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Biocompatibility of magnesia-partially stabilized zirconia (Mg-PSZ) ceramics

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The biocompatibility of Mg-PSZ ceramics aged to peak strength at 1100° C was assessed by *in vitro* and *in vivo* experiments. The former consisted of immersing the material in saline solution, boiling under reflux, for 1000 hours. A 6% loss in strength was the only discernible change in the ceramic. The *in vivo* experiments comprised implanting Mg-PSZ samples in the paraspinalis muscles of rabbits for 6 months. There was no significant adverse soft tissue response to the implants. Neither was there any change in the surface phase content, surface roughness or strength of the implants during the course of the experiment.

1. Introduction

The most commonly used materials for partial and total joint prostheses are metal alloys and high density polyethylene (HDPE). Usually, these hard tissue implants are bonded to the host bone by methyl methacrylate cement. This materials system has deficiencies which often result in failure. A recent analysis of total hip replacement operations showed a survival rate of only 53% for one type of Stanmore prosthesis; the criterion for failure was removal of the prosthesis for whatever reason [1]. The most common mode of failure was loss of integrity of the implant–bone interface with frequent loosening of the device. A suggested failure mechanism is adverse tissue response to wear debris formed from the moving parts of the implant. Details of the proposed mechanism are presented schematically in Fig. 1 [2]. Fracture of the stem of the metal prosthesis by fatigue is also a common mode of failure. In addition the HDPE component of the prosthesis is prone to creep under stress which breaks the bond of the interface. In recent years alumina has been used successfully to replace the metal alloys. To date about 50 000 implant operations using this ceramic have been performed in Europe, using this ceramic [3]. An important factor in this success is that the wear rate of the oxide is orders of magnitude below the values obtained for metal/metal or HDPE/metal contacts [4].

Recently a new class of high performance oxide ceramics known as magnesia-partially stabilized zirconia (Mg-PSZ) has been developed [5]. These transformation toughened materials are characterized by high values of strength (~ 700 MPa), toughness ($K_{Ic} \sim 8$ to $15\,MPa\,m^{1/2}$), Weibull modulus ($m \sim 22$) and stress corrosion susceptibility (or slow crack growth) parameter ($n \sim 65$) [6–8]. With the exception of the Weibull modulus, these values are all significantly superior to those of even the best quality alumina. The strength and Weibull modulus reported for two bioceramic grades of alumina amounted to 409 MPa, $m = 36$ and 511 MPa, $m = 16$, respectively [4]. Values of the toughness, K_{Ic}, for alumina are typically ~ 3 to $5\,MPa\,m^{1/2}$ whilst the slow crack growth parameter n varies markedly from 10 to 52 [9, 10]. However, it is the outstanding wear properties of Mg-PSZ compared to alumina, as shown in a variety of experiments, which suggests that it would be a successful bioceramic candidate material. For example, in an abrasive wear test in which cylindrical test samples were rotated in a bed of alumina grains, the rate of loss of the alumina samples was $160\,mm^3\,cm^{-2}\,m^{-1}$, whilst the value of PSZ was only $40\,mm^3\,cm^{-2}\,m^{-1}$ [11]. In another experiment, the rate of self-attrition of PSZ grinding media in water and sodium soap solutions was an order of magnitude less than the rate for alumina media [12]. In a

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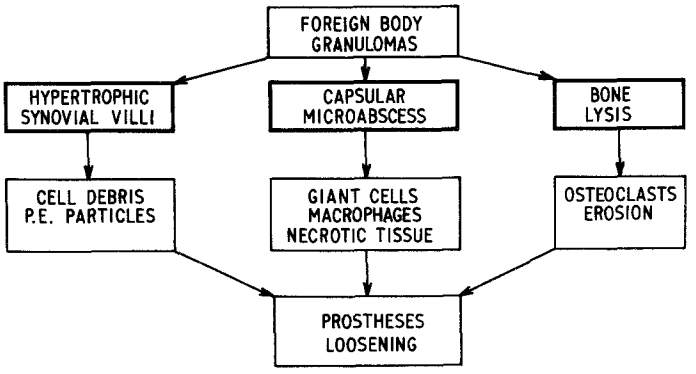

Figure 1 Schematic outline of prostheses failure mechanisms.

ring–ring rubbing test, the wear losses for PSZ and alumina were 0.15×10^{-4} mm^3 m^{-1} and 0.6×10^{-4} mm^3 m^{-1}, respectively [13]. The steady state rate of wear loss of several ceramics, including PSZ, was measured recently in this laboratory in an abrasive slurry test. Test cylinders were tumbled in a variety of aqueous abrasive slurries and the rate of wear loss was measured. Mg-PSZ was the most wear resistant of the materials tested in general and had only ~ 0.05 to 0.2 of the wear rate of alumina, in particular, over the range of slurries tested [14]. The impressive wear resistance of PSZ discussed above is a consequence of the surface strengthening phenomenon in which tetragonal ZrO_2 precipitates are transformed to the monoclinic structure by the particular wear process [15, 16]. The region undergoing wear is thereby placed in compression which tends to inhibit further removal of material.

The purpose of this paper is to report on the biocompatibility of PSZ, as judged by the results of preliminary *in vitro* and *in vivo* tests.

2. Experimental procedure

Mg-PSZ samples containing ~ 3.4 wt% of stabilizer were prepared by first solution-firing isostatically pressed test bars at 1700° C. The furnace cooled bars were then aged to peak strength at 1100° C for 11 h. The maximum strength also coincided with maximum toughness. Ageing Mg-PSZ at 1100° C rather than the conventional value of 1400° C produces superior thermomechanical properties [6]. The aged samples were diamond ground to ~ 3 mm x 3 mm x 40 mm. For the *in vitro* experiment, one surface was immersed polished and then etched after the experiment using a hot aqueous solution of ammonium fluoride–hydrofluoric acid.

Both *in vitro* and *in vivo* experiments were performed to assess the biocompatibility of Mg-PSZ. In the former experiment, samples were immersed for 1000 h in 0.9 wt% saline solution, boiling under flux. The samples were characterized before and after the experiment with respect to flexural bend strength, surface roughness (measured with a Talysurf 10 profilometer), density, optical microstructure and phase analysis by X-ray diffraction. Details of the strength and X-ray measurements have been given elsewhere [17, 18].

The *in vivo* experiments consisted of implanting four samples in the paraspinalis muscles of each of twenty adult female rabbits, 6 to 8 months old. The sample dimensions were 3 mm x 3 mm x 20 mm and all surfaces were ground. Each animal also had two sham operations (an incision without implant) to serve as a control. The rabbits were divided into four equal groups which were sacrificed at 1 week, 1 month, 3 months and 6 months respectively. The sites for implant and sham operations were chosen at random. The tissue reaction was assessed histologically, using the criteria employed by Hulbert *et al.*, as follows [19]:

slight: thin fibrous tissue capsule of uniform thickness and with no inflammatory reaction.

moderate: thin fibrous tissue capsule with some localized thickening and with little or no inflammatory reaction.

severe: uniform thick fibrous tissue capsule associated with a chronic inflammatory response.

The samples were characterized before and after the *in vivo* tests in the manner described above except that there was no examination of the microstructure nor measurement of the density.

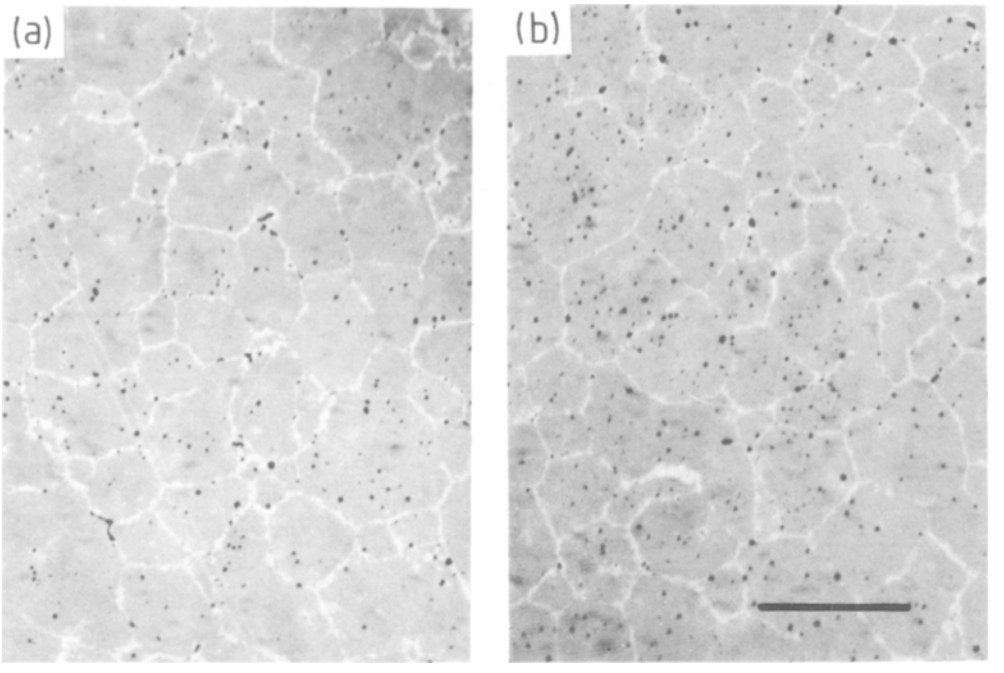

Figure 2 Optical micrograph of PSZ samples before (a) and after (b) immersion in boiling saline solution, bar = 100 μm.

3. Results

Body fluids and tissues comprise a severe environment which can induce degradation of materials by stress corrosion. The *in vitro* experiment is an accelerated screening test which can eliminate candidate materials prone to attack by this mechanism [20]. The optical microstructure of the PSZ before the *in vitro* experiment is shown in Fig. 2a. The grain size is typically ~ 50 μm with a porosity of ~ 2%. The grain boundary material is monoclinic ZrO_2 [5]. There was no visible change in the microstructure after the immersion experiment (Fig. 2). The influence of the *in vitro* experiment in the properties of PSZ are shown in Table I. The most significant change was the loss in strength which amounted to 6% and 14% for the MOR measured with a ground and a polished surface in tension, respectively. (The enhanced values of samples with the ground surface in tension, rather than the polished surface is a consequence of the well-known surface strength effect [15].) No loss in strength occurred when the experiment was repeated using samples which had been sealed in a glass ampoule. These facts suggest that the strength loss is due to stress corrosion. These losses in strength are not considered to be serious on the following grounds. Stress corrosion, in part, is an activated, chemical process. It has long been known that many such processes approximately double or triple their rate for every 10° C rise in

TABLE I Property data for the *in vitro* experiment

Property	Initial value	Final value
MOR (ground)/MPa	618 ± 23	578 ± 40
MOR (polished)/MPa	570 ± 15	492 ± 36
MOR (ground, sealed)/MPa	618 ± 23	616 ± 25
% Monoclinic (ground)	30	34
% Monoclinic (polished)	12	14
*HPW (ground)° 2θ	0.62	0.64
HPW (polished)° 2θ	0.43	0.38
R_a (polished)/μm	0.010 ± 0.008	0.010 ± 0.008
Density/g cm^{-3}	5.651	5.766

*HPW = half-peak width.

TABLE II Implant characterization data

Time *in vivo*	Surface monoclinic content (%)	Surface roughness, R_a (μm)	MOR* (MPa)
0	33	0.49	638
7 days	33	0.52	627
1 month	33	0.32	766
3 months	32	0.48	663
6 months	29	0.51	633
Mean value	32	0.46	680

*The initial strength was measured in four-point bending whilst the remaining values were obtained using three-point bending.

temperature in the neighbourhood of room temperature [21]. This implies that the strength losses noted above at 100° C would be reduced by at least an order of magnitude if the temperature were reduced to the normal human body temperature, 37° C. This supposition is supported by slow crack growth data obtained at various temperatures for soda-lime-silica glass immersed in water [22]. For a value of the stress intensity factor $\sim 4.5\ \text{MPa m}^{1/2}$, the crack velocity was reduced by more than two orders of magnitude when the temperature was reduced from 90° C to 25° C.

The X-ray phase analyses showed a small increase in monoclinic content between the initial and final values for both ground and polished surfaces. This change could be related to the strength loss but it is difficult to rationalize any such connection. The increase in the monoclinic content of a ground surface compared to one that is polished is due to the transformation of tetragonal ZrO_2 precipitates to the monoclinic structure by the grinding stresses; i.e. the surface strengthening effect [15]. The half-peak width (HPW) of the cubic/tetragonal (1 1 1) X-ray diffraction profile showed no significant change during the test for the ground surface and a 12% decrease for the polished surface. HPW values are indicative of the level of microstrain in the material. Again, there is no obvious connection between the HPW values and loss in strength during immersion. The roughness average value (R_a) and the density both showed no change during the course of the *in vitro* experiment.

The simplest explanation of the strength loss consistent with the data of Table I is that the critical flaw size is increased by means of a stress corrosion mechanism. The initial critical flaw size was estimated from the Griffith equation to be $\sim 79\ \mu\text{m}$ using strength data for the polished samples and the published value for K_{Ic} obtained for peak aged Mg-PSZ [6]. The critical flaw size would have to increase to only $\sim 107\ \mu\text{m}$ to account for the observed strength loss. It is suggested that an increase of this order would not involve significant changes in the other material properties such as the surface phase content, surface roughness, etc. The percentage decrease in strength measured with a ground surface in tension is less than that for a polished surface. The reason is that the surface compressive stresses of the former condition tend to inhibit the growth of the critical flaws.

The implants experienced no degradation during the *in vivo* experiment, as shown by the data presented in Table II. The surface monoclinic content, surface roughness and the strength all showed no significant trend during the course of the experiment. Table III presents data on the soft tissue response to the implants using the criteria of Hulbert *et al.* [19].

The data for moderate and severe response were pooled because values for the latter were small. The resulting 2 × 2 contingency tables were analysed using Pearson's χ^2 test along with the null hypothesis that the data for both the sham and implant operations were from the same populations [23]. All the χ^2 values were low, in the range 0.02 to 0.15. The probability of a greater value in each case was high, in the range 0.7 to 0.9, thereby indicating that it was reasonable to accept the null hypothesis, i.e. there is no statistical difference between the tissue response of the sham and implant operations. This result is in accord with earlier work by Bortz and Onesto who reported that zirconia was biocompatible on the basis of an *in vivo* experiment [24]. The data of Tables I, II and III are encouraging and suggest that further work is warranted to assess the merits of Mg-PSZ as a candidate bioceramic.

TABLE III Soft tissue response to the implants

Time *in vivo*	Procedure	Total number	Number with "slight" response	Number with "moderate" response	Number with "severe" response
7 days	sham	10	7	3	0
	implant	20	14	6	0
1 month	sham	10	6	4	0
	implant	20	10	9	1
3 months*	sham	8	5	3	0
	implant	16	9	6	1
6 months	sham	10	5	4	1
	implant	20	10	8	2

*One animal from this group developed a superficial wound infection so the tissue specimens from this animal were excluded from the study.

4. Conclusions

1. The small loss in strength experienced by Mg-PSZ system in boiling saline solution is probably due to extension of the critical flaw size by a stress corrosion mechanism.

2. No degradation of the properties of Mg-PSZ occurs in contact with living tissue.

3. There is no adverse soft tissue response to Mg-PSZ implants.

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