Acta Biomaterialia 46 (2016) 308–322

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Selective etching of injection molded zirconia-toughened alumina: Towards osseointegrated and antibacterial ceramic implants

Quentin Flamant [a,b,*], Carlos Caravaca [c], Sylvain Meille [c], Laurent Gremillard [c], Jérôme Chevalier [c], Katia Biotteau-Deheuvels [d], Meinhard Kuntz [d], Rona Chandrawati [e,1], Inge K. Herrmann [e,2], Christopher D. Spicer [e], Molly M. Stevens [e], Marc Anglada [a,b,*]

[a] Department of Materials Science and Metallurgical Engineering, Universitat Politècnica de Catalunya, Av. Diagonal 647, 08028 Barcelona, Spain
[b] Center for Research in Nano-Engineering, CRNE, Universitat Politècnica de Catalunya, C. Pascual i Vila, 15, 08028 Barcelona, Spain
[c] Univ Lyon, INSA-Lyon, MATEIS UMR5510, 7 avenue J. Capelle, 69621, Villeurbanne Cedex, France
[d] CeramTec GmbH, 73207 Plochingen, CeramTec-Platz 1-9, Germany
[e] Department of Materials, Department of Bioengineering and Institute of Biomedical Engineering, Imperial College London, London SW7 2AZ, United Kingdom

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 29 July 2016
Accepted 14 September 2016
Available online 14 September 2016

Keywords:
Surface modification
Roughness
Topography
Bioceramic
Drug delivery

ABSTRACT

Due to their outstanding mechanical properties and excellent biocompatibility, zirconia-toughened alumina (ZTA) ceramics have become the gold standard in orthopedics for the fabrication of ceramic bearing components over the last decade. However, ZTA is bioinert, which hampers its implantation in direct contact with bone. Furthermore, periprosthetic joint infections are now the leading cause of failure for joint arthroplasty prostheses. To address both issues, an improved surface design is required: a controlled micro- and nano-roughness can promote osseointegration and limit bacterial adhesion whereas surface porosity allows loading and delivery of antibacterial compounds. In this work, we developed an integrated strategy aiming to provide both osseointegrative and antibacterial properties to ZTA surfaces. The micro-topography was controlled by injection molding. Meanwhile a novel process involving the selective dissolution of zirconia (selective etching) was used to produce nano-roughness and interconnected nanoporosity. Potential utilization of the porosity for loading and delivery of antibiotic molecules was demonstrated, and the impact of selective etching on mechanical properties and hydrothermal stability was shown to be limited. The combination of injection molding and selective etching thus appears promising for fabricating a new generation of ZTA components implantable in direct contact with bone.

Statement of Significance

Zirconia-toughened alumina (ZTA) is the current gold standard for the fabrication of orthopedic ceramic components. In the present work, we propose an innovative strategy to provide both osseointegrative and antibacterial properties to ZTA surfaces: we demonstrate that injection molding allows a flexible design of surface micro-topography and can be combined with selective etching, a novel process that induces nano-roughness and surface interconnected porosity without the need for coating, avoiding reliability issues. These surface modifications have the potential to improve osseointegration. Furthermore, our results show that the porosity can be used for drug delivery and suggest that the etched surface could reduce bacterial adhesion.

Abbreviations: AFM, atomic force microscopy; DPPC, 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; FE, finite elements; FIB, Focused Ion Beam; HCl, hydrochloric acid; HF, hydrofluoric acid; LTD, low temperature degradation; OPA, *o*-phtaldialdehyde; PBS, phosphate buffered saline; SEM, scanning electron microscopy; WLI, white light interferometry; XPS, X-ray photoelectron spectroscopy; Y-TZP, Yttria-stabilized tetragonal zirconia polycrystal; ZTA, Zirconia toughened alumina.

* Corresponding authors at: Department of Materials Science and Metallurgical Engineering, Universitat Politècnica de Catalunya, Av. Diagonal 647, 08028 Barcelona, Spain.
E-mail addresses: quentin.flamant@upc.edu (Q. Flamant), marc.j.anglada@upc.edu (M. Anglada).
[1] Present address: School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, NSW 2006, Australia.
[2] Present address: Department Materials Meet Life, Swiss Federal Laboratories for Materials Science and Technology (Empa), 9014 St Gallen, Switzerland.

http://dx.doi.org/10.1016/j.actbio.2016.09.017
1742-7061/

1. Introduction

Zirconia-toughened alumina (ZTA) ceramics combine the advantageous properties of monolithic alumina and zirconia: they exhibit high strength, high toughness, outstanding wear resistance and excellent biocompatibility [1–4]. Thanks to these remarkable properties, in the last decade they have become the new gold standard in orthopedics for the fabrication of ceramic bearing components. In particular, in the case of hip replacements, their superior mechanical properties when compared to alumina improve the reliability and enable the manufacture of larger femoral heads and thinner liners, providing a larger range of motion in the joint [5,6].

Nevertheless ZTA is a bioinert material, which means that the host tissue forms a non-adherent fibrous capsule around the implant [7]. In the absence of adequate surface modification, this can lead to poor osseointegration and subsequent aseptic loosening [8]. For this reason, in current hip replacement systems, a metal shell with an osseointegrative surface needs to be placed between the acetabular bone and the external surface of the ceramic liner, which restricts the maximal head diameter because of the limited anatomical space [9]. This limitation confines the range of motion of the patient for maximal positions and can cause impingement, which can be followed by subluxation or even luxation [9]. It would thus be beneficial to develop surface modification processes that enable the implantation of ZTA monoblock components in direct contact with bone.

Despite the high success rate of joint replacement surgeries, approximately 10% of implants still fail within the first 10–20 years [10]. Infections are responsible for approximately 20% of these failures and have become the leading cause for arthroplasty revision [11–13]. Indeed, it is well known that biomedical implants provide a substrate for the adhesion of bacteria, which can proliferate and form biofilms, dramatically increasing the resistance to therapeutic agents [14]. The so-called "race for the surface" between bacteria and host cells makes it therefore critical to eliminate or contain pathogens as early as possible [15,16] and there is a strong interest in developing surfaces that can prevent infection.

Osseointegration and infection prophylaxis are often treated as separated issues. However, as has been recently highlighted by Raphel et al. they are intimately related and should be addressed simultaneously [13]. The key to achieve both objectives is an adequate surface design. On the one hand, controlling topography is crucial to obtain successful osseointegration. In particular it has been shown that rough surfaces exhibit a better bone response than smooth ones and that the combination of micro- and nano-scale roughness can have synergistic effects [17–19]. On the other hand, numerous surface engineering strategies have been explored to prevent infection. Most of them involve coatings, either to prevent bacterial adhesion or to release antibacterial agents [13].

There is little literature regarding surface modifications of ZTA ceramics, and, as discussed above, it would be highly valuable to develop processes that allow the design of implants with controlled micro- and nano-topography and antibacterial properties. Among the diverse surface micro-structuring techniques existing for ceramics, injection molding appears very promising [20]. In contrast to grinding or sandblasting for instance, it does not induce additional surface defects. Besides, it provides a high flexibility since it is theoretically possible to obtain any kind of micro-topography. Finally, it enables the mass production of complex components, which is an advantage from an industrial point of view. In the last decade, injection molding of ZTA has been successfully implemented by several authors [21–24]. However it has not yet been applied to surface micro-structuring which shows the need for further development. On the other hand, among the numerous types of coating proposed for implants, alumina with pores in the 10 nm–200 nm range (nanoporous alumina) appears an appealing solution for the combination of osseointegrative and antibacterial properties: it can be used as a carrier for drug delivery [25–28] and *in vitro* studies have suggested that thanks to its nano-structure it could improve osteoblast adhesion and proliferation, increase matrix production and induce osteogenic differentiation [29–31]. Nevertheless, coatings present several disadvantages; in particular they induce residual stresses and risks of delamination, which may lead to implant failure.

Long-term reliability is a major concern for orthopedic implants, and ceramics can be sensitive to surface alterations. In particular surface defects have a strong influence on their strength [32]. Furthermore, even a moderate porosity can have a substantial impact on their elastic modulus, strength and resistance to contact damage [33–35]. Finally, zirconia-containing ceramics require special attention: the tetragonal to monoclinic phase transformation, which accounts for their exceptional toughness, can occur spontaneously at low temperature in the presence of water, potentially deteriorating the material properties [36,37]. The kinetics of this phenomenon, known as low temperature degradation (LTD) or ageing, are highly sensitive to processing changes, as attested by the failure of Prozyr® zirconia femoral heads in 2002 [38]. Even if ZTA is much more resistant to LTD than monolithic zirconia, it has been shown that it can still present a certain degree of surface tetragonal to monoclinic phase transformation in the presence of water [39–41]. All these elements lead to the following conclusion: to ensure long-term reliability and patient safety, any change in the processing of zirconia-containing ceramics should be accompanied with a careful assessment of its impact on mechanical properties and ageing sensitivity, especially in the presence of porosity.

To address the issues mentioned above, here we develop new methods for the fabrication of reliable ZTA ceramics with surface properties tailored for promoting osseointegration and preventing infections, with the perspective of enabling the implantation of ZTA components in direct contact with bone in the future. To achieve this goal, we hypothesize that surface topography should be controlled at both the micro- and the nano-scale to induce an adequate bone response, and that local drug delivery can reduce dramatically the risk of infections. Our approach was the following: samples with a tailored micro-topography were obtained by injection molding and a novel process, based on the selective dissolution of the zirconia phase (selective etching), allowed the induction of nano-roughness and the formation of an interconnected porous alumina layer. A careful assessment of the impact of selective etching on mechanical properties and ageing sensitivity was conducted and a proof of concept that the porous layer can be used as a carrier for drug delivery was demonstrated.

2. Materials and methods

2.1. Fabrication of samples with a controlled micro-topography by injection molding

The ZTA composites produced in this study were fabricated at CeramTec GmbH (Plochingen, Germany) and consisted of an alumina matrix (80 vol%) containing a small amount of chromia (about 0.3 wt%) reinforced with a secondary phase composed of yttria-stabilized zirconia (Y-TZP, 17 vol%) and $SrAl_{12}O_{19}$ platelets (3 vol%).

An aqueous slurry containing a mixture of alumina, zirconia, strontia, chromia and yttria powders was prepared using electrosteric dispersants. Wet milling was performed in a rotary mill, using zirconia milling balls. The slurry was spray-dried without any organic additive. The ceramic powder was then mixed with an organic binder system (about 45 vol%), mainly consisting of