Research Article

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Synthesis of nano zirconium oxide and its application in dentistry

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Abstract: Zirconium oxide (ZrO_2) is the general material in dental area, with natural color, high toughness and strength. Recent years, small blocks of ZrO_2 such as micro/nano powders have been studied and developed widely. Nano scale ZrO_2 , which shows improved mechanical characteristics and superior biocompatibility, are usually incorporated into different applications used in dentistry and tissue engineering. This review provides an overview of nano- ZrO_2 materials and its applications in dentistry. The synthesis of nano- ZrO_2 powders were mainly prepared by coprecipitation, hydrothermal method and sol-gel method. Then different applications of nano- ZrO_2 biomaterials in dental ceramics, implants, radio pacifying agents, basement and tissue engineering fields were briefly introduced.

1 Introduction

Teeth are essential to oral and overall health, esthetics, speaking, and quality of life. A large majority of the population is suffering from oral diseases, including caries, pulpitis, and periodontal diseases, some of them may lead to defect of teeth and functions [1, 2]. There is thereby an urgent need but it is still a significant challenge to reconstruct or regenerate the heterogeneous and dynamic dental anatomical structure [3–5]. To solve this, the variety of

dental materials are studied and develop to be used in rebuilding the curve, color, shape and function of teeth.

In the past few decades, dental materials have developed rapidly, providing more personalized functions for dental treatment. The common materials application in dental restorations and prosthesis are ceramic crown [6, 7] and implants [8]. Ceramic fused metal and all-ceramic crown are often served to repair tooth defects. Compared with ceramic fused metal restorations, all-ceramic materials are preferred due to their natural color, wear resistance, biocompatibility and aesthetics [9]. Titanium implant is the most frequently used in clinic nowadays [10], while recent developments of ZrO_2 implants have attracted much attention [11, 12]. Both *in vivo* and *in vitro* studied have demonstrated that ZrO_2 implants retain the similar or even superior osseointegration than Ti implants [13–16].

High purity ZrO_2 is the general material in dental area, ZrO_2 is a kind of biomaterial with good natural white color, high toughness, excellent strength, steady chemical properties, good corrosion resistance, which is a source of high-performance ceramic material and especially biocompatible implant materials [17–20]. In fact, the high strength of ZrO_2 indicates that this material is hard to be processed and formed. Although CAD/CAM technique can be used for solving such problems, however, it is hard to reach high accuracy demanded and the fabrication cost is high [21–23]. Hence, it is acceptable to introduced the small blocks of ZrO_2 such as micro/nano powders to resolve the problems. Nano- ZrO_2 provides more application scenarios, such as nano powders filling [24], nano coating [25, 26], sintering raw material [27] and so on. ZrO_2 nanopowders are employed in promoting the bionics and mechanical properties of dental ceramics and tissue engineering scaffolds. Recent studies indicated that the cooperation of ZrO_2 nanopowders can significantly strengthen the flexural strength, fracture toughness and shear bond strength of the materials [28, 29]. In another scenario, nano- ZrO_2 can served as a powerful porous coating of solid surfaces to provide a nanostructured surface through the modification method that could improve the biocompatibility. For example, nano- ZrO_2 coating on the surface of Ti implants or the nano porous ZrO_2 implants are able to

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enhance the process of osseointegration [30]. It is considered that surface treatment and bioactivation accelerate the new bone formation.

This review provides an overview of Nano-ZrO₂ biomaterials and its applications in dentistry. Two aspects were discussed in detail. Firstly, the synthesis of nano-ZrO₂ was introduced, and then the applications of nano-ZrO₂ biomaterials on dental ceramics, implants, membranes, basement and tissue engineering are extensively reviewed.

2 Synthesis of nano-ZrO₂

Among the metal oxide ceramics, ZrO₂ has one of the best high-temperature thermal stability and thermal insulation performance. There are three different crystal structure of ZrO₂: cubic (c-ZrO₂), tetragonal (t-ZrO₂) and monoclinic (m-ZrO₂), with each crystal structure keeps stable in different range of temperature. Under certain condition, like pressure and temperature, each of the structure can be transformed mutually, at the same time, their physical properties, volume change in a way that t-ZrO₂ holds the best performance while m-ZrO₂ is the usually form at room temperature. Therefore, it is important to synthesis t-ZrO₂ at moderate temperature to prevent expansion [31]. The advanced application of nano-ZrO₂ powders are containing refractories, abrasives, ceramic pigments, oxygen sensors, catalytic materials [32]. Nano-ZrO₂ powders are mainly prepared by wet-chemical synthesis approaches, such as coprecipitation [27, 33], hydrothermal synthesis [34], sol-gel preparation [35]. The physical method cannot meet the requirement of nano size, while gas-chemical method costs too high to repeat it in practical production.

Coprecipitation is the primary means of wet-chemical precipitation for synthesis ZrO₂ nanopowders. Coprecipitation technique is processing by adding precipitating agent into the mixture solution of water-soluble zirconium salts and stabilizers like Y₂O₃. After the precipitation reaction, the insoluble precipitation as hydroxides is formed which are then dried or calcined to obtain nano-ZrO₂ powders. The group of Wang and Zhai prepared the MgO-Doped ZrO₂ nanopowders with nanosize of 10 mol% [36]. A mixture of water and ethanol (ratio of 1: 1) served as the precipitating and washing solvents. On the base of the capability ethanol holds to alleviate the hydrogen bond existing inside of the formed zirconium hydroxide gels, the homogeneous nano-MgO-ZrO₂ were formed, presenting satisfying sintering property. Another study investigated how pH value and residual NH₄Cl interfere crystallization of nano-ZrO₂ powders [37]. Coprecipitation technique is sim-

ple and the production is demonstrated to be nice, however, there are a few elements in the initial solution would residue, which could have effects on the sintering properties of the nanopowders.

Sol-gel method is extensively used to prepare solid materials from small molecules at the relatively lower temperature. During the sol-gel process, the main step is the conversion of the precursors into the colloidal or polymeric solution through hydrolysis and condensation reactions [38, 39]. The initial precursors are often metal alkoxides or metal chlorides, which could have an effect on the properties of sol-gel, like drying or firing behavior. Huang and colleague [31] explored how the organic addition influenced the characterization of ZrO₂ nanocrystals. Zirconium oxychloride octahydrate (ZrOCl₂) was used as precursor, while glacial acetic acid (HAc) was applied as the chelating agent during vigorous stirring. N,N-dimethylformamide (DMF) as drying control chemical additives (DCCA) was also added to reduce the cracks when stirring. After calcination, the size of ZrO₂ nanocrystals decreased to 13.94 nm by adding HAc and DMF. Shukale and Seal have successfully synthesized nanocrystalline ZrO₂ particles using the sol-gel method [40]. It is worthwhile to highlight that the metastable t-ZrO₂ is stabilized at normal temperature within pure ZrO₂ displaying nonspherical morphology. The unique nature maybe result from the contribution of the interfacial, and strain energies, which balance the size and the shape, stabilizing the t-ZrO₂ nanoparticles.

Hydrothermal method is an advanced technology for preparing inorganic materials particularly particles with nano-sized to submicron crystals by chemical reaction in aqueous solution under high temperature and pressure. Vapors or fluids acts as the transformation agent for pressure, heat, and mechanical energy [41]. These characteristics facilitate the formation of prepared powders that have uniform microstructure, shape and components. Researchers think that hydrothermal method is considered to be one of the most promising methods to prepare fine particles with controlled forms [41]. Szepesi and colleagues [42] have developed the high yield hydrothermal precipitation procedure and synthesized zirconia or yttrium-doped tetragonal zirconia polycrystals (YTZP) with average size of 8-10 nm. Bicine was served as the complexing solution to reducing the tendency of agglomeration in high-yield batches. Another work built novel ZrO₂ nanorods and nanoparticles from ZrO₂ powders through hydrothermal processing [43]. This long-drawn-out synthesis process was performed in autoclave with NaOH solution as the mineralizer at a temperature of 200°C for totally 7 days. The NaOH mineralizer had different concentrations of 15 M, 20 M and 25 M. Under electron microscopy, the formed

Table 1: Different methods for synthesis of nano-ZrO₂

Synthesis approaches	Advantages	Disadvantages	Size	Morphology
coprecipitation	simple in preparation; low equipment requirements; commercialized	low yield and purity of finished products; agglomeration; influenced by many factors like washing solvent, pH value, drying method.	few nm to hundreds nm	particles
sol-gel preparation	handy operation; high purity; homogeneous distribution; commercialized	Time-consuming; poor sintering properties	few nm to hundreds nm	particles; nanotubes
hydrothermal synthesis	high purity; time-saving; perfect dispersion; various crystal shape; controllable size; minimization of agglomeration.	equipments for stringent; high temperature	few nm to several μm	particles; nanotubes; nanorods; nanobars

Figure 1: Bright field image of ZrO₂ nanobars (20 M NaOH); HRTEM image of zirconia nanobar (25 M NaOH) [43]

nanorods had diameters spanned from 25 to 200 nm and lengths ranging several hundred nm to 2 μm (Figure 1).

3 Application of nano-ZrO₂ in dentistry

3.1 Application of nano-ZrO₂ as dental ceramics

Over the past few decades, the increasing demand of functional and aesthetics effect has hastened the development of ceramic restoration crowns, which are of satisfying natural-tooth like color, bionics and mechanical properties [44, 45]. Among the various dental ceramic materials, ZrO₂ is of very superior strength and toughness. ZrO₂ is widely used as inlays, partial crowns, veneers and full ceramic crowns. Nevertheless, the high mechanical ZrO₂ dooms for the difficulty to machine [46]. To solve this, the

block or powder form ZrO₂ can be considered to gain more formability.

Researchers have employed nano-ZrO₂ for resistance enhancement in diatomite-based ceramics. The method of layer-by-layer (LBL) assembly modification was organized in order to enhance the adsorption of electropositive nano-ZrO₂ [29]. The surface of diatomite-based ceramic powder was modified using allylamine hydrochloride (PAH) and sodium 4-styrenesulfonate (PSS), then nano-ZrO₂ particles with positive electricity were absorbed to the ceramic powders. After PAH/PSS polyelectrolyte dispersants modification, the size of diatomite particles decreased (from 0.12 to 35 μm); radius narrowed to 0.42 μm . The sintered and shaped ceramics were prepared for further tests, and the results suggested that addition of nano-ZrO₂ has led to the higher flexural strength, fracture toughness and shear bond strength value with reduced porosity. The reasons may lay in composite particles with a smaller wideness distribution and less aggregation; the addition of nano-sized, uniform ZrO₂, which formed a dense unity with diatomite-based ceramic powders [47, 48]. Another experiment [49] verified that the silica ceramics filled with nano-ZrO₂ showed excellent heat shielding and high-temperature ablation properties.

As a biologically inert ceramic, ZrO₂ need to combine with other bioactive phase. Nano-ZrO₂ can acts as the second phase to enhance the fatigue resistance to nano-HA ceramics [50–54]. When compared with pure nano-HA ceramics, the hybrid ceramics of nano-HA/nano-ZrO₂ showed similar cytocompatibility. Besides, wettability of the interfaces of ZrO₂-based dental ceramics seems to affect the adhesion properties. Marefati *et al.* have studied the effect of different size yttria-stabilized tetragonal zir-

Figure 2: AFM pictures of nano-ZrO₂ surface: (a) machining through common grinding method; (b) ultrasonic assistant grinding method [57]

conia polycrystals(Y-TZP) cores on wetting behaviour of a molten feldspathic glass-ceramic [55]. There was an enhancement of wettability in nano-sized Y-TZP group. This may be related with the diffusion-assisted atoms through increased surface defects such as grain boundaries and triple junctions.

In the midst of common processing, fracture among the block material can be brought about. This is the main limitation when applying nano-ZrO₂. Therefore, the impacts during consolidation process should be deeply studied. Park *et al.* [56] have explored the method that combined application of magnetic pulsed compaction (MPC) and subsequent sintering for densification of ZrO₂ nanopowders. The high density (98%) ZrO₂ bulks were obtained. At experiment condition, the authors have found that with increasing MPC pressure, the grain size of zirconia block decreased, while the additional ratio of PVA did not have an obvious effect on the grain size. According to the paper, the optimum way was implemented as following: MPC process (1 GPa compaction pressure and using 1.0 wt. % PVA) and then two-step sintering (first at 1000°C and then at 1450°C). A novel ultrasonic assistant grinding device was designed by the group of Gao [57] to process nanoceramics. The data and AFM picture (Figure 2) revealed the critical ductile depth of cut is deeper compared to whether common grinding or traditional ZrO₂ engineering ceramics.

3.2 Application of nano-ZrO₂ as dental implants

It is known that dental implants manufactured by titanium (Ti) and its alloys has gradually become the rou-

tine treatment for tooth defect or missing. With their excellent mechanical strength and biocompatibility, Ti implants are considered as the suitable substitutes for natural teeth. The dense oxide film on the surface of Ti can form a chemical combination with bone tissue [58–60], however, this level of osseointegration is not able to meet the requirements of the stresses [61, 62]. The close contact between the implants material and alveolar bone tissue means that implant surface modification like roughness and surface treatment play a role in the process of bone regeneration [63, 64]. Therefore, nano-ZrO₂ can be served as the promising implants or coating material for better integration.

Considerable research efforts have been devoted to that ZrO₂ implants present the similar or even superior osseointegration than Ti implants. ZrO₂ is particularly attractive as dental implants or coatings due to the highly chemical stability, biocompatibility, suitable fracture resistance and flexural strength compared with alveolar bone [65, 66]. Fabrication of ZrO₂ basement including acid etching [67, 68], plasma spraying [69, 70] and deposition of bioactive layer [71–73] can further increase surface hydrophilic properties. An example of the application of nano-technology treatment of ZrO₂ implants is reported by the group of Lee [74]. The authors used micro-structured ZrO₂ implants (ZiUnitet™) as substrate and chemical deposited method was applied. ZiUnitet™ were immersed firstly into the phosphorous-rich solution then calcium-rich solution to form the nano coating with a Ca/P ratio of 1.67. Nevertheless, 3-6 weeks *in vivo* healing study proved there was no significantly difference between the groups, given that it is hard to gain improvement on the base of commercial implants with high level of osseointegration. Another group have used the creative selective infiltration-

Figure 3: The image of sintered nano-porous zro_2 scaffolds and SEM image of a sintered zro_2 scaffold with interconnectivity [85].

etching (SIE) technique to build a highly retentive nano-porous surface beyond ZrO_2 basement material. 4-6 weeks *in vivo* research showed that SIE group had significantly higher bone-implant contact and bone density compared to Ti and control ZrO_2 implant group [68].

Electrochemical deposition is also a common used method for the preparation of metal oxide nano-structured arrays [75]. Researchers have prepared a composite layer consisting of nano- ZrO_2 /hydroxyapatite coating on the surface of Ti alloy through the electrochemical method [76, 77]. The tensile test showed the combined strength between uniformly nano- ZrO_2 /hydroxyapatite coating and titanium basement was 16.3 MPa, owing to the homogeneously distributed nano- ZrO_2 were served as buffer layer connecting the mismatching thermal expansion coefficient of HA and Ti alloys.

3.3 Application of nano- ZrO_2 as bone tissue engineering scaffolds

Tissue engineering usually combines seed cells, engineering methods, biomaterial scaffolds and physical and chemical factors to restore, maintain, or improve function of organ. And bone tissue engineering method is recognized as the ideal approach to rebuild the bone defects [78, 79]. Biomaterial scaffolds need good mechanical strength to meet the requirement stressed zone. Besides, these scaffolds are required to have certain osteoinductivity and cytocompatibility properties, as well as the interconnection structure to support the growth of osteoblasts, vessels and new bone [80–84].

Researchers have fabricated porous nano- ZrO_2 scaffolds through replication technique [85]. A coating polyurethane foam was employed as the template. Then a process of coating-drying-sintering was taken. The pre-

pare scaffolds presented a nano-porous structure with good interconnectivity (Figure 3). ZrO_2 ceramic nanoparticles can be an excellent filling material in composite scaffold for the satisfying cytocompatibility and high strength. Gaihre and collaborators functionalized chitosan scaffolds by adding nano- ZrO_2 nanopowders [86]. They have found that the additional nano- ZrO_2 can significantly enhance the compressive strength and modulus of original porous chitosan, simultaneously the pre-osteoblasts (OB-6) showed higher proliferation on the chitosan scaffolds filled with nano- ZrO_2 .

Bioactive factors are also the common way to increasing bone regeneration ability of biomaterial scaffolds. MicroRNAs (miRNA) are small non-coding RNAs, which play a role in RNA silencing and post-transcriptional up or down regulation of gene expression. The group of Balagangadharan have synthesized and characterized nano- ZrO_2 /chitosan scaffolds along with miR-590-5p [24], a miRNA that can enhance Runx2 expression, which is a vital signal pathway in osteogenic differentiation of cells. *In vitro* osteogenic differentiation experiment showed that ALP activity and calcium deposition had significantly increased in miR-590-5p group. Thus, the presence of nano- ZrO_2 enhanced the strength of the scaffolds so that they can be used in load-bearing bone defect area.

3.4 Application of nano- ZrO_2 as radiopacifying agent

Root canal therapy is considered as the preferred method for treating pulpal and periapical diseases. It should be pointed out that root canal obturation determine whether the success of therapy. Within the process, X-ray film is the primary path to evaluate the root canal obturation. And thus the desired root filling material needs good radiopac-

ity [87, 88]. Some metal dioxides can be nominated as the good candidates as the radiopacifiers in cement-base filling material, like Bismuth oxide, Niobium oxide and ZrO_2 .

Mineral trioxide aggregate (MTA) is a widely used dental material for root filling and pulp capping for its biocompatibility, seal ability, leading surrounding tissues mineralization. MTA is mainly composed of Portland cement(PC). Researchers have found that ZrO_2 nanoparticles can be the promising radiopacifier as supplement in PC for expediting hydration kinetics without weaken biocompatibility [89]. The group of Tanamaru [90] evaluated the properties of MTA and PC with micro-sized or nano-sized ZrO_2 . The results indicated that both nano or micro ZrO_2 can significantly aggrandize the radiopacity of original PC material, simultaneously, their radiopacity reached the minimum standards by ISO/ADA of 3.0 mmAl. These two researches have supported nano- ZrO_2 could be proper alternative radiopacifier.

3.5 Application of nano- ZrO_2 denture base material

The desired denture repair requires accurate tissue fitting, easy to make, matching the natural color, satisfying fracture strength and aging resistance. Denture base is the important branch of removable partial dentures and complete denture. It covers on the alveolar ridge and hard palate, providing the attachment for artificial teeth. According to the curing methods, denture base resins can be classified into the following three categories: heat-curing resin, self-curing resin, light-curing resin. Among these denture base resins, polymethyl methacrylate (PMMA) is the major constituent. Although PMMA can meet the most demand of the denture repair, the lack of flexural strength and impact strength limit its service life when it occurs to masticating accidents or suddenly drops [91–93].

The incorporation of ZrO_2 nanopowders into PMMA has been put forward in order to improve the performance. The effect of different addition levels of ZrO_2 nanopowders on the repair strength of PMMA has been investigated by group of Mohammed and colleagues [28]. Prior to prepare ZrO_2 /PMMA nanocomposite, a silanization process of nano- ZrO_2 particles was taken to active reaction area on the surface so that there will be more firm adhesion between nano- ZrO_2 and the resin [94]. Different quantity of silanized nano- ZrO_2 was added into autopolymerized acrylic polymer powder to obtain the final concentration of 2.5 wt%, 5 wt%, and 7.5 wt%. The results displayed that the addition of nano- ZrO_2 increased flexural strength of resin material with great significance. The highest value of flex-

ural strength was shown in 7.5 wt% nano- ZrO_2 group. This may be related with that well-distributed nano- ZrO_2 filled the minute space inside the repair resin matrix, arresting the tiny crack propagation [95]. On the contrary, impact strength test implied that 2.5 wt% nano- ZrO_2 group provided the maximum impact strength, whereas the 5 wt%, and 7.5 wt% nano- ZrO_2 group lowered the resin impact strength. The results was similar to Asopa's group [96]. This may be due to self-aggregation of high level ZrO_2 nanoparticles, causing cluster structure formation.

Another group has explored the transverse strength of autopolymerized acrylic resin reinforced with nano- ZrO_2 [97]. Their experiment has demonstrated that nano- ZrO_2 reinforcing denture repair resin can significantly enhance the transverse strength. They thought it was owing to favourable distribution of nano- ZrO_2 that allowed the nanoparticles fill into the space within polymeric chains. In this case, the interfacial shear strength was increased. Nevertheless, further studies need to be investigated to know how nano- ZrO_2 affect the denture resin mechanical properties and what section the best concentration locates.

4 Conclusion and prospective

With the excellent performance, ZrO_2 has gradually become one of the widest used ceramic material in the fields of oral prosthodontics. The nano scale of ZrO_2 , including reinforcing fillings, nano-porous coating, noncrystalline powders, provide more opportunity in different application solutions. In this review, we focus on various synthesis method of nano- ZrO_2 and recent progress dental field using nano- ZrO_2 and related nano-composite. The outstanding properties of nano- ZrO_2 such as natural color, high toughness and strength, steady chemical properties, good corrosion resistance determine the wide application prospect.

As clearly highlighted in the paper, nano- ZrO_2 can be employed in dental ceramics, implants, radiopacifying agents, denture basement and tissue engineering. Nearly all the showed works have displayed the characteristics improvement following adding nano- ZrO_2 . Besides, nano- ZrO_2 exhibits the superior biocompatibility. Nevertheless, greater depth investigation about the interaction between nano- ZrO_2 and stem cells need to be explored, and more *in vivo* animal experiments are deserved to be carried out. Overall, the role of nano- ZrO_2 in dental field is essential. With more reliable trials, more of it will be seen.

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References

- [1] Cochran D.L., Inflammation and bone loss in periodontal disease, *J. Periodontol.*, 2015, 79, 1569.
- [2] Simón S., Mira A., Solving the etiology of dental caries, *Trends Microbiol.*, 2015, 23, 76-82.
- [3] Sloan A.J., Smith A.J., Stem cells and the dental pulp: Potential roles in dentine regeneration and repair, *Oral Dis.* 2010, 13, 151-157.
- [4] Lin Y., Zheng L., Fan L., Kuang W., Guo R., Lin J., Wu J., Tan J., The epigenetic regulation in tooth development and regeneration, *Curr. Stem Cell Res. Ther.*, 2018, 13.
- [5] Dong Z., Yang Q., Mei M., Li L., Sun J., Li Z., Zhou C., Preparation and characterization of fluoride calcium silicate composites with multi-biofunction for clinical application in dentistry, *Composites Part B.*, 2018, 143, S1368203228.
- [6] Sailer I., Makarov N.A., Thoma D.S., Zwahlen M., Pjetursson B.E., All-ceramic or metal-ceramic tooth-supported fixed dental prostheses (FDPs)? A systematic review of the survival and complication rates. Part I: Single crowns (SCs), *Dent. Mater.*, 2015, 31, 603-623.
- [7] Azer S.S., Ayash G.M., Johnston W.M., Khalil M.F., Rosenstiel S.F., Effect of esthetic core shades on the final color of IPS Empress all-ceramic crowns, *J. Prosthet. Dent.*, 2006, 96, 397-401.
- [8] Morton D., Chen S.T., Martin W.C., Levine R.A., Buser D., Consensus statements and recommended clinical procedures regarding optimizing esthetic outcomes in implant dentistry, *Int. J. Oral. Max. Impl.*, 2014, 29 Suppl, 216.
- [9] Pjetursson B.E., Sailer I., Makarov N.A., Zwahlen M., Thoma D.S., All-ceramic or metal-ceramic tooth-supported fixed dental prostheses (FDPs)? A systematic review of the survival and complication rates. Part II: Multiple-unit FDPs, *Dent. Mater.*, 2015, 31, 624-639.
- [10] Yamazoe J., Nakagawa M., Takeuchi A., Ishikawa K., Matono Y., The development of Ti alloys for dental implant with high corrosion resistance and mechanical strength, *Dent. Mater. J.*, 2007, 26, 260.
- [11] Cannizarro, Torchio G., Felice C., Leone P., Esposito M., Marco., Immediate occlusal versus non-occlusal loading of single zirconia implants. A multicentre pragmatic randomised clinical trial, *Europ. J. Oral Implantol.*, 2010, 3, 111-120.
- [12] Hisbergues M., Vendeville S., Vendeville P., Zirconia: Established facts and perspectives for a biomaterial in dental implantology, *J. Biomed. Mater. Res. B*, 2010, 88B, 519-529.
- [13] Sailer I., Zembic A., Jung R.E., Siegenthaler D., Holderegger C., Hämmerle CH., Randomized controlled clinical trial of customized zirconia and titanium implant abutments for canine and posterior single-tooth implant reconstructions: Preliminary results at 1 year of function, *Clin. Oral Implants Res.*, 2010, 20, 219-225.
- [14] Zembic A., Sailer I., Jung R.E., Hämmerle C.H.F., Randomized-controlled clinical trial of customized zirconia and titanium implant abutments for single-tooth implants in canine and posterior regions: 3-year results, *Clin Oral Implants Res.* 2010, 20, 802-808.
- [15] Brakel R.V., Noordmans H.J., Frenken J., Roode R.D., Wit GCD., Cune M.S., The effect of zirconia and titanium implant abutments on light reflection of the supporting soft tissues, *Clin. Oral Implants Res.*, 2011, 22, 1172-1178.
- [16] Lops D., Bressan P.E., Chiapasco D.M., Rossi D.A., Romeo D.E., Zirconia and titanium implant abutments for Single-Tooth implant prostheses after 5 years of function in posterior regions, *Int. J. Oral Maxillofac Implants*, 2013, 28, 281-287.
- [17] Sato H., Yamada K., Pezzotti G., Nawa M., Ban S., Mechanical properties of dental zirconia ceramics changed with sandblasting and heat treatment, *Dent. Mater. J.*, 2008, 27, 408.
- [18] Theunissen G.S.A.M., Bouma J.S., Winnubst A.J.A., Burggraaf A.J., Mechanical properties of ultra-fine grained zirconia ceramics, *J. Mater. Sci.*, 1992, 27, 4429-4438.
- [19] Gautam C., Joyner J., Gautam A., Rao J., Vajtai R., Zirconia based dental ceramics: Structure, mechanical properties, biocompatibility and applications, *Dalton T.*, 2016, 45, 10-1039.
- [20] Yuan Y., Zhen Q., Wei Z., Yang T., Cao Y., Mei X., Yu K., Toxicity assessment of nanoparticles in various systems and organs, *Nanotechnol. Rev.*, 2016, 6.
- [21] Hamza T.A., Ezzat H.A., Elhossary M.M.K., Katamish H.A.E.M., Shokry T.E., Rosenstiel S.F., Accuracy of ceramic restorations made with two CAD/CAM systems, *J. Prosthet. Dent.*, 2013, 109, 83-87.
- [22] Park J.H., Park S., Lee K., Yun K.D., Lim H.P., Antagonist wear of three CAD/CAM anatomic contour zirconia ceramics, *J. Prosthet. Dent.*, 2014, 111, 20-29.
- [23] Kim J.W., Covell N.S., Guess P.C., Rekow E.D., Zhang Y., Concerns of hydrothermal degradation in CAD/CAM zirconia, *J. Dent. Res.*, 2010, 89, 91-95.
- [24] Balagangadharan K., Viji C.S., Arumugam B., Saravanan S., Devanand V.G., Selvamurugan N., Chitosan/nano-hydroxyapatite/nano-zirconium dioxide scaffolds with miR-590-5p for bone regeneration, *Int. J. Biol. Macromol.*, 2018, 111, 953-958.
- [25] Wang J., Huang C., Wan Q., Chen Y., Chao Y., Characterization of fluoridated hydroxyapatite/zirconia nano-composite coating deposited by a modified electrocodeposition technique, *Surf. Coat. Technol.*, 2010, 204, 2576-2582.
- [26] Hakim L.F., George S.M., Weimer A.W., Conformal nanocoating of zirconia nanoparticles by atomic layer deposition in a fluidized bed reactor, *Nanotechnology*, 2005, 16, 375-381.
- [27] Vasyukiv O., Sakka Y., Synthesis and colloidal processing of zirconia nanopowder, *J. Amer. Ceram. Soc.*, 2010, 84, 2489-2494.
- [28] Gad M.M., Rahoma A., Al-Thobity A.M., Arrejaie A.S., Influence of incorporation of ZrO₂ nanoparticles on the repair strength of polymethyl methacrylate denture bases, *Int. J. Nanomed.*, 2016, 11, 5633-5643.
- [29] Lu X., Xia Y., Liu M., Qian Y., Zhou X., Gu N., Zhang F., Improved performance of diatomite-based dental nanocomposite ceramics using layer-by-layer assembly, *Int. J. Nanomed.*, 2012, 2012, 2153-

- 2164.
- [30] Aboushelib M.N., Salem N.A., Taleb A.L.A., Moniem N.M.A.E., Influence of surface nano-roughness on osseointegration of zirconia implants in rabbit femur heads using selective infiltration etching technique, *J. Oral Implantol.*, 2013, 39, 583-590.
 - [31] Huang W., Yang J., Meng X., Cheng Y., Wang C., Zou B., Khan, Z., Zhen W., Cao X., Effect of the organic additions on crystal growth behavior of ZrO₂ nanocrystals prepared via sol-gel process, *Chem. Eng. J.*, 2011, 168, 1360-1368.
 - [32] Ossai C.I., Raghavan N., Nanostructure and nanomaterial characterization, growth mechanisms, and applications, *Nanotechnol. Rev.*, 2017, 7.
 - [33] Tok A.I.Y., Boey F.Y.C., Du S.W., Wong B.K., Flame spray synthesis of ZrO₂ nano-particles using liquid precursors, *Mater. Sci. Eng. B-Adv.*, 2006, 130, 114-119.
 - [34] Duran C., Jia Y., Sato K., Hotta Y., Watari K., Hydrothermal Synthesis of Nano ZrO₂ Powders, *Key Eng. Mater.*, 2006, 317-318, 195-198.
 - [35] Liao J., Zhou D., Yang B., Liu R., Zhang Q., Sol-gel preparation and photoluminescence properties of tetragonal ZrO₂:Y³⁺, Eu³⁺ nanophosphors, *Opt. Mater.*, 2012, 35, 274-279.
 - [36] Wang S., Zhai Y., Li X., Yang L., Wang K., Coprecipitation synthesis of MgO-doped ZrO₂ nano powder, *J. Amer. Ceram. Soc.*, 2010, 89, 3577-3581.
 - [37] Liu H., Xue Q., Investigation of the Crystallization ZrO₂ (Y₂O₃ 3 mol %) Nanopowder, *J. Mater. Res.*, 1996, 11, 917-921.
 - [38] Hench L.L., West J.K., The sol-gel process, *Chem. Rev.*, 1990, 90, 33-72.
 - [39] Nogami M., Tomozawa M., ZrO₂-Transformation-Toughened Glass-Ceramics Prepared by the Sol-Gel Process from Metal Alkoxides, *J. Mater. Sci. Lett.*, 2010, 69, 99-102.
 - [40] Shukla S., Seal S., Thermodynamic tetragonal phase stability in sol-gel derived nanodomains of pure zirconia, *J. Phys. Chem. B*, 2016, 108, 3395-3399.
 - [41] Yoshimura M., Sōmiya S., Hydrothermal synthesis of crystallized nano-particles of rare earth-doped zirconia and hafnia, *Mater. Chem. Phys.*, 1999, 61, 1-8.
 - [42] Szepesi C.J., Adair J.H., High yield hydrothermal synthesis of Nano-Scale zirconia and YTZP, *J. Amer. Ceram. Soc.*, 2011, 94, 4239-4246.
 - [43] Espinoza-González R.A., Diaz-Droguett D.E., Avila J.I., Gonzalez-Fuentes C.A., Fuenzalida V.M., Hydrothermal growth of zirconia nanobars on zirconium oxide, *Mater Lett.* 2011, 65, 2121-2123.
 - [44] Mclean J.W., New dental ceramics and esthetics, *J. Esthet. Restor. Dent.*, 2010, 7, 141-149.
 - [45] Spear F., Holloway J., Which all-ceramic system is optimal for anterior esthetics? *J. Amer. Dent. Assoc.*, 2008, 139, S19-S24.
 - [46] Denry I., Kelly J.R., State of the art of zirconia for dental applications, *Dent. Mater.*, 2008, 24, 299-307.
 - [47] Guazzato M., Albakry M., Ringer S.P., Swain M.V., Strength, fracture toughness and microstructure of a selection of all-ceramic materials. Part I. Pressable and alumina glass-infiltrated ceramics, *Dent. Mater.*, 2004, 20, 441-448.
 - [48] Guazzato M., Albakry M., Ringer S.P., Swain M.V., Strength, fracture toughness and microstructure of a selection of all-ceramic materials. Part II. Zirconia-based dental ceramics, *Dent. Mater.*, 2004, 20, 449-456.
 - [49] Daud M.H.M., Hsu Zenn Y., Zaman J.Q., Yahaya N., Muchtar A., Evaluation of shear bond strength of a novel nano-zirconia and veneering ceramics, *Ceram. Int.*, 2017, 43, 1272-1277.
 - [50] Lian X.J., Qiu Z.Y., Wang C.M., Guo W.G., Zhang X.J., Dong Y.Q., Cui F.Z., Structural and biomedical properties of Zirconia-Hydroxyapatite Nano-Crystal ceramics, *J. Biomater. Tiss. Eng.*, 2013, 3, 330-334.
 - [51] Zhou C., Yi J., Sun Z., Li Y., Hong Y., Biological effects of apatite nanoparticle-constructed ceramic surfaces in regulating behaviours of mesenchymal stem cells, *J. Mater. Chem. B*, 2018, 6, 10-1039.
 - [52] Pei X., Ma L., Zhang B., Sun J., Sun Y., Fan Y., Gou Z., Zhou C., Zhang X., Creating hierarchical porosity hydroxyapatite scaffold with osteoinduction by three-dimensional printing and microwave sintering, *Biofabrication*, 2017, 9.
 - [53] Zhou C., Deng C., Chen X., Zhao X., Chen Y., Fan Y., Zhang X., Mechanical and biological properties of the micro-/nano-grain functionally graded hydroxyapatite bioceramics for bone tissue engineering, *J. Mech. Behav. Biomed.*, 2015, 48, 1-11.
 - [54] Zhou C., Xie P., Ying C., Fan Y., Tan Y., Zhang X., Synthesis, sintering and characterization of porous nano-structured CaP bioceramics prepared by a two-step sintering method, *Ceram. Int.*, 2015, 41, 4696-4705.
 - [55] Marefati M.T., Hadian A.M., Hooshmand T., Hadian A., Yekta B.E., Wetting characteristics of a nano Y-TZP dental ceramic by a molten feldspathic veneer, *Procedia Mater. Sci.*, 2015, 11, 157-161.
 - [56] Park H.Y., Kilicaslan M.F., Hong S.J., Densification behaviour analysis of ZrO₂ nanopowders for dental applications compacted by magnetic pulsed compaction, *Mater. Chem. Phys.*, 2013, 141, 208-215.
 - [57] Gao G.F., Zhao B., Xiang D.H., Kong Q.H., Research on the surface characteristics in ultrasonic grinding nano-zirconia ceramics, *Key Eng. Mater.*, 2009, 375-376, 258-262.
 - [58] Geetha M., Singh A.K., Asokamani R., Gogia A.K., Ti based biomaterials, the ultimate choice for orthopaedic implants – a review, *Prog. Mater. Sci.*, 2009, 54, 397-425.
 - [59] Li L.H., Kong Y.M., Kim H.W., Kim H.E., Heo S.J., Koak J.Y., Improved biological performance of Ti implants due to surface modification by micro-arc oxidation, *Biomaterials*, 2004, 25, 2867-2875.
 - [60] Song P., Hu C., Pei X., Sun J., Sun H., Wu L., Jiang Q., Fan H., Yang B., Zhou C., Fan Y., Zhang X., Dual modulation of crystallinity and macro-/microstructures of 3D printed porous titanium implants to enhance stability and osseointegration, *J. Mater. Chem. B*, 2019, 7, 2865-2877.
 - [61] Yan W.Q., Nakamura T., Kobayashi M., Kim H.M., Miyaji F., Kokubo T., Bonding of chemically treated titanium implants to bone, *J. Biomed. Mater. Res.*, 2015, 37, 267-275.
 - [62] Tonetti M.S., Schmid J., Pathogenesis of implant failures, *Periodontology*, 2010, 4, 127-138.
 - [63] Wong H.M., Zhao Y., Tam V., Wu S., Chu P.K., Zheng Y., To M.K., Leung F.K., Luk K.D., Cheung K.M., In vivo stimulation of bone formation by aluminum and oxygen plasma surface-modified magnesium implants, *Biomaterials*, 2013, 34, 9863-9876.
 - [64] Giavaresi G., Fini M., Cigada A., Chiesa R., Rondelli G., Rimondini L., Torricelli P., Aldini N.N., Giardino R., Mechanical and histomorphometric evaluations of titanium implants with different surface treatments inserted in sheep cortical bone, *Biomaterials*, 2003, 24, 1583-1594.
 - [65] Sennerby L., Dasmah A., Larsson B., Iverhed M., Bone tissue responses to surface-modified zirconia implants: A histomorphometric and removal torque study in the rabbit. *Clin Implant*

- Dent Relat Res. 2010, 7, s13-s20.
- [66] Clarke I.C., Manaka M., Green D.D., Williams P., Pezzotti G., Kim Y.H., Ries M., Sugano N., Sedel L., Delauney C., Current status of zirconia used in total hip implants, *J. Bone Joint Surg. Amer.*, 2003, 85, 73.
 - [67] Saulacic N., Erdösi R., Bosshardt D.D., Gruber R., Buser D., Acid and alkaline etching of sandblasted zirconia implants: A histomorphometric study in miniature pigs, *Clin. Implant Dent. Relat. Res.*, 2014, 16, 313-322.
 - [68] Aboushelib M.N., Salem N.A., Taleb A.L., El Moniem N.M., Influence of surface nano-roughness on osseointegration of zirconia implants in rabbit femur heads using selective infiltration etching technique, *J. Oral Implantol.*, 2013, 39, 583-590.
 - [69] Huang Z., Wang Z., Li C., Yin K., Hao D., Lan J., Application of plasma sprayed zirconia coating in dental implant: Study in implant, *J. Oral Implantol.*, 2018, 44, 17-124.
 - [70] Yang Y., Ong J.L., Tian J., Deposition of highly adhesive ZrO₂ coating on Ti and CoCrMo implant materials using plasma spraying, *Biomaterials*, 2003, 24, 619-627.
 - [71] Kirsten A., Hausmann A., Weber M., Fischer J., Fischer H., Bioactive and thermally compatible glass coating on zirconia dental implants, *J. Dent. Res.*, 2015, 94, 297-303.
 - [72] Marchi J., Amorim E.M., Lazar D.R., Ussui V., Bressiani A.H., Cesar P.F., Physico-chemical characterization of zirconia-titania composites coated with an apatite layer for dental implants, *Dent. Mater.*, 2013, 29, 954-962.
 - [73] Liang H., Qi W., Li Y., Liang H., Qi W., Li Y., Coating strategies for atomic layer deposition, *Nanotechnol. Rev.*, 2017, 6.
 - [74] Jaebum L., Sieweke J.H., Rodriguez N.A., Peter S., HaKan L.M., Cristiano S., Wikesj UME., Evaluation of nano-technology-modified zirconia oral implants: A study in rabbits, *J. Clin. Periodontol.*, 2015, 36, 610-617.
 - [75] Oskam G., Long J.G., Natarajan A., Searson P.C., Electrochemical deposition of metals onto silicon. *J. Physics D Appl. Phys.*, 1999, 31, 1927.
 - [76] Pang X.F., Huang Y., Cao X.Y., Preparation and Features of Nano-ZrO₂ / HA Coating on Surface of Titanium Materials in Dental-Implant, *Adv. Mater. Res.*, 2011, 295-297, 491-495.
 - [77] Pang X., Huang Y., Physical properties of Nano-HAs/ZrO₂ coating on surface of titanium materials used in Dental-Implants and its biological compatibility, *J. Nanosci. Nanotechnol.*, 2012, 12, 902-910.
 - [78] Luan C., Ping L., Chen R., Chen B., Hydrogel based 3D carriers in the application of stem cell therapy by direct injection, *Nanotechnol. Rev.*, 2017, 6.
 - [79] Goonoo N., Bhaw-Luximon A., Goonoo N., Bhaw-Luximon A., Analyzing polymeric nano fibrous scaffold performances in diabetic animal models for translational chronic wound healing research, *Nanotechnol. Rev.*, 2017, 6.
 - [80] Hasan A., Memic A., Annabi N., Hossain M., Paul A., Dokmeci M.R., Dehghani F., Khademhosseini A., Electrospun scaffolds for tissue engineering of vascular grafts, *Acta Biomater.*, 2014, 10, 11-25.
 - [81] Okamoto M., John B., Synthetic biopolymer nanocomposites for tissue engineering scaffolds, *Prog Polym. Sci.*, 2013, 38, 1487-1503.
 - [82] Liu Y., Lim J., Teoh S.H., Review: Development of clinically relevant scaffolds for vascularised bone tissue engineering, *Biotechnol. Adv.*, 2013, 31, 688-705.
 - [83] Yasmin R., Shah M., Khan S.A., Ali R., Gelatin nanoparticles: A Potential candidate for medical applications, *Nanotechnol. Rev.*, 2017, 6, 191-207.
 - [84] Michałowski M., Simulation model for frictional contact of two elastic surfaces in micro/nanoscale and its validation, *Nanotechnol. Rev.*, 2018, 7, 355-363.
 - [85] Zhu Y., Zhu R., Ma J., Weng Z., Wang Y., Shi X., Li Y., Yan X., Dong Z., Xu J., Tang C., Jin L., In vitro cell proliferation evaluation of porous nano-zirconia scaffolds with different porosity for bone tissue engineering, *Biomed Mater.*, 2015, 10, 55009.
 - [86] Gaihre B., Jayasuriya A.C., Comparative investigation of porous nano-hydroxyapatite/chitosan, nano-zirconia/chitosan and novel nano-calcium zirconate/chitosan composite scaffolds for their potential applications in bone regeneration, *Mater. Sci. Eng. C-Mater.*, 2018, 91, 330-339.
 - [87] Gu S., Rasimick B., Deutsch A., Musikant B., Radiopacity of dental materials using a digital X-ray system, *Dent. Mater.*, 2006, 22, 765-770.
 - [88] Camilleri J., Sorrentino F., Damidot D., Investigation of the hydration and bioactivity of radiopacified tricalcium silicate cement, Biodentine and MTA Angelus, *Dent. Mater.*, 2013, 29, 580-593.
 - [89] Li Q., Deacon A.D., Coleman N.J., The impact of zirconium oxide nanoparticles on the hydration chemistry and biocompatibility of white Portland cement, *Dent. Mater. J.*, 2013, 32, 808-815.
 - [90] Guerreiro T.J.M., Storto I., Da S.G., Bosso R., Costa B.C., Bernardi M.I., Tanomarufilho M., Radiopacity, pH and antimicrobial activity of Portland cement associated with micro- and nanoparticles of zirconium oxide and niobium oxide, *Dent. Mater. J.*, 2014, 33, 466-470.
 - [91] Gad M.M., Fouda S.M., Alharbi F.A., Năpănkangas R., Raustia A., PMMA denture base material enhancement: A review of fiber, filler, and nanofiller addition, *Int. J. Nanomed.*, 2017, 12, 3801-3812.
 - [92] Sasaki H., Hamanaka I., Takahashi Y., Kawaguchi T., Effect of reinforcement on the flexural properties of Injection-Molded thermoplastic denture base resins, *J. Prosthodont.*, 2017, 26, 302-308.
 - [93] Costa ESAV., Teixeira J.A., Mota CCB., Cabral CLEC., de Melo JPC., de Souza LMG., Arnaud M., Galembeck A., Gadelha A.T., Dias PJR., Gomes ASL., Rosenblatt A., In Vitro morphological, optical and microbiological evaluation of nanosilver fluoride in the remineralization of deciduous teeth enamel, *Nanotechnol. Rev.*, 2018, 7, 509-520.
 - [94] Hameed H.K., Rahman H.A., The effect of addition nano particle ZrO₂ on some properties of autoclave processed heat cure acrylic denture base material, *J. Baghdad Coll. Dent.*, 2015, 27.
 - [95] Ahmed M.A., Ebrahim M.I., Effect of zirconium oxide Nano-Fillers addition on the flexural strength, fracture toughness, and hardness of Heat-Polymerized acrylic resin, *World J. Nano Sci. Eng.*, 2014, 04, 50-57.
 - [96] Asopa V., Suresh S., Khandelwal M., Sharma V., Asopa S.S., Kaira L.S., A comparative evaluation of properties of zirconia reinforced high impact acrylic resin with that of high impact acrylic resin, *Saudi J. Dent. Res.*, 2015, 6, 146-151.
 - [97] Gad M., Arrejaie A.S., Abdel-Halim M.S., Rahoma A., The reinforcement effect of Nano-Zirconia on the transverse strength of repaired acrylic denture base, *Int. J. Dent.*, 2016, 1-6. 7094056.