

Interlink of Dental Infection, Implant Dentistry, Surface Topography and Molecular Biology: A Systematic Review

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Background: The ingress of advanced biomaterials increased the use of dental implants in oral rehabilitation. Clinically to assess such developmental benefits suitable analytical techniques are needed. It includes evaluating physical, chemical, mechanical and biological properties to improve biological reactions and implant durability.

Data source: Data was collected from MEDLINE, Web of Science, and Lilacs databases over the past 30 years in English, Spanish & Portuguese idioms

Results: A strong link is there in between chemical composition, wettability, roughness and topography of dental implant surfaces with the biological regulation in cell interactions, osseointegration, bone tissue and periimplant mucosa preservation

Conclusion: Consistent results had been demonstrated using additive and subtractive methods involving laser treatment or embedding of bioactive nanoparticles. But when it comes to study design and technique, the literature is inconsistent, which makes it difficult to compare different studies with one other

to define the critical determinants of optimal cell response.

Keywords: dental, implant, biology, molecular, titanium.

1. Introduction

The advancements in oral rehabilitation have made Dental implants a preferred and reliable option for replacing missing teeth through which they can restore the stomatognathic system's normal functioning by suitable mechanical qualities, stability, sufficient bone integration and regeneration (Londono et al.,2021,Esposito et al.,2019,Mombelli et al.,2012). Around 600 AD, the first dental implant was reported. Since then of materials like gold, silver, porcelain and other materials have been tested as dental implants(Bobbio.,1972).In 1950, research conducted by Professor Per-Ingvar Brånemark showed that titanium structures may be permanently integrated into the bone, which enables removal of this interface only by fracture (Branemark.,1959).The phrase "osseointegration" was used in this sense to refer to a direct, structurally and functionally connected bond between the surface of an implant and living bone that occurs without the involvement of soft tissue (Branemark.,1959,Branemark et al.,1983). Bone is an incredibly complicated tissue that connects bones built out of a matrix of organic material (70%) that gives elasticity and flexibility and a mineralized matrix (30%) supplying mechanical strength. It is an adaptive framework that changes through molding and remolding and plays an essential role in the healing of microfractures and the adaptability of the skeleton. The four cell types that compose up bone tissue include osteoblasts and osteoclasts, both are involved in the mechanisms of bone resorption and bone apposition events brought by molecular stimuli that ultimately results in the emergence of mesenchymal stem cells (MSCs) (Florencio-Silva et al.,2015,Pellegrini et al.,2018). The event of osseointegration, initially defined by Professor Brånemark, arises from a sequence of molecular and cellular reactions that initiates right after implant insertion in response to interactions between the implant, biological fluids, and peri-implant tissues(Branemark et al.,2001, Lee et al.,2019,Ajami et al.,2021,Le Guéhennec.,2007).

The osteointegration process involves three key phases:

- a) Initial Tissue Response: This phase begins immediately after implant placement, with calcium ions and plasma proteins adhering to the implant surface within the first 4 hours. Inflammation starts due to surgical trauma, activating the complement system and attracting neutrophils. Macrophages then differentiate into pro-inflammatory (M1) or anti-inflammatory (M2) types. A clot forms, providing a scaffold for leukocytes and mesenchymal cell migration and proliferation over the next 1 to 3 days.
- b) Peri-Implant Osteogenesis: Between 3 and 4 days post-surgery, angiogenesis and blood clot reorganization become more pronounced. By 7 to 14 days, mesenchymal stem cells (MSCs) differentiate into osteoblasts, producing a noncollagenous extracellular matrix rich in calcium, phosphorus, osteopontin, and bone sialoprotein, forming primary bone tissue.
- c) Peri-Implant Bone Remodeling: At around 2 weeks, primary bone begins to appose directly to the bone and implant surface, and initial bone remodeling starts. Osteoclasts facilitate the transition from immature to highly mineralized lamellar bone. By 3 months, both lamellar and non-lamellar bone may be present around the implant, but complete

osseointegration can take up to a year or more. (Pellegrini et al.,2018,Mosser et al.,2008,Amengual et al.,2021,Chawla et al.,2010,Kim et al.,2021,Lee et al.,2019,Rupp et al.,2018,Irandoust et al.,2020)

The materials and biomimetic qualities of implant surfaces will be the mainstay of this work.

2. Search Strategy and Data Retrieval

We searched PubMed, LILACS, Web of Science, and the Cochrane Library for studies on how surface modifications affect the biological responses of hard and soft peri-implant tissues. The search terms included dental implant, implant surface, roughness, coating, bioactivity, bioactive, functionalization, zirconia, titanium, poly-ether-ether-ketone, osteoblast, fibroblast, and biological response. We included pre-clinical (in vitro and animal) and clinical studies, excluding those without surface characterization. The search was limited to articles from the past 30 years in English, Spanish, and Portuguese. Two authors independently selected the studies, resolving disagreements through discussion, and we also manually reviewed references for additional relevant publications.

3. Dental implants base materials

Dental materials fall into three main chemical categories: metals, ceramics, and polymers. Biologically, they are classified as biotolerant, bioinert, or bioactive. This variability in biocompatibility highlights that no dental material is entirely biologically ideal. Therefore, materials should be chosen to minimize adverse biological responses while ensuring proper functionality (Gupta et al.,2021,Sykaras et al.,2000)

a. Titanium

The melting and boiling points of pure titanium (Ti), a transition metal with atomic number 22, are 1668 and 3287 degrees Celsius, respectively(Steinemann.,2000).When exposed to air, it creates a special coating of titanium oxide that grows larger in biological settings, improving its biocompatibility. When combined with other elements like as vanadium, aluminum, niobium, iron, magnesium, or zirconium, titanium can be utilized as a pure metal. Based on quantities of oxygen, nitrogen, hydrogen, and carbon, the American Society for Testing and Materials (ASTM) divides titanium into four categories. Grade V, or titanium-aluminum alloy, contains 4% vanadium (Ti6AL4V)(Huang et al.,2017).

Grade IV titanium is commonly used for dental implants due to its high strength and superior properties, including excellent biocompatibility, corrosion resistance, and mechanical strength. While titanium implants generally have high success rates, issues like hypersensitivity, varying elasticity modulus, wear resistance, electrical conductivity, and color concerns exist. Alternative materials have been developed to enhance biological stability and offer better or comparable mechanical properties (Sharma et al.,2021,Contaldo et al.,2021,Bosshardt et al.,2017).

b. Zirconia

The crystalline oxide form of the transition metal zirconium, atomic number 44, is known as
Nanotechnology Perceptions Vol. 20 No.7 (2024)

zirconia (ZrO_2). Zirconia is a polymorphic mineral with three different structural forms: cubic, tetragonal, and monoclinic. There could be some microcracks during the cooling process. Oxides including magnesium oxide (MgO), yttrium oxide (Y_2O_3), calcium oxide (CaO), and cerium oxide (Ce_2O_3) are added to prevent this by controlling the stress and maintaining the tetragonal structure at room temperature (Yin et al., 2017, Webber et al., 2021).

Tetragonal polycrystalline zirconia (TZP), often stabilized with 3–6% yttrium oxide (YTZP), is a zirconia-based ceramic known for its high fracture strength, flexural strength, thermal stability, low thermal conductivity, chemical resistance, and biocompatibility. Its white, opaque color and low bacterial affinity make it suitable for implant dentistry. Studies indicate that zirconia and titanium offer similar bone tissue integration. However, zirconia's mechanical performance is limited by aging, which causes degradation at low temperatures, leading to crack formation and potential fractures (Webber et al., 2021, Sivaraman et al., 2018).

Recent reviews suggest that zirconia implants are a promising alternative to titanium due to their superior soft tissue behavior, biocompatibility, and aesthetics, while offering comparable osseointegration (Sivaraman et al., 2018, Chopra et al., 2022)

Studies indicate that treated zirconia surfaces may show equal or better clinical outcomes at the bone-to-implant interface compared to titanium. However, some reviews favor titanium, partly because they did not consider surface parameters that could affect material performance. Further research with detailed surface characterization is needed to confirm these findings (Webber et al., 2021, Chopra et al., 2021, Hafezqoran et al., 2017, Esposito et al., 2019, Assal P., 2013)

c. Polyether ether eketone

Polyether ether eketone (PEEK) is a versatile organic polymer used widely in the medical field due to its excellent biocompatibility, radiolucency, chemical resistance, and similarity to human bone (Dua et al., 2021). It is increasingly recognized as an alternative to metal alloys in various biomedical applications, including dental, orthopedic, and cardiovascular devices. PEEK's favorable properties, including its resistance to biodegradation and aesthetic appeal, make it a strong candidate for dental implants. Its mechanical and physical characteristics are similar to bone, which helps reduce stress and bone resorption in orthopedic applications (Kurtz et al., 2007, Anand et al., 2015). PEEK has been shown to enhance bone and soft tissue behavior, improving cell adhesion, viability, and proliferation, especially with increased surface wettability. Porous PEEK surfaces can support osteoblast activity like titanium, and surface modifications can further enhance its biocompatibility and bioactivity (Evans et al., 2015, Torstrick et al., 2018).

4. Biomimetic surface properties

Surface Parameters include chemical composition, topography, roughness, and wettability, all of which are crucial for successful osseointegration—the process by which the implant integrates with the bone (Elias et al., 2008, Gupta et al., 2022, Le Guehennec et al., 2007)

a. Topography

Based on the scale, the surface topography can be separated into three levels:

- Macro-Scale: Ranges from 10 μm to mm. Most implants on the market feature cylindrical shapes and threaded designs at this scale, which improve implant stability.
- Micro-Scale: Ranges from 1–10 μm . Enhances bone-to-implant contact and clinical outcomes by promoting better adhesion between the bone and the implant.
- Nano-Scale: Ranges from 1–100 nm. Influences protein adsorption and cell adhesion, though its effects in living organisms are still being researched(Albrektsson et al.,2005,Buser et al.,1991).

There is no clarity in considering characteristic dimensions or physical topography might be important for biomedical applications(Cooper .,2000,Von Wilmowsky et al.,2014)

b. Roughness

Rough surfaces generally improve osteogenic response and overall clinical success by increasing bone-to-implant contact and reducing healing times(Elias et al.,2008,Pellergini et al.,2018,Hotchkiss et al.,2019). The measurement and definition of roughness can vary, with common methods including contact profilometry,optical profilometry and atomic force microscopy(Ponche et al.,2010,Santos et al.,2013,Chen S et al.,2018).

Roughness Classification

- Smooth or machined ($<0.5 \mu\text{m}$)
- Minimally rough ($0.5\text{--}1 \mu\text{m}$)
- Moderately rough ($1\text{--}2 \mu\text{m}$)
- Rough ($\geq 2 \mu\text{m}$) (Yamano et al.,2011,Gahlert et al.,2011,Al Qahtani et al.,2017,Cionica et al.,2017)

Research indicates that moderately rough surfaces are most effective for bone cell behavior. However, very rough surfaces may pose a higher risk for bacterial colonization. Despite this, clinical studies generally do not show an increased risk of peri-implantitis with moderately rough surfaces(Albouy et al.,2009).

c. Wettability

Wettability, measured by contact angle (ranging from hydrophilic at 0° to hydrophobic at 140°), affects how proteins and cells adhere to the surface, bacterial colonization, and the rate of osseointegration(Junkar et al.,2016,Rupp et al.,2018).

Hydrophilic surfaces are generally preferred as they support better tissue healing and cell interactions. However, there is less research on the impact of wettability compared to surface topography(Arima et al.,2007,Gittens et al.,2014,Makowiecki et al.,2019).

5. Implant Surface Modifications

To improve dental implant performance, various surface modifications are used to enhance osseointegration and reduce the waiting period from implant insertion to loading. This is particularly important in cases of low bone density, low primary stability, or systemic diseases affecting bone healing (Pellegrini et al., 2018, Yeo., 2020, Zhu., 2021). Recent Advances in Biomimetic Modifications are Manufacturers are now designing implant surfaces to mimic the extracellular matrix (ECM) of bone, aiming to accelerate and improve the quality of osseointegration. These surfaces feature complex topographies and varying roughness and chemical compositions, including macro, micro, and nanostructures. The ideal surface design for optimal osseointegration is still under investigation (Lee et al., 2019).

5.1 Modification Methods

- Subtractive Methods: Involve removing material from the implant surface using techniques such as anodizing, sandblasting, and acid etching.
- Additive Methods: Involve adding materials to the implant surface (Rupp et al., 2018, Wennerberg et al., 2009, Chandra et al., 2020).

5.1.1 Additive manufacturing includes

☐ Plasma Spray

Commonly used for titanium surfaces, this method applies hydroxyapatite through a high-temperature plasma torch, creating a rough surface. Despite its effectiveness, issues like delamination and bone resorption have led to a preference for moderately rough surfaces over plasma-sprayed ones (Huang et al., 2017, Becker et al., 2015).

☐ Addition of Bioactive Components

Enhances interaction with cells and reduces bacterial colonization. Bioactive components like fluoride, silver, zinc, copper, and nickel are incorporated for their antibacterial properties. For example, fluoride nanoparticles reduce bacterial colonization, while metals like silver and zinc improve antimicrobial activity. Hydroxyapatite (HA) and beta-tricalcium phosphate (β TCP) are used to promote biocompatibility and osseointegration, though challenges remain in maintaining cell adhesion and material strength. (Gittens et al., 2014, Anselme et al., 2000, Blank et al., 2021, Liao et al., 1997, Gittens et al., 2013, Rupp et al., 2018). Advanced coating methods include a biomimetic coating process that deposits calcium phosphate crystals onto titanium surfaces at room temperature, inspired by natural biomineralization (Barre Re et al., 2003, Habibovic et al., 2005). Incorporation of growth factors like transforming growth factor-beta (TGF- β) and bone morphogenetic proteins (BMPs) shows promise for bone healing, though their limited and non-progressive release poses challenges (Beshe et al., 1999, Liu et al., 2005).

5.1.2 Subtractive manufacturing

☐ Anodizing

It is by using strong acids (sulfuric, phosphoric, hydrofluoric, or nitric) to increase surface roughness and form an oxide layer on titanium implants. Results will be improved bone-to-implant contact (BIC) compared to machined implants. Popular in implants like TiUnite by Nanotechnology Perceptions Vol. 20 No.7 (2024)

Nobel Biocare (Rocci et al.,2013,Traini et al.,2018,Shalabhi et al.,2006).

☐ Blasting and Acid Etching

It uses high-speed particles (e.g., titanium oxide or alumina) to roughen the surface. Acid Etching Employs strong acids (HF, HNO₃, H₂SO₄, or HCL) to remove oxide impurities (le Guéhennec et al.,2007,Chandra et al.,2020) and modify chemical composition. Combined Approach (SBAE) is a Sandblasting followed by acid etching enhances surface roughness and protein adhesion, improving mechanical fixation and osteoblastic differentiation. Commercially known as SLA (Straumann) (Grassi et al.,2006,Hirano et al.,2015,Kim et al.,2015).

5.1.3 Biomimetic surface patterning : It Involves creating biologically-inspired topographies to guide cell behavior and collagen matrix alignment. Rough surfaces typically enhance osteoblast adhesion, while smooth surfaces support fibroblast growth (Brunette.,1986,Chehroudi.,1988).

☐ Milling is a machining process to create textures on surfaces. While it influences osteoblast differentiation, evidence on its effect on cell proliferation is mixed (Smeets et al.,2016).

☐ Laser Technology ,Various lasers (e.g., Nd: YAG, CO₂) are used to create precise surface textures on implants, particularly zirconia. Lasers provide clean, homogeneous textures at multiple scales and have shown potential in improving osseointegration and reducing crestal bone loss.(Lee et al.,2019,De Tullio et al.,2020,Dumas et al.,2012,Coathup et al.,2016).

6. Conclusion

This review highlights key research on how implant surface properties impact biological integration. Key factors include surface chemistry, roughness, and topography, which influence interactions between implants, proteins, and cells. Various techniques for enhancing implant surfaces, such as physical and chemical functionalization, are discussed. Promising results have emerged from subtractive methods like laser treatment and the incorporation of bioactive or antibacterial nanoparticles. Despite challenges in immobilizing and controlling the release of growth factors, their inclusion is a promising avenue for surface functionalization. However, variability in surface characterization methods, cell culture conditions, and cell types across studies complicates comparisons. Currently, no clinical evidence indicates that any one surface type is superior. Future research should focus on standardizing methods and identifying key factors for clinical success to develop effective biologically-inspired surfaces for improved tissue integration.

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