

## REVIEW

# Nano modified zirconia dental implants: Advances and the frontiers for rapid osseointegration

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## Abstract

Nanotechnology has created a revolution in implant dentistry. It is an established technology in the field of titanium implant dentistry and is slowly evolving when it comes to ceramic implants. The aim of this review article was to survey the use of nanotechnology for the purpose of implant surface modification in order to improve the osseointegration process of ceramic implants, but also, the various techniques and methods by which nano features can be applied to zirconia implant surfaces. With the application of this advanced technology, the composition, surface energy, roughness and topography of dental implants can be modified for enhanced and potentially faster osseointegration. Furthermore, nanotechnology implant surface modification can also influence the biological processes that occur at the bone-implant interface. The cellular activity and tissue responses occurring at the bone-zirconia interface can be enhanced by nanomodifications and result in better treatment outcomes. This review also highlights the 'state of the art' of nanomodified zirconia surfaces and the perspectives of introducing new technologies in biomedical implantology.

## KEYWORDS

bioceramics, biomaterials, implants, nanoscale, osseointegration, surfaces, topography, zirconia

## 1 | INTRODUCTION

Molecular engineering or molecular nanotechnology, or as it is more commonly known, nanotechnology, is the control of matter at the nanoscale with measurements between 1 and 100 nm. A new stream of nanodentistry has risen since the introduction of nanotechnology in dentistry (AlKahtani, 2018; Lavenus, Louarn, & Layrolle, 2010). Various dental products, materials and processes have greatly improved since the introduction of nanotechnology and dental implants are undergoing a similar transformation. Thanks to Branemark's work, which is the foundation of modern implants in dentistry. The relatively low failure rate of dental implants can be attributed to enhanced macro and microscopic designs. Insufficient bone formation around and apposition to the implant surface is the most common cause of implant failure (Chrcanovic, Kisch, Albrektsson, & Wennerberg, 2016). It is well documented that tissue interface and implant surface macro and micro-characteristics play

an important role in osseointegration (Gupta, 2016; Wennerberg & Albrektsson, 2010). New methods and techniques of implant surface modification have emerged with the advent of nanotechnology (AlKahtani, 2018; Lavenus et al., 2010) and it is therefore hypothesized that by mimicking the surface topography of the extracellular matrix (ECM) components of natural tissues, implant surfaces may well be improved and be conducive to bone-forming cell apposition with greater new bone formation. The components of these ECM are of nanometre scale and range in size between 10 and 100 nm, suggesting a better bone cells to implant surface interaction (AlKahtani, 2018; Lavenus et al., 2010; Naganuma, 2017).

The four material related factors, which can impact events at the bone-implant interface are surface roughness, implant surface material composition, surface topography and surface energy. These properties can be modified using different methodologies such as sandblasting, acid etching, laser etching and surface anodization, among others (AlKahtani, 2018; Chrcanovic et al., 2016;

Gupta, 2016; Lavenus et al., 2010; Naganuma, 2017; Wennerberg & Albrektsson, 2010). With regard to the surfaces themselves, there are three levels of surface structure namely nano, micro and macroscale surface topography. At best, current surface structures are controlled at the micron level, but primarily, processes controlled at the nanoscale level determine tissue response. A critical role is played by surface profiles in the nanometre range with regard to the adsorption of proteins, osteoblastic cell adhesion and ultimately the rate, level and quality of osseointegration (AlKahtani, 2018; Chrcanovic et al., 2016; Gupta, 2016; Lavenus et al., 2010; Naganuma, 2017; Wennerberg & Albrektsson, 2010).

Osteogenic differentiation is promoted on the surface of titanium implants that are modified to a nano structural level and have shown to enhance the osseointegration process (Naganuma, 2017). On the other hand, zirconia implants surface modification is done by subtractive methods using sand blasting, acid etching, laser etching or combination of acid etch and sand blasting (Hafezeqoran & Koodaryan, 2017; Schünemann et al., 2019). There is very active research now on modifying ceramic implant surfaces to the nanoscale level. There seems to be two trends in nanoscale modification of zirconia either by patterning the implant's surfaces or by applying novel ceramic coatings. However, the literature is very limited with regard to nanoscale surface modification and enhancement, and at the time of writing this paper, there are no clinical investigations that have been made to evaluate and compare the levels and quality of osseointegration (Schünemann et al., 2019; Siddiqi, Khan, & Zafar, 2017; Wennerberg & Albrektsson, 2010).

From the available literature and acquired knowledge, this critical review aims to clarify the main methodologies achieved so far to improve zirconia implant surfaces on a nanometric scale. This literature review also highlights the observed results and their advantages compared to the conventional surfaces. In addition, the review also discusses the future possibilities in the evolution of zirconia nanotextured surfaces.

## 2 | SURFACE MODIFICATIONS AND NANO INTERACTIONS

Many chemical, physical and mechanical modification systems like thermal processing, sandblasting, acid etching and coatings are used to roughen implant surfaces (Lavenus et al., 2010; Schünemann et al., 2019; Wennerberg & Albrektsson, 2010). Multiple clinical studies have shown that rough implant surfaces have higher levels of osseointegration compared to smooth or machined surfaces (Lavenus et al., 2010; Wennerberg & Albrektsson, 2010). This is not only because of a strong interface between implants and bone but also because of a better quality of bone formation, improved osteogenesis and better capacity to form interfacial molecular attachments (Naganuma, 2017). The success of titanium implants with micro-scale roughness, in particular, is supported by substantial scientific literature and long-term clinical data (Wennerberg & Albrektsson,

2010; Wennerberg, Albrektsson, & Chrcanovic, 2018). However, a technical plateau appears to have been reached with the improvement of roughened titanium surfaces and the creation of a titanium implant that is more osteoconductive than the existing ones using nano-roughness technology (Figure 1) has been a real challenge (AlKahtani, 2018).

The original ceramic implants had highly polished and smooth surfaces, this led to poor osseointegration and high implant failure rates (Siddiqi et al., 2017). Currently, focus is on research in improving zirconia implant surfaces, in particular in the development of surface roughening and functionalization methods (Mostafa & Aboouselib, 2018; Rezaei et al., 2018; Thakral, Thakral, Sharma, Seth, & Vashisht, 2014). Cellular reaction and function has been successful and enhanced using thermochemical, chemical and physical surface modifications protocols. However, roughness levels achieved for titanium implants are usually higher than that of zirconia implants. The percentage of bone formation around implants and the strength of the bone-implant interface as a result remain slightly higher for titanium compared to zirconia implants (Rezaei et al., 2018). Unlike with titanium implants, studies evaluating long-term performance of acid and laser-etched ceramic implants are rare.

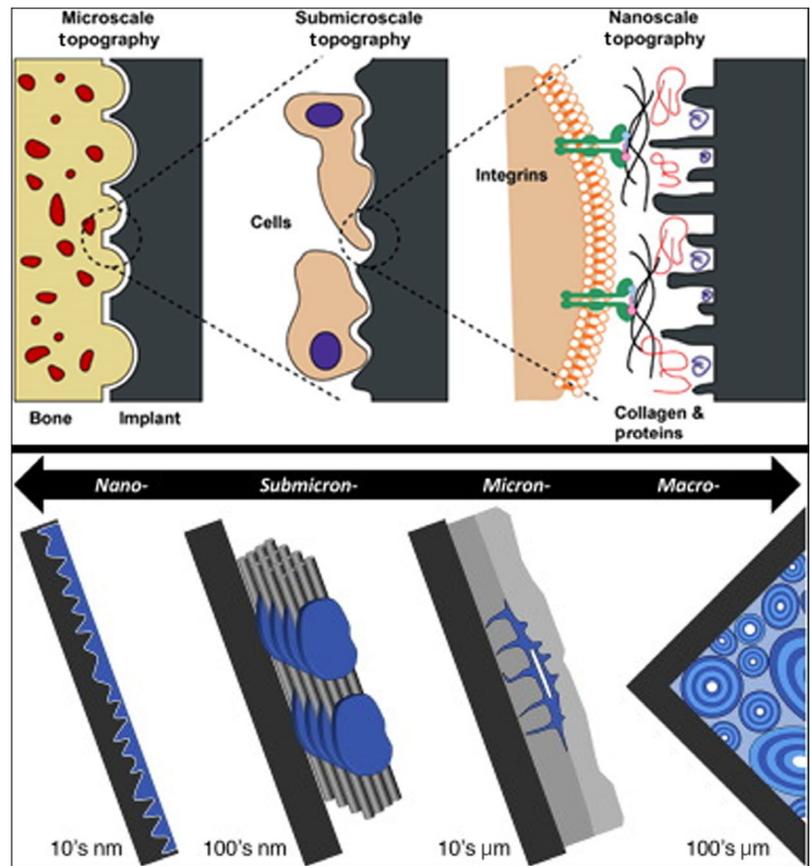
Nano interactions, as well as surface functionalizations, stimulate the process of cell spreading and adhesion with great intensity. Extracellular matrix proteins and components communicate more easily through chemical bonds with the nanoscale surface, triggering a faster process of cell adhesion, differentiation and proliferation (Naganuma, 2017; Zhukova & Skorb, 2017), as can be seen in Figure 2.

There are great technical and logistic challenges in the treatment and modification of ceramic implant surfaces. Literature on nanotexturization methodologies for ceramic implant surfaces is scarcer compared to titanium methodologies. However, with the evolution of technologies such as intense laser utilization, anodization and modified acid etching. With this growing interest and rapid technological evolution, zirconia surface modification to nanotexturization levels is sufficient to establish bone formation in less than a month.

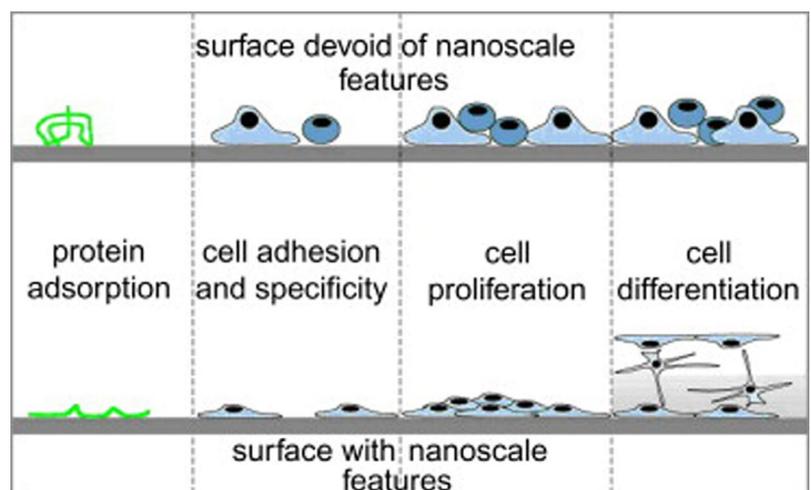
## 3 | IN VITRO STUDIES

Use of laser surfacing technology to roughen a Y-TZP zirconia implant surface was created with distinct hierarchical surface morphology comprising of nano-, meso- and micro-scale roughness, in an original study by Rezaei et al. (2018). Rezaei and colleagues studied the bone integration and biological capabilities of the smooth machined zirconia compared to the hierarchically roughened zirconia. A significant rise in osseointegration levels compared to machined-smooth zirconia related with enhanced differentiation of osteoblasts was observed with nano-/meso-/micro-scale rough zirconia. Unlike on the surface of micro roughened titanium, proliferation and cell attachment were not compromised on rough zirconia because of different roughness and morphologies. This was the first report that presented a rough zirconia surface that has a distinctive hierarchical

**FIGURE 1** Interactions between bone and the implant surface at different scales of roughness and morphologies are schematically shown. Reprinted and adapted with permission from Elsevier (Gittens et al., 2011; Shah et al., 2018)



**FIGURE 2** Schematic illustration of surface nanotopography affects cell interactions at surfaces and alters cell behaviour compared with conventional size topography. Reprinted with permission from Elsevier (Mendonça, Mendonça, Aragao, & Cooper, 2008)



morphology and delivered an effective technique to develop and improve zirconia implant surfaces (Rezaei et al., 2018).

Because of its stability and distinctive bioactivity, the most commonly used bioactive-ceramic component in bone augmentation and regeneration field is Hydroxyapatite (HA). It promotes bone tissue growth directly on the surface coating allowing for reduced healing time and faster bone formation (Liu, Morra, Carpi, & Li, 2008; Schünemann et al., 2019; Wu, Ramaswamy, Liu, Wang, & Zreiqat, 2008). Bioceramic HA coatings have been applied on titanium implant fixtures, it stimulates cell proliferation and cell attachment of

a range of cells that include periodontal ligament cells, osteoblasts and fibroblasts (Liu et al., 2008; Schünemann et al., 2019). Bioactive glass-coated zirconia implants would have been suggested as a good option for geriatric patients with poor quality and osteoporotic bone (Liu et al., 2008). However, numerous factors must be considered for bioactive coatings to attain their intended purposes effectively. The thickness and properties of the layered coating are also important since coatings have a tendency to delaminate and separate from the implant body over time. These characteristics must be analysed critically to introduce a new surface methodology in the market.

Aboushelib, Feilzer, & Kleverlaan, 2010, introduced SIE technique (Coating with infiltration glass, thermal heating and, washing of glass residues), a surface treatment technique that employ shear-induced development and ceramic grain boundary distribution principles. This technique changes the comparatively smooth and dense non-bonding zirconia surface into a rough and retaining surface of nano-porous texture. This technique significantly improved the bonding and wetting capabilities of zirconia. High wettability surfaces are known to readily attract early and greater number of bone-forming cells (Aboushelib et al., 2010).

Methodologies, as described in study above, are promising to increase bioactive layers retention on the selective infiltration surface engraving zirconia implants, this principle could even be used where the formed nano-pores may be packed with the preferred layer material without the chance of coated material delamination, forming a unique bioactive-hybrid ceramic surface. The only condition, to insure precise pore filling, is that the filling materials need to be smaller in their diameter measurement compared to the typical pore diameter (Rasouli, Barhoum, & Uludag, 2018). Based on study observations, it is hypothesized that the osseointegration of zirconia implants will be better with the combination of a nano-porous surface infiltrated with a bioactive material (Rasouli et al., 2018).

Oshima, Iwasa, Tachi, and Baba (2017) showed the use of a zirconia-derived material, Ce-tetragonal zirconia polycrystal (TZP) based,

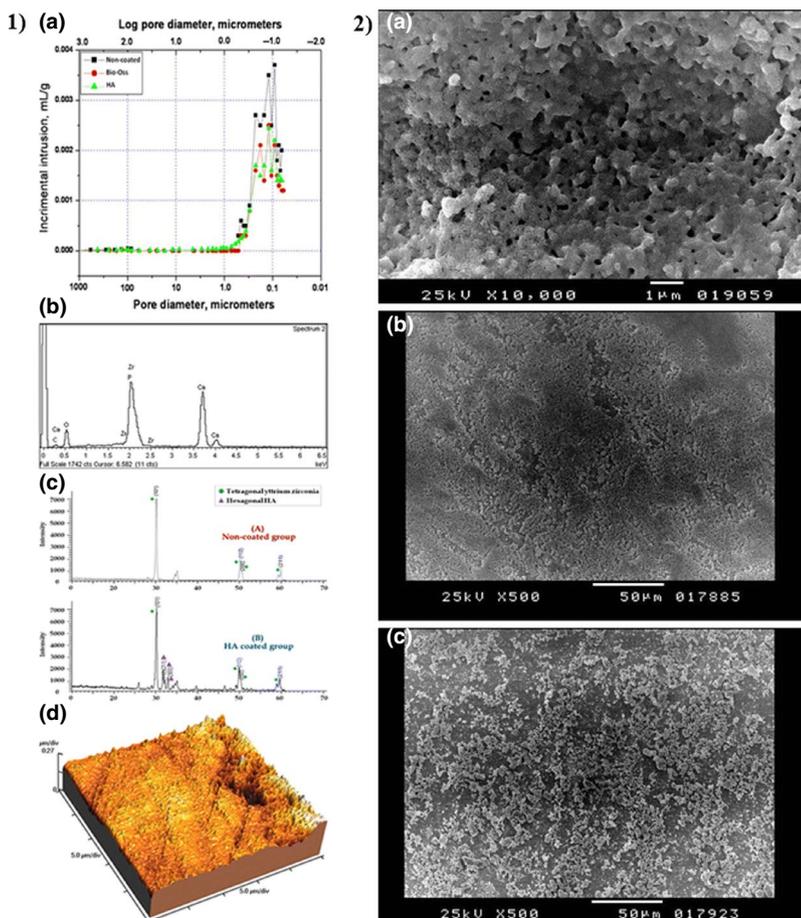
where by means of acid treatments modified to acquire a nanotopography. Their in vitro and in vivo analysis showed increased osteogenic activity and osseointegration when compared to controls. With these results, the authors suggest the zirconia-derived base material as promising for the development of new implants and further investigations must be made.

On the other hand, superficial characteristics on a nanoscale, need excellent characterization methods to be proven and few current studies provide excellent information on detailed nanomorphology as described and registered by Mostafa and Aboushelib (2018) (Figure 3).

## 4 | IN VIVO STUDIES

In vivo studies can show results closer to the clinical reality and are extremely important in applications of new technologies.

In a study by Mostafa and Aboushelib (2018), found that selective infiltration etched surface treatment improved osseointegration in rabbit femur heads as shown by histometric studies, which revealed higher percentage of bone-implant contact (BIC) compared to as-sintered zirconia and titanium implants. Osseous healing at the bone-implant interface is enhanced by the nano-porous characteristic surface, demonstrating the beneficial impact of roughening zirconia implant surface. These findings are in line with earlier studies



**FIGURE 3** Characterization and measurements of surface roughness with nanotexturization using AFM, EDX, XRD (1). Morphologies of the surface formed nano-pores using SEM (2). Adapted and Reprinted from Mostafa and Aboushelib (2018)

comparing osseointegration of nanotexturization on titanium and zirconia implants (Schünemann et al., 2019).

Lee et al. (2009), in one of their earliest studies on evaluation of nanotechnology modified zirconia implants showed a favourable tissue response to CaP nanotechnology modified ZiUnite as well as to control ZiUnite and TiUnite implants without statistically significant or meaningful differences between the implant surface characteristics, following 3- and 6-week healing intervals using a rabbit trabecular bone model. In conclusion, ZiUnite implant surfaces exhibit high levels of osseointegration with osteoconductive properties.

In another in vivo study, performed on white rabbits by Aboushelib, Salem, Taleb, and Moniem (2013), twenty implants of each group were inserted in 40 adult New Zealand white male rabbits. After 4 and 6 weeks, bone blocks containing the implants were retrieved, sectioned and processed to evaluate bone-implant contact (BIC) and peri-implant bone density. The zirconia implants with new treatment had significantly higher BIC and marginally higher bone density. The results suggest that selective infiltration etched zirconia implant surface may improve implant osseointegration. SIE could be a potential technique to enhance osseointegration of zirconia implants.

These studies have compared selective infiltration etched zirconia implants with sintered zirconia implants and titanium implants (sandblasted and etched) and found that selective infiltration etching zirconia implants have showed greater BIC (75%) than both sintered zirconia (62%) and rougher titanium implants (68%).

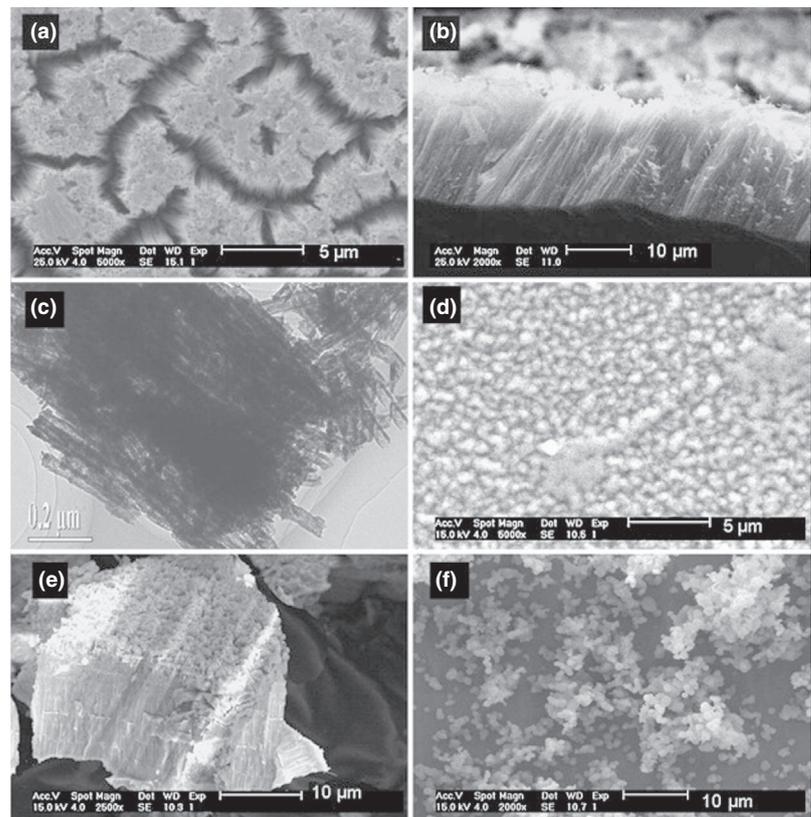
On the other hand, a study (Han et al., 2016) using two types of zirconia, one with nano-roughness and one with micro roughness surface, evaluated osseointegration in rabbits through pull-out and

histology tests. Their results showed advantages in nanotexturing only after 4 weeks in removal torque and not significant differences in bone-implant contact (BIC) assessment results. This result shows the great difficulty of technological evolution in zirconia to overcome the micro-scale barrier to nanoscale.

In addition, a in vivo study by, de la Hoz et al. (2019), focused on rats showed that  $ZrO_2$  anodized at 60 Voltz is able to promote a significant increase in cancellous bone volume, in trabecular thickness and in trabecular number with the consequent decrease in trabecular separation when compared with the control after 15 days of implantation. These facts suggest that the new bone microarchitecture in contact with anodized implants at 60 Voltz is able to improve the osseointegration process period. This consequently improves the primary stability of implants which is a key factor to reduce patient's mobility and lead to quicker recovery when this technology reaches to the market.

## 5 | PERSPECTIVES ON ZIRCONIA BIOACTIVE NANOSURFACES

The most innovative surfaces in the biomedical implant field show osseointegration periods of less than a month (Rasouli et al., 2018; Shah, Thomsen, & Palmquist, 2018). The use of intense changes in the wettability of materials such as titanium and zirconia through reactive plasmas, heat treatments and the use of UV lights accelerate the process of adhesion and cell migration along the entire surface (Canullo et al., 2016; Jemat, Ghazali, Razali, & Otsuka, 2015).



**FIGURE 4** Formation of nanotubes on zirconia surfaces using anodization treatment. Potential surface treatment to be functionalized with drugs or nanoparticles. Reprint with permission from Elsevier (Guo et al., 2009)

Recent studies report the creation of multifunctional surfaces, using biodegradable coatings incorporated with drugs such as antibiotics, osteoinducers, proteins, among other drugs (Civantos et al., 2017; Kunrath, Hubler, Shinkai, & Teixeira, 2018). This type of technology is fully applied to both titanium and zirconia, opening numerous research opportunities on modified zirconia surfaces.

Further to the addition of coatings, such as promising drug delivery systems, the zirconia surface can be anodized by developing a nanotube-filled nanostructured surface (Figure 4) (Guo et al., 2009; Minagar, Li, Berndt, & Wen, 2015a; Patel et al., 2017). These can be loaded with various compounds or drugs that can speed up osseointegration. They also potentially be carriers for antibacterial factor if loaded with the correct compound.

The nanotubes formation in zirconia is technically challenging and has some difficult factors as the material hardness (Lucas, Lawson, Janowski, & Burgess, 2015) so the literature is still scarce in relation to drug delivery systems based on zirconia. However, the constant progress in research shows that the tendency of surface treatments on zirconia is to quickly match the results of surface treatments observed on titanium. As a result, we are short strides away from biomedical zirconia implant surfaces having healing time less than a month.

To summarize the investigations in nano modified zirconia implants, Table 1 shows the current studies published with results in nano scale implant surface texturing.

The critical analysis of the most current studies to date shows the intense search for different methodologies to arrive at a nanoscale surface. This can be achieved using additive or subtractive methods, or by using innovative technologies and functionalities. Opening innumerable paths for investigations in this research theme.

On the other hand, controlled clinical studies are not yet reported in the literature, as trademarks do not yet have an implant with full surface nanomorphology on the market. However, the promising results from in vitro and in vivo studies stimulate technological growth for the development of a clinical implant with these properties, where clinical research can be carried out and followed-up.

## 6 | CONCLUSIONS

Nanotechnology for roughening of zirconia dental implant surfaces is still evolving. Our review of latest studies shows that there is limited research done on nanoscale surfacing of Zirconia implants so far. This can be fulfilled by conducting research on this aspect and the enhanced osseointegration process through nanosurfacing of

**TABLE 1** Current studies on zirconia nanotexturization surfaces

Treatment on zirconia	Methods	Study analyses	Observations	Reference
Solid-state laser	Subtractive	In vitro and In vivo Morphology and Roughness analyses, bone molecular expression and osseointegration	The new surface methodology shows better results in vitro and better forces to osseointegration tests	Rezaei et al. (2018)
Calcium phosphate nano coating	Additive	In vivo Roughness analyses, bone-implant contact	Nano coating shows similar results to micro surfaces. However, high osseointegration level against control surfaces	(Lee et al., 2009)
Selective infiltration etched	Subtractive	In vivo, Roughness, bone-implant contact	Significantly high bone-implant contact	Aboushelib et al. (2013)
Nd:Yag Laser ablation + Ag/Au particles deposition	Subtractive/Additive	In vitro, Morphology, Atomic composition, Surface functionalization, Adhesion of particles	Functionalization of the surface with Ag and Au particles. High adhesion level of particles on surface	Madeira et al. (2019)
Anodization	Subtractive	In vitro, Morphology, Roughness, biocompatibility, molecular expression	Significantly more bone mineralization factors than control surfaces	Minagar et al. (2015b), Patel et al. (2017), Guo et al. (2009), Minagar et al. (2015b)
Coating Sol-gel derived TiO <sub>2</sub>	Additive	In vitro, biocompatibility	Promote blood coagulation	Shahramian, Abdulmajeed, Kangasniemi, Söderling, and Närhi (2019)
Femtosecond Laser	Subtractive	In vitro, In vivo Morphology, Roughness	Nanotopography significantly influences in cell adhesion.	Gnilitskyi et al. (2019)
Self-assembly nanoislands	Subtractive	In vitro, morphology, Roughness, biocompatibility	High bone mineralization in nanosurfaces	Soon, Pingguan-Murphy, and Akbar (2017)
Hydrothermal treatment	Subtractive	Physicochemical tests	Promote nanotexturization on surface	Blackert et al. (2018)

zirconia. Nanometre controlled surfaces have an excellent impact on healing after implant placement, as several in vitro and animal studies have shown. It positively affects the blood clot formation, adsorption of proteins and cell division and differentiation occurring upon implantation. The strategies and techniques developed should be appropriate to clinical practice. Nanotechnology has opened a new range of possibilities for improvement of zirconia implants.

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