Dental implants and biological coating: the evolution of osseointegration

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ABSTRACT

Titanium plays a predominant role as the material of choice in dental and orthopedic implants. Currently, surface topography modifications and non-biological/ biological coatings have been integrated into implants to simulate the surrounding biological environment as well as depress the infection/inflammation that may occur. Until now, a variety of implant surface modifications, including physical, chemical, and biological techniques, have been applied to a wide selection of materials to reach these outcomes. Best modifications improve the interaction between implants surface and its surrounding bone tissue helping osseointegration while minimizing bacterial colonization.

This review article aimed to analyze one specific type of biological implants coating, using growth factors, that can have an important impact on cells behavior both in vivo and in vitro.

Keywords: dental implants; growth factors; BMPs; IGFs; osseointegration.

INTRODUCTION

Dental implant is a prosthetic device made of alloplastic material, such as steel or titanium and its alloys; this last one is the best choice for its excellent chemical and physical properties and, most of all, its biocompatibility. Depending on the improvement of dental implant technology and biomaterials, dental implant has become a significantly popular treatment for replacement of missing teeth. The success of the osseointegration and the following implant survival depend on many casual factors, such as physiological conditions of the host, preparation of the implant site, implant design, and properties of implant surface [1]. Moreover, the nature of the implant surface and the implant placement procedure can also contribute to the final outcome of osseointegration. Both the implant as a foreign body and the implant insertion as a traumatic operation naturally cause an important response of the immune system and the sequential biological behavior of bone cells, which finally determine the outcome of long-term survival of the implant [2]. Nevertheless, current research on bone biomaterials and implants mainly concentrates on inducing osteogenesis and stimulating implant osseointegration.

Brånemark defined osseointegration as a direct contact of vital bone with the surface of an implant at the light microscopic level of magnification [3]. It consists of two types of

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osteogenesis: direct and indirect osteogenesis; this notion is important in the healing process after surgical implant insertion. After surgical step, "indirect osteogenesis" occurs when osteoblasts lay down on the damaged pre-existing bone surface, so that new bone formation takes place from the bone surface. Meanwhile, some osteoblasts are assembled on the implant surface, leading to "direct osteogenesis": bone formation takes place from the implant surface [4]. Speaking about the timing of implant placement, there are three protocols for dental implant surgeries: early implant placement, with implant placement following complete soft tissue coverage of the extraction site; immediate implant placement into fresh extraction sockets directly after extraction; late placement after a post-extraction healing period of at least six months. Although there is still a lot of argument on which protocol is more clinically effective, a study revealed that there are no statistically significant differences in the implant outcomes between early, immediate, or delayed implant placement protocols in terms of risk of implant failure [5]. Furthermore, it was told that there are no statistically significant differences in the temporal healing process at the bone-implant interface between delayed or immediate placement groups at a cellular grade [6]. Acquiring "secondary implant stability", which is the stability of the implant related to both types of osteogenesis, is important for successful implant outcome: excessive implant movement after surgical insertion will induce a fibrous tissue development around the abutment of implant, which eventually leads to implant failure. Therefore, promoting both types of osteogenesis could provide acquiring faster, better ang longer lasting osseointegration, preventing clinical failure soon after insertion [7].

Titanium has excellent biocompatibility, corrosion resistance, and mechanical strength, peculiarities that make this material highly used in the medical field, mostly in orthopedic and dental surgery, or as cover-up materials and tissue engineering scaffold for many medical devices [8]. For these reasons, there is a remarkable claim to adjust the biological activity for clinical applications and the evolution of innovative biomaterial [9], particularly as titanium surfaces do not actively interact with cells and tissues, requiring ionic bridges to attract them as they act as bioinert implantable materials [10].

Trying to overcome these obstacles, a variety of chemical, physical, and biological modulations has been applied to titanium implant surfaces to improve their osseointegration outcomes and biological performances [11]. This systematic review aimed to go into detail about a specific biological method that involves growth factors coating and its effect on osseointegration and host reaction.

MATERIALS AND METHODS

A systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analysis [12] and registered on PROSPERO - International prospective register of systematic reviews, with temporary code ID 398277 [13].

Literature Search

To identify significant studies exploring the development of new technologies to implement osseointegration of dental implants using growth factors coating, a comprehensive search of *Pubmed*, *Scopus*, and WHO databases, using the Patient/Population/Problem, Intervention, Comparison and Outcome (PICO) format, was conducted from 2017 until 2022.

- Population: humans and animals;
- Intervention: titanium implant coated with growth factors;
- Comparator: titanium implant coated with other molecules;
- Outcomes: correlation between biological coating and osseointegration/wound healing.

The following MeSH were used: dental implant and growth factors coating. An additional manual literature research was performed from the relevant articles. No au-

tomation tools and language restriction were applied.

Eligibility Criteria

The inclusion criteria were as follows: all studies analyzing growth factors coating of dental implant, in association with other molecules or not, in human beings and animals.
The exclusion criteria were as follows: research about other biological coating; papers about other type of coating; systematic reviews; metanalyses.

Data Extraction

Studies were screened by two reviewers independently, and a matrix of relevant data was produced. Disagreements were resolved by consensus with a third reviewer. Data extraction included general details relating the characteristics of the studies (e.g., author, year of publication, sources of funding) and specific details about the type of biological coating.

Assessment of Methodological Quality

The methodological quality of included studies was assessed using the prediction model risk of bias assessment tool Newcastle-Ottawa Quality Assessment Scale [14] (Table 1). A qualitative description of the characteristics of the included studies as well as a narrative data synthesis was performed.

RESULTS

Overall scenario

The initial website search provided a total of 57 items; in detail, there were from 30 *Pubmed* and 27 from *Scopus*. No paper was removed because ineligible by automation tools, 3 records were removed for being duplicates while 36 papers were removed for other reasons, for example, for the study of other type of coating, or for the analyses of other type of implants, such as orthopedic ones.
18 articles accessed the screening phase, and a total of four items were removed because of lack of interest in shown data; 14 reports were assessed for eligibility, from which 3 were removed for being systematic reviews with or without metanalysis and one for being an abstract. Finally, a total of 10 papers were involved for the inclusion phase (Figure 1). A detailed table was drawn up including each eligible article, authors, year, type of experiment, cellular line or test animals used for the experiments, type of coating, growth factors used (Table 2) and a brief narrative summary (Table 3).

#	Author	Year	Selection	Comparability	Exposure
1	Nemcakova I. et al.	2022	3	1	2
2	Palermo A. et al.	2022	3	2	2
3	Takanche JS et al.	2022	3	1	2
4	Albashari AA. et al.	2021	2	1	2
5	Aragoneses J. et al.	2021	3	2	2
6	Ye J. et al.	2021	3	1	2
7	Nguyen HT. et al.	2019	2	1	2
8	Tsujino T. et al.	2019	3	1	2
9	Al-Jarsha M. et al.	2018	2	1	1
10	Xing H. et al.	2017	3	1	2

Table 1 – Newcastle-Ottawa Quality Assessment Scale. Possible total points were 4 points for selection; 2 points for comparability, and 3 points for exposures.

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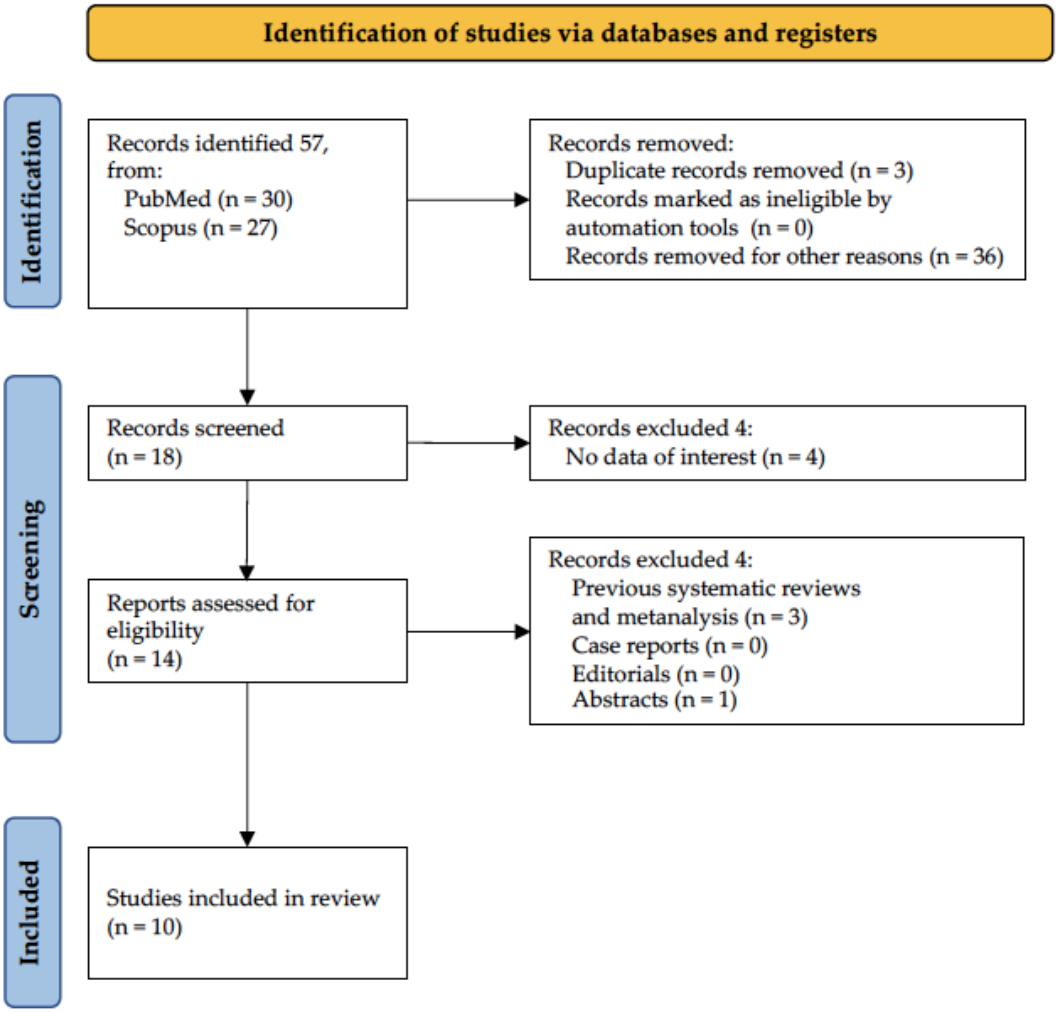

Figure 1. PRISMA flowchart.

Detailed results

Three of ten papers referred to in vitro study, using specific cellular lines to analyze their reaction when in contact with activated titanium discs or pellets in terms of proliferation, maturation, and differentiation. Two papers spoke about only in vivo experiments, using animal tests (minipigs or beagle dogs) and a split mouth protocol to study how peri-implant tissues reacted to different type of coating (biological, chemical of physical coating). The other 5 papers talked about both in vitro (with mesenchymal cellular lines) and in vivo experiments: four of them using animal tests and only one speaking about results of a split mouth protocol on humans.

All the authors agreed that biological coating with growth factors enhance the migration, differentiation, and proliferation of mesenchymal cells into the osteogenic lineage, resulting in better, faster, and harder osseointegration of the dental implant.

DISCUSSION

Metallic alloys are the most used materials for the creation of dental implants that need impressive mechanical properties such as strength, fatigue life, and excellent ductility [15]. Titanium-based alloy has remarkably lower density and toughness, comparable to cortical bone properties much more closely than other metal-based alloys or steel; it has greater biocompatibility, the highest rate of

#	Author	Year	Conclusions
1	Nemcakova I. et al.	2022	More pronounced cell osteogenic maturation, increased extracellular matrix mineralization, faster osteointegration and limited allergic reactions to the metal alloy of the implant
2	Palermo A. et al.	2022	CGF induced hBMSC differentiation in osteogenic lineage in vitro; CGF-coated titanium implants showed better and faster osseointegration, better results of post-surgical complications
3	Takanche JS et al.	2022	IGFBP-3 restored osteogenesis and bone formation in MGO-stress induced cells; it increased bone mineral density, bone volume and new bone formation, reducing oxidative stress and inflamation
4	Albashari AA. et al.	2021	Enhanced osteogenic differentiation, bacterial inhibition (due to Ag properties), pro-inflammatory factors reduction
5	Aragoneses J. et al.	2021	Biofunctionalization with FGF-2 of titatium implant surfaces speeded up mineralization of bone-implant interface, reducing time of osseointegration
6	Ye J. et al.	2021	Acceleration of implant osseointegration and improvement of regeneration of peri-implant nerves
7	Nguyen HT. et al.	2019	BMP-2 promotes bone formation in far away from marrow bone areas; bone marrow suppresses BMP-2 function in marrow environment via cell to cell interaction with osteoblasts
8	Tsujino T. et al.	2019	PRP pre-treatment of dental implants increased the amount of platelets, growth factors and anti-inflammatory factors, improving initial stability and osseointegration of the implants
9	Al-Jarsha M. et al.	2018	Functionalize titanium surfaces with low concentration of growth factor and promote mesenchimal cells differentiation toward osteoblasts, cells migration and proliferation
10	Xing H. et al.	2017	Bone consolidation promoted under osteoporotic conditions both in vitro and in vivo; better osseointegration of the implants

Table 2. Articles matching inclusion criteria.

#	Author	Year	Type of experiment	Cellular line / test animal	Coating	Growth factor
1	Nemcakova I. et al.	2022	IN VITRO/IN VIVO	hFOB 1.19 / New Zeland white rabbits n = 44, y = NF, w = >3,4 kg; n1 = control, n2 = O-NCD, n3 = O-NCD+BMP-7	O-NCD/BMP-7	BMP-7
2	Palermo A. et al.	2022	IN VITRO/IN VIVO	hBMSCs / humans n = 10, y = 60-72 years old; n1 = 10 control, n2 = 10 CGF-Ti	CGF	CGF
3	Takanche JS et al.	2022	IN VITRO/IN VIVO	MC3T3-E1 cells / Sprague-Dawley rats n = 48, y = 6 weeks old, w = NF; n1 = 12 control, n2 = 12 MGO, n3 = 12 MGO-*LacZ* , n4 = 12 MGO-*IGFBP-3*	Ch-GNP/IGFBP-3	IGFBP-3
4	Albashari AA. et al.	2021	IN VITRO	DPSCs	TNT/PDA/Ag/bFGF	bFGF
5	Aragoneses J. et al.	2021	IN VIVO	minipigs n = 6, y = 6-8 months old, w = 20-25 kg	HO2C-CR1H-CR2H-P03H2/FGF-2	FGF-2
6	Ye J. et al.	2021	IN VIVO	Beagle dogs n = 6, y = 15 months old, w = 13-15kg	NGF-CS/HA	NGF
7	Nguyen HT. et al.	2019	IN VITRO/IN VIVO	C2C12-BRE cells and MC3T3-E1 cells co-cultured with marrow or blood cells / beagle dogs n = 6, y = over 1 year old, w = NF; mice n = NF, y = 8-12 months old, w = NF	BMP-2	BMP-2
8	Tsujino T. et al.	2019	IN VITRO	blood samples from healthy volunteers n = 6, y = 23-58 years old	cp-Ti	PRP
9	Al-Jarsha M. et al.	2018	IN VITRO	hMSCs	Ti/PEA/FN/BMP-7	BMP-7
10	Xing H. et al.	2017	IN VITRO/IN VIVO	BMMSCs / Sprague-Dawley rats n = NF, y = NF, w = 200-230g; n1 = control (SHAM rats), n2 = OVX rats	TNS/PEM/IGF-1/100	IGF-1

Table 3. Narrative summary of matching criteria articles.

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osseointegration with the host and the best corrosion resistance. Research proved that the surface properties of dental implants can condition bone healing rate, the strength of bone bonding and its grade [16]. To change surface implants means to modify the surface morphology and composition of abutments by biological, physical, or chemical methods to raise bone-tissue growth around the implants, enhancing osseointegration rate and shortening the osseointegration period [17].

"Surface bioactivation" is a biochemical method of surface modification, based on the immobilization of proteins, peptides, or enzymes that promote a specific cellular response at the bone-implant interface [18]. Among all the biological methods that can be used to obtain this result, this article meant to focus on the growth factors coating and its future development in daily clinical outcomes.

Most of the studies stated that the use of only growth factors, without a proper scaffold/other molecule that can activate the growth factor itself, is not so efficient and useful as it could be. In their in vitro study on dental pulp stem cells, Albashari et al. talked about titanium nanotube (TNT) treated with polydopamine (PDA) and heparin, silver, and basic growth factor (bFGF) and its enhanced osteogenic properties, its bacterial inhibition and anti-inflammatory action due to the cross-linking among all these factors [19]. Al-Jarsha et al. used a PEA/FN/BPM-7 (polyethylacrylate/fibronectin/Bone Morphogenetic Protein-7) coating for their in vitro study, showing that this very powerful growth factor, when bound to PEA/FN, is able to promote cell differentiation at very low dose of BMP-7, because of the cross-linking between this molecule and some receptors of the other two [20]. Also, Tsujino T. et al. asserted that PRP-coating is more active when implants are treated with $CaCl_2$, letting platelet immediately adhere on the implant and release biomolecules useful for osseointegration and wound healing [21].

Some studies tried to prove the efficacy of this type of coating in sick models of animal tests, opening about some future perspective research. Takanche J.S. et al., for instance, wanted to determine the effect of IGFBP-3 (Insulin Growth Factor Binding Protein-3) on the restraint of glucose oxidative stress and the exaltation of bone generation around the implant site in rat models where bone loss was previously induced by administration of methylglyoxal (MGO), a precursor of Advanced Glycation End products (AGE) involved in the rise and development of diabetes [22]. Moreover, Xing H. et al. investigated a new type of implant coating with Insulin-like Growth Factor 1 (IGF1) under osteoporotic conditions, speculating that proliferation and differentiation of bone marrow mesenchymal stem cells (BMMSCs) and extracellular matrix are sped up [23].

In contrast to the previous ones, Nguyen H.T. and colleagues were the first to determine that bone marrow cells can suppress BMP-2 activity in the marrow environment, directly interacting with osteoblasts: BMP-2-coated implant could not improve osseointegration when placed in or near bone marrow [24]. Another important paper, the first of its kind, was the Palermo A. et al. study, talking about a split mouth protocol on human volunteers using CGF implant coating that proved how growth factors releasing in the implant site can quicken wound healing e improving osseointegration [25].

CONCLUSIONS

The success of dental implants and good control in the post-operative period is still a challenge in daily clinical routine and new strategies are needed to speed up wound healing and prevent post-operative complications. Modern implant can be improved by adding molecules through physical, chemical, or biological method and growth factors coating is one of the most promising and rising, that needs to be further investigated, especially in human trials.

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