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Review article

Review of zirconia-based bioceramic: Surface modification and cellular response

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A B S T R A C T

Zirconia is gaining interest as a ceramic biomaterial for implant applications due to its biocompatibility and desirable mechanical properties. At present, zirconia-based ceramic is often seen in the applications of hip replacement and dental implants. This paper briefly reviews different surface modification techniques that have been applied to zirconia such as polishing, sandblasting, etching, biofunctionalization, coating, laser treatment, and ultraviolet light treatment. The cellular response of osteoblast-like cell, osteoblast cell, fibroblast, and epithelial cell to the modified surface is discussed in terms of their adhesion, proliferation, and metabolic activity. The potential of surface modification to make zirconia a successful implant material in the future is highly dependent on the establishment of successful *in vitro* and *in vivo* studies. Hence, further effort should be made in order to deepen the understanding of tissue response to the implant and the tissue regeneration process. The review concludes with future prospect of research and further challenges in developing better zirconia bioceramics.

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1. Introduction

Zirconia is widely used in implants due in particular to its biocompatibility and desirable mechanical properties [1–3]. Zirconia exists in polymorphs; monoclinic, tetragonal, and cubic. The use of a dopant such as yttria, ceria or magnesia stabilizes the tetragonal or the cubic phase of zirconia [1]. A noteworthy characteristic of zirconia is its white or tooth color which gives it aesthetic value [1,4,5]. The importance of aesthetic value is well appreciated because of the known cases of metallic discoloration. For instance, titanium alloy prosthesis was reported to cause metallic discoloration of the right shin in a patient [6]. Bluish

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discoloration of overlying tissue caused by metal implant has also been reported [7]. Tooth-colored ceramics including zirconia have been proposed as a solution to overcome these problems [7,8]. In fact, it is particularly suggested to replace titanium when the amount of soft tissue is not sufficient to cover up the greyish titanium implant [9].

Many implant studies have revealed that zirconia implants exhibit comparable results to titanium implants in terms of osseointegration and biocompatibility [8,10,11]. Further, zirconia has several characteristics which are superior such as a high affinity for bone tissue [12], non-carcinogenic properties, and the absence of an oncogenic effect [1]. This makes it a good choice in many implant applications. A further advantage brought by zirconia is that zirconia grain has been shown to serve as a nucleation site for the development of calcium-based minerals. This is particularly important for implant material design, as the calcium-based mineral, hydroxyapatite is an essential component of bone. Unlike zirconia, alumina showed no affinity towards calcium and hydrogen phosphate ions in Barrere et al. study [13]. Zirconia grain serves as a nucleation site which promotes the development of calcium phosphate minerals. Cauliflower-like growth of calcium phosphate minerals can also be seen to extend across the gap and spread over the whole surface of zirconia [14].

The use of zirconia as a biomaterial has largely been restricted to hip joint replacement [15]. Lately, zirconia has also found use as a restorative material in the dental applications [15]. Although alumina has been used for dental applications, some implants have been removed from the market due to mechanical failure issues [8], including Tübingen implant (despite its high survival rate 80 to over 90% in clinical studies) [16–18]. However, despite the superior wear performance of zirconia over alumina, one of the major issues of zirconia ceramics in implantation is that aging of zirconia happens due to the presence of water, which in turn promotes the transformation of tetragonal to monoclinic phase, and eventually leads to surface roughening and cracking [19]. Partially stabilized zirconia has been introduced to prevent the transformation to a monoclinic phase. One example of this is yttria stabilized zirconia, in which yttria is added to stabilize the tetragonal or cubic phase. There has been an increased interest in yttria-stabilized tetragonal zirconia polycrystals, which is highly used in clinical application, due to their higher fracture resistance and flexural strength [20]. These characteristics make them less susceptible to stress concentrations that lead to mechanical failure [20].

Other than developing zirconia-based ceramics with enhanced mechanical features for long term implantation, it is also important to investigate the interaction between cells and materials in order to establish successful *in vitro* and *in vivo* studies. Thus, surface modification techniques have been introduced to study and improve the biological response of tissue. Many studies have investigated the effect of surface characteristics such as surface topography, surface chemistry, and surface energy on cellular response. It has been shown that the surface topography, including the surface roughness, affects cell growth and activity [21–26]. Surface properties affect cell response and eventually the extent of osseointegration of an implant and ultimate clinical success [27]. Osseointegration, which is a process of bone healing and new bone generation, has long been used as a parameter to assess the success of *in vivo* studies [28]. The topological and physicochemical properties of implant surfaces are crucial for their osteoconductive capacity [29]. Osteoconductivity, as indicated by the level of peri-implant osteogenesis, has been reported to accelerate and enhance osseointegration [30]. Improved physicochemical properties, which enhance the wettability, cell adhesion, and proliferation, would eventually result in a higher contact area between the bone and the implant and strengthen the biomechanical interaction [31]. Alterations in the physicochemical properties also play a role in regulating inflammation, bone remodeling activities, and bone formation response [32,33].

Surface topographies are also involved in regulating and altering cell morphology [34–36]. In addition, pattern on the surface is proven to guide cell growth and orientation [37,38]. According to Sennerby et al., bone formation has been observed to occur directly on the surface-modified implant; it was deduced that surface topography has contributed greatly to this phenomenon [8]. The significance of surface modification for implant has also been established, resulting in enhanced biocompatibility and reduced healing time before loading the implant [39]. The healing process relies on material properties which are in turn influenced by the interaction between materials, cells, and tissues in the biological environment [40]. It has been proven that healing time can be reduced when there is quicker tissue integration [41].

Altering the surface characteristics of zirconia for osseointegration to occur by nature without using the cemented fixation technique has become the current focus of studies [42]. Several studies have also proven the ability of surface modification to enhance osseointegration and bone-implant contact [10,24,43,44]. Excellent bone-implant contact not only indicates good biocompatibility, but also signifies the achievement of firm connection of the surface structure with the bone [8]. According to Turner et al., osseointegration is determined by the evaluation of biomechanical strength at the bone-implant interface [45]. Biomechanical stability is also one of the important aspects to be included in implant design and consideration. Such elements are associated with the remodeling of bone in the surrounding of implants, whereby bone remodeling involves alteration of bone structure to adapt to the presence of implant [46]. Other than altering bone structure to fulfill mechanical needs, bone remodeling also helps to avoid old bone accumulating by repairing defects in bone matrix [47]. Plenty of studies regarding surface modification of zirconia bioceramic have been conducted to explore the cellular and biological response. The aim of this paper is to review surface modified zirconia biomaterial's role in influencing cellular response and its performance in *in vivo* studies.

2. Surface modification techniques and cellular response

A material's surface is known to be uniquely reactive, with properties different from the bulk. The purpose of surface modification is to alter these surface properties to enhance the biological performance of the surface, without changing the bulk properties of the material. Liu et al. has claimed that surface properties greatly affect the biological performance of a solid biomaterial. These properties include surface energy, surface charge, wettability, surface chemistry, and surface topography [48]. For zirconia, milling and sandblasting still remain as popular choices for surface treatment. However, studies in recent years have started to explore other novel techniques including laser irradiation to improve the surface treatment of zirconia [49].

2.1. Sandblasting

Different approaches have been applied to improve surface properties of an implant material. Two key approaches, optimization of roughness (by sandblasting and acid-etching) and application of bioactive coating, can be applied to achieve improvement of surface properties [7]. To date, machined surfaces (often classified as unmodified surfaces) as well as sandblasted surfaces have been commonly seen in studies of zirconia as a biomaterial [8,10,20,27,50–54]. Sandblasting is used to produce a rougher surface compared to a machined and polished surface (Fig. 1). Also