully proposed experimental setup is obligatory for the proper translation of the findings to clinics.

FUTURE PERSPECTIVE

Evidently, osseointegration of dental implants in compromised bone environment is endangered. Consequently, it is wise to be cautious with the treatment planning of oral implants in patients with challenging conditions that can alter the process of bone regeneration (particularly in trabecular bone) and cause a significant decrease in the amount of bone interfacing the implant surface.

In view of this, advances in biomaterials research continuously encourage the marketing of new implant designs that are claimed to stimulate new bone regeneration around dental implants and to favor the clinical outcome. Currently, there is an outstanding progress in the development of bone implants with a bioactive (instructive) surface that show favorable osteopromotive capacity in preclinical model with suboptimal bone conditions. Nevertheless, a better understanding of the in vivo biological response at the implant-bone interface is still needed to create effectively a dedicated implant to target the on-site bone disorder around dental implants. Despite, more than four decades of research and extensive commercialization of titanium dental implants, the biological mechanisms that are responsible for the osseointegration process of titanium are still poorly understood. Local multicellular mediator mechanisms were stressed by Frost\(^\text{46}\) already in 1989 as master switches of bone fracture healing by initiating and controlling the release of the biochemical cues that ultimately determine the fate of osteoblasts and osteoclasts. These early findings were confirmed in numerous other studies, which provided firm evidence that the cellular inflammatory...
response contributes to bone healing by the production of cytokines and growth factors. Also, the initial presence of monocytes/macrophages and their transition to multinucleated cells coincides with ectopic bone formation around biomaterials. This relation between ectopic bone formation and the formation and activity of multinucleated cells has additionally been demonstrated to depend on specific biomaterial properties, including surface morphology. Currently, the role of blood clot and inflammatory cells in engineering instructive bone implants that trigger a dedicated bone healing response, also in compromised conditions, is largely ignored. A blood clot typically consists of a fibrin-based ECM that acts as scaffold for platelets and macrophages as key resident cells. These two cell types are the essential source of cytokines and growth factors that govern the migration and infiltration of regenerative cells (e.g. osteoprogenitor cells) to sites of (bone) tissue damage. Platelets contain α-granules, which are a unique source of growth factors, like insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β) and platelet factor 4 (PF-4). Growth factors are released from the α-granules into the plasma upon activation of the platelets. The resultant effect of platelet activation is the nourishment of the blood clot with endogenous signaling factors, which as such becomes a 3D provisional matrix to which inflammatory and regenerative cells are attracted and in which the initial wound healing processes (i.e. inflammation and proliferation) can be effectively initiated. Macrophages are cells produced from the multipotential hematopoietic stem cell. First, monocytes are formed. When monocytes leave the blood circulation and enter into surrounding tissue, they differentiate into mature tissue macrophages. Macrophages can be activated and then function in the defense of the organism against foreign intruders. An important role of macrophages is to mediate the degree of inflammatory response, tissue remodeling and material clearance, e.g. upon the installation of a biomaterial. Activated macrophages synthesize and secrete growth factors (such as PDGF, IGF and TGF-β), cytokines (interleukins, interferons) as well as enzymes and extracellular matrix (ECM components) (e.g. fibronectin and osteopontin). As such, there is growing evidence about the relevance of the macrophage population in terms of tissue formation following biomaterial implantation.

Closure of the existing knowledge gap related to biological processes acting to initiate osseointegration will establish a benchmark for the design of custom-made instructive dental implants, which will facilitate dental implant installation for challenging patient groups (i.e. elderly and compromised patients).

REFERENCES


