

Review

Zirconia as a ceramic biomaterial

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Abstract

Zirconia ceramics have several advantages over other ceramic materials, due to the transformation toughening mechanisms operating in their microstructure that can give to components made out of them, very interesting mechanical properties. The research on the use of zirconia ceramics as biomaterials started about twenty years ago, and now zirconia (Y-YZP) is in clinical use in THR, but developments are in progress for application in other medical devices. Recent developments have concentrated on the chemistry of precursors, in forming and sintering processes, and on surface finish of components. Today's main applications of zirconia ceramics is in THR ball heads. This review takes into account the main results achieved up to now, and is focused on the role that microstructural characteristics play on the TZP ceramics behaviour in ball heads, namely mechanical properties and their stability, wear of the UHMWPE paired to TZP, and their influence on biocompatibility. © 1998 Published by Elsevier Science Ltd. All rights reserved

Keywords: Zirconia; Mechanical properties; Stability; Biocompatibility; Wear; Radioactivity

1. Introduction

Zircon has been known as a gem from ancient times. The name of the metal, zirconium, comes from the Arabic *Zargon* (golden in colour) which in turn comes from the two Persian words *Zar* (Gold) and *Gun* (Colour). Zirconia, the metal dioxide (ZrO_2), was identified as such in 1789 by the German chemist Martin Heinrich Klaproth in the reaction product obtained after heating some gems, and was used for a long time blended with rare earth oxides as pigment for ceramics.

Although low-quality zirconia is used as an abrasive in huge quantities, tough, wear resistant, refractory zirconia ceramics are used to manufacture parts operating in aggressive environments, like extrusion dies, valves and port liners for combustion engines, low corrosion, thermal shock resistant refractory liners or valve parts in foundries. Zirconia blades are used to cut Kevlar, magnetic tapes, cigarette filters (because of their reduced wear). High temperature ionic conductivity makes zirconia ceramics suitable as solid electrolytes in fuel cells and in oxygen sensors. Good chemical and dimensional

stability, mechanical strength and toughness, coupled with a Young's modulus in the same order of magnitude of stainless steel alloys was the origin of the interest in using zirconia as a ceramic biomaterial.

The R&D on zirconia as a biomaterial was started in the late sixties. The first paper concerning biomedical application of zirconia was published in 1969 by Helmer and Driskell [1], while the first paper concerning the use of zirconia to manufacture ball heads for Total Hip Replacements (THR), which is the current main application of this ceramic biomaterial, was introduced by Christel et al. [2].

In the early stages of the development, several solid solutions (ZrO_2 -MgO, ZrO_2 -CaO, ZrO_2 - Y_2O_3) were tested for biomedical applications (Table 1). But in the following years the research efforts appeared to be more focused on zirconia-yttria ceramics, characterised by fine grained microstructures known as Tetragonal Zirconia Polycrystals (TZP).

Nowadays, TZP ceramics, whose minimal requirements as implants for surgery are now described by the standard ISO 13356 [3], are the materials selected by almost all the manufacturers that are introducing into the market zirconia ball heads (Table 2). More than 300 000 TZP ball heads has been implanted [4], and only two failures were reported [5] up to now.

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Table 1
Characteristics of some ceramics for biomedical applications

Property	Units	Alumina	Mg-PSZ	TZP
Chemical composition		99.9% Al ₂ O ₃ +MgO	ZrO ₂ +8 ÷ 10 mol% MgO	ZrO ₂ + 3 mol% Y ₂ O ₃
Density	g cm ⁻³	≥3.97	5.74–6	>6
Porosity	%	<0.1	—	<0.1
Bending strength	MPa	>500	450–700	900–1200
Compression strength	MPa	4100	2000	2000
Young modulus	GPa	380	200	210
Fracture toughness K _{IC}	MPa m ^{-1/2}	4	7–15	7 – 10
Thermal expansion coeff.	K ⁻¹	8 × 10 ⁻⁶	7–10 × 10 ⁻⁶	11 × 10 ⁻⁶
Thermal conductivity	W mK ⁻¹	30	2	2
Hardness	HV 0.1	2200	1200	1200

Table 2
Producers of zirconia ball heads for THR

Producer	Country
Astromet	USA
Ceraver	France
Ceramtec	Germany
Norton	France
Kyocera	Japan
Metoxit	Switzerland
Morgan Matroc	United Kingdom
NGK	Japan
SCT	France
Xylon	USA

2. Microstructural properties

Zirconia is a well-known polymorph that occurs in three forms: monoclinic (M), cubic (C) and tetragonal (T). Pure zirconia is monoclinic at room temperature. This phase is stable up to 1170°C. Above this temperature it transforms into tetragonal and then into cubic phase at 2370°C. During cooling, a T–M transformation takes place in a temperature range of about 100°C below 1070°C. The phase transformation taking place while cooling is associated with a volume expansion of approximately 3–4%. Stresses generated by the expansion originate cracks in pure zirconia ceramics that, after sintering in the range 1500–1700°C, break into pieces at room temperature. It was in 1929 that Ruff and coworkers [6] showed the feasibility of the stabilisation of C-phase to room temperature by adding to zirconia small amounts of CaO.

The addition of ‘stabilising’ oxides, like CaO, MgO, CeO₂, Y₂O₃, to pure zirconia allows to generate multiphase materials known as Partially Stabilized Zirconia (PSZ) whose microstructure at room temperature generally consists [7] of cubic zirconia as the major phase,

with monoclinic and tetragonal zirconia precipitates as the minor phase. These precipitates may exist at grain boundaries or within the cubic matrix grains. In 1972 Garvie and Nicholson [8] showed that the mechanical strength of PSZ was improved by an homogeneous and fine distribution of the monoclinic phase within the cubic matrix. The development of zirconia as an engineering material was marked by Garvie et al. [9], who in their paper ‘Ceramic Steel?’ showed how to make the best of T–M phase transformation in PSZ improving mechanical strength and toughness of zirconia ceramics. They observed that tetragonal metastable precipitates finely dispersed within the cubic matrix were able to be transformed into the monoclinic phase when the constraint exerted on them by the matrix was relieved, i.e. by a crack advancing in the material. In that case, the stress field associated with expansion due to the phase transformation acts in opposition to the stress field that promotes the propagation of the crack. An enhancement in toughness is obtained, because the energy associated with crack propagation is dissipated both in the T–M transformation and in overcoming the compression stresses due to the volume expansion. A schematic representation of this phenomenon is given in Fig. 1. The development of such tetragonal metastable precipitates may be obtained by the addition of some 8% mol of MgO to ZrO₂. This allows the formation a fully cubic microstructure at 1800°C, and the nucleation within the matrix of a tetragonal metastable phase, during controlled cooling and ageing.

PSZ can also be obtained in the ZrO₂–Y₂O₃ system (Fig. 2). However in this system it is also possible to obtain ceramics formed at room temperature with a tetragonal phase only, called TZP. This result was reported first by Rieth et al. [10], and by Gupta et al. [11].

TZP materials, containing approximately 2–3% mol Y₂O₃, are completely constituted by tetragonal grains with sizes of the order of hundreds of nanometers. The fraction of T-phase retained at room temperature is

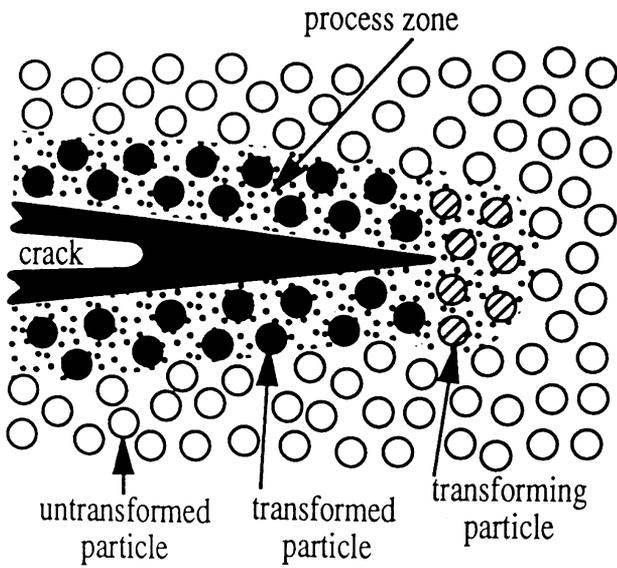


Fig. 1. Representation of stress-induced transformation toughening process. Energy of the advancing crack is dissipated in phase transformation and in overcoming the matrix constraint by transforming grains (Reprint with permission from Butler EP, Transformation toughened zirconia ceramics. *Mat Sci Tech* 1985;1:417–32.).

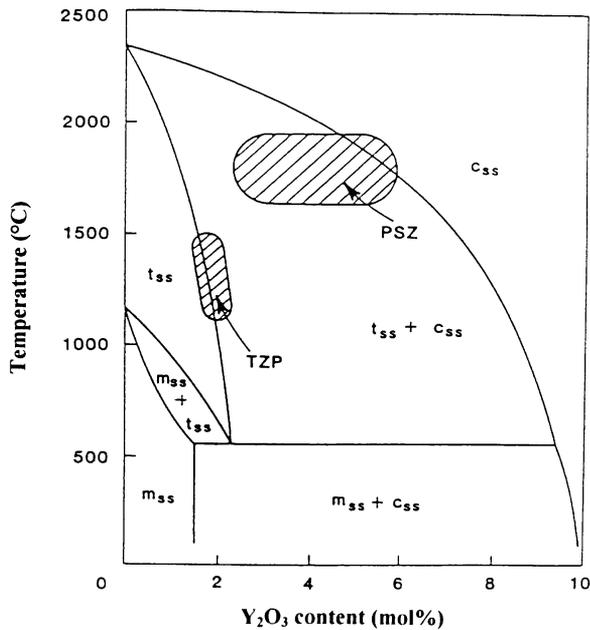


Fig. 2. High zirconia part of zirconia–yttria phase diagram. Commercial PSZ and ZTP composition and processing temperatures are indicated by shaded regions (Reprint with permission from Scott HG, Phase relationship in zirconia–yttria systems. *J Mater Sci* 1975; 10:1527–35.).

dependent on the size of grains, on the yttria content, on the grade of constraint exerted on them by the matrix. Mechanical properties of TZP ceramics (Figs. 3 and 4) depend on such parameters.

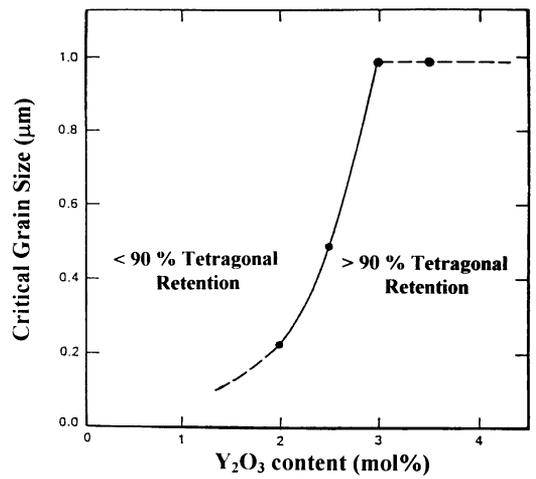


Fig. 3. Retention of tetragonal phase. Critical grain size against Yttria content in tetragonal zirconia (Reprint with permission from Lange FF, Transformation toughening, Part 3—Experimental observations in the ZrO₂–Y₂O₃ system. *J Mater Sci* 1982;17:240–6.).

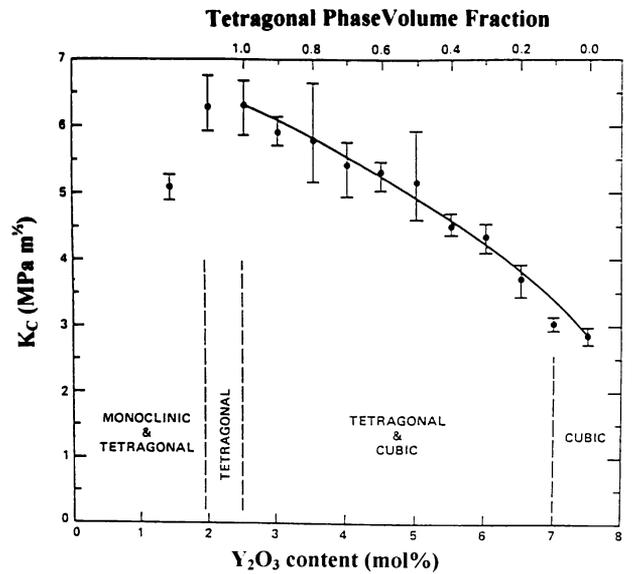


Fig. 4. Fracture toughness vs. yttria content (Reprint with permission from Lange FF, Transformation toughening, Part 3—Experimental observations in the ZrO₂–Y₂O₃ system. *J Mater Sci* 1982;17:240–6.).

It is very important to consider the metastable nature of the tetragonal grains. A critical grain size exists, linked to the yttria concentration, above which spontaneous T–M transformation of grains takes place, whereas this transformation would be inhibited in a too fine grained structure [12].

An interesting characteristic of transformation toughened zirconia ceramics is the formation of compressive layers on their surface [13]. Surface tetragonal grains are not constrained by the matrix, and can transform to monoclinic spontaneously or due to abrasive processes

that can induce compressive stresses at a depth of several microns under the surface.

The surface phase transition and the consequent surface hardening may have a relevant role in improving the mechanical and wear properties of zirconia parts, the thickness of the transformed layer being one of the limit conditions. Progresses in T–M surface transformation may originate surface cracking, followed by ejection of grains from the surface with catastrophic effects on mechanical behaviour and joint wear.

Several PSZ were tested as ceramic biomaterials, especially Mg–PSZ, which was extensively tested with favourable results. But R&D on this material for biomedical applications appears to have to be stopped in the early 1990s. Several reasons can account for this fact: Mg–PSZ are characterised by a residual porosity as is normal in materials with grain sizes in the range 30–40 μm . This can influence negatively the wear rate of UHMWPE sockets that are currently coupled with zirconia ball heads. Also technological aspects may have been taken into account. Mg–PSZ sinter at higher temperatures than TZP (1800°C vs. 1400°C), implying the need of special furnaces. The precipitation and development of the metastable tetragonal precipitates, that occurs during cooling, requires a strict control of the cooling cycle in terms of temperature and time, especially in the ageing step that takes place at about 1100°C, during which the precipitation of T-phase occurs.

Difficulties in obtaining Mg–PSZ precursors free of SiO_2 , Al_2O_3 and other impurities [14], increase in SiO_2 contents due to the wear of milling media during powder processing before firing [15] may have contributed to shift the interest of ball head manufacturers towards TZP materials. In ceramics containing MgO, magnesia silicates like enstatite (MgSiO_3) and forsterite (Mg_2SiO_4) may form at grain boundaries [14], lowering the MgO contents in the grains and promoting the formation of the monoclinic phase, reducing the mechanical properties of the material and its stability in a wet environment. Nevertheless, Mg–PSZ ball heads were used in the USA [16] and Australia. Also TZP precursors can contain silica, which is sometimes used as a liquid phase forming additive to achieve full density at temperatures lower than 1500°C limiting grain growth. Lin et al. [17] observed that aluminosilicate glasses in the grain boundaries scavenge yttrium ions from TZP grains, leading to

a loss of stability of the tetragonal phase. Moreover, mullite ($3\text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2$) pockets were detected in the aluminosilicate glass, which leads to a loss of stability of the material in a wet environment. The use of such additives is hence to be avoided in TZP as ceramic biomaterials.

3. Mechanical properties

There is no doubt that zirconia ceramics have mechanical properties better than other ceramic biomaterials, i.e. alumina [18], as shown in Table 1. Comparison among Young's moduli, strength and hardness of some biomaterials, including ceramics, are shown in Table 3.

3.1. Results of compression tests on TZP ball heads

Ultimate Compressive Load (UCL) of ball heads is tested following the ISO 7206-5 standard [19]. The test procedure consists of the application of static loads to the ball head inserted in a metallic spigot until fracture, and it may be considered a useful tool to compare different designs.

It can be observed from UCL tests that using TZP ceramics, ball heads of $\varnothing 22.22$ mm can withstand static loads ranging several times the physiologic ones. Ball heads UCL depends on design and material characteristics both of the ball head and of the metallic spigot: the angle mismatch between bore and taper, and the surface roughness controls the magnitude and position of maximum stress in the ceramic ball head. Finite elements analysis on different designs [20–22] of ceramic ball heads has shown that two main stress concentrations are localized in the inner surface of the ceramic bore, one (bending stress) at the top of the cavity, and one (hoop stress) at the ceramic–metal taper interface. The magnitude of such stresses is dependent on the position, the metal–ceramic contact area, the roughness of the surfaces and the friction coefficient of the two counterfaces.

Tests performed on TZP ball heads [23] show that to minimize the concentration of stresses it is necessary to maintain a gap ≥ 2 mm between the spigot and the top of the conical cavity, and maximize the extension of the

Table 3
Properties of some materials for biomedical applications

Property	Units	Ti 6Al 4V	316 SS	CoCr Alloy	TZP	Alumina
Young's modulus	GPa	110	200	230	210	380
Strength	MPa	800	650	700	900–1200	> 500
Hardness	HV	100	190	300	1200	2200

contact area, taking care of the rise of hoop stresses in the rim portion of the ball head when the taper is not completely inserted into the conical bore.

In standard prostheses design, taper to ceramic bore coupling is made with a tolerance of some 0 to $-5'$ on the taper and 0 to $+5'$ on the conical bore [24]. Angle mismatch is selected in such a way that contact takes place first in the upper part of the ceramic bore, and is extended to the complete taper surface due to the metallic taper strain following loading. Drouin and Calés [23], reported that the angle mismatch ($10'$) can be more than doubled in TZP ball heads before observing a decrease in ball heads UCL.

There is experimental evidence [25, 26] that UCL of zirconia ball heads is 2–2.5 times higher than the UCL of alumina ball heads of the same diameter and neck length. Also Tateishi et al. [27, 28] observed UCL of TZP ball heads of $\varnothing 22.2$ mm on Ti6Al4V spigots almost double the UCL of alumina ball heads of $\varnothing 28$ mm on CoCr spigots, but it must be remarked that the failure loads reported by these authors are far below the ones of currently manufactured ball heads.

It is clear that variations in the spigot material and roughness, in the roughness of the ceramic bore, in the mismatch of the bore/taper angle, and in the taper insertion depth all play an important role on the results obtained by this test. A summary of results, obtained by several authors [23, 28–30] is reported in Table 4. A comprehensive summary of the main parameters of the taper influencing the head-Trunion assembly was recently published [164].

3.2. Stability of the tetragonal phase

Mechanical properties of zirconia relate to its fine grained, metastable microstructure. The stability of this structure during the lifetime of TZP components is the key point to attain the expected performances.

Mechanical property degradation in zirconia, known as 'ageing', is due to the progressive spontaneous transformation of the metastable tetragonal phase into the monoclinic phase. This behaviour is well known in the temperature range above 200°C in the presence of water vapour [31, 32].

The main steps of TZP ageing were summarised by Swab [33] in the following way:

- (1) The most critical temperature range is $200\text{--}300^\circ\text{C}$.
- (2) The effects of ageing are the reduction in strength, toughness and density, and an increase in monoclinic phase content.
- (3) Degradation of mechanical properties is due to the T–M transition, taking place with micro and macro-cracking of the material.
- (4) T–M transition starts on the surface and progresses into the material bulk.
- (5) Reduction in grain size and/or increase in concentration of stabilising oxide reduce the transformation rate.
- (6) T–M transformation is enhanced in water or in vapour.

The models proposed to explain the spontaneous T–M transformation in TZP are based on the formation of zirconium hydroxides [31, 32, 34] or yttrium hydroxides

Table 4
UCL of TZP ball heads on different tapers

Ref.	Taper material	Taper type	Taper roughness (μm)	Ball head diameter (mm)	Neck length	UCL (kn)	Remarks		
22	Ti6Al4V	10/12	200	28	– 3.5 mm (S)	110			
					0	105			
					+ 3.5 mm (L)	85			
					– 3.5 mm (S)	140			
					0	130			
					+ 3.5 mm (L)	110			
27	Ti614VA	8/10 10/12	3	22.22	0	78			
					30	22.22	0	98	
					Not specified	22.22	Not specified	45	
								34	
28	Ti alloy Ti alloy CoCr alloy CoCr alloy NiCrMo alloy	12/14	4.6	28	L	80	HV ₁₀ :352		
			48.4			93	HV ₁₀ :320		
			2.7			44	HV ₁₀ :435		
			2.7			47	HV ₁₀ :644		
			60.3			108	HV ₁₀ :310		
29	Ti614VA	4°	Not specified	32	0	122 \pm 16			
				28	0	97 \pm 11			
				28	+ 3 mm (L)	84 \pm 6			
				28	– 3 mm (S)	133 \pm 13			

[35] promoting phase transition for local stress concentration or variation of the yttrium/zirconium ratio.

It is worthwhile to remark that the strength degradation rate is not the same for all TZP ceramics. As it was reported by Swab [33], in the ten materials tested in presence of water vapour at low temperature, different levels of strength degradation occurred in all the materials but one, where strength remained the same after the treatment. This variability in ageing behaviour is related to the differences in equilibria of microstructural parameters like yttria concentration and distribution, grain size, flaw population and distribution in the samples tested [36]. Table 5 contains a summary of the results of ageing tests reported by several authors.

The strength degradation in wet environments of zirconia was studied from the early phases of the development of zirconia for biomedical applications [37]. Garvie et al. [38] reported a reduction up to 14% of the Modulus Of Rupture (MOR) of Mg-PSZ samples maintained for 1000 h in a boiling saline solution. On the other hand, the content of monoclinic phase in the surface of the specimens of the same material implanted in paraspinal muscles of rabbits, although rather high (32%), did not show significant variations.

Bending strength variation of TZP samples implanted in the marrow cavity and in the paraspinal muscles of NZW rabbits or maintained in a saline solution at 37°C for 12 months was investigated by Kumar et al. [39]. An increase in the bending strength was observed after six months, associated with 2% M-phase formation on the surfaces of samples. Experimental data reported by Schwartz [26] and by Christel [40, 41] are in agreement with those of Kumar's [39]. Christel [40, 41] showed that gamma sterilization or ageing in Ringer's solution for 100 d did not induce significant variations in the strength of TZP samples. Also, Ichikawa et al. [42] did not observe variation in the bending strength of TZP samples after 12 months ageing in air, saline, or subcutaneous tissues of Wistar rats.

Conflicting results were reported by Drummond [43, 44] and by Thomson and Rawlings [45]. Drummond performed an extensive study on ageing of TZP [43]. Reduction in MOR of about 20% was observed in TZP samples after ageing for 730 d in Ringer's, saline solutions or distilled water at 37°C. Reduction takes place in the time interval 140–304 d, and no significant correlation with the testing environment was found. Also control specimens, maintained in air, showed similar behaviour. The samples tested contained 5.5–8.5 wt% Y_2O_3 , slightly above the optimal composition, and contained phases different from tetragonal, probably cubic. This fact makes the samples tested not representative of TZP for implants.

Thomson and Rawlings [45] reported the M-phase as reaching 10% after 18 months ageing in Ringer's solution. They calculated that the M-phase might reach

a maximum transformation of 72% at 37°C in a time ranging from 7 to 30 yr, encompassing a THR expected lifetime. But it must be remarked that such results were obtained on TZP ceramics characterized at the start of the test by an M-phase content of approximately 5%, and by a rather high defect population, indicated by a low Weibull modulus ($m = 6.5$) and MOR below 700 MPa measured in three-point bending tests. Bending strength shows little variations during the test, showing that material strength in the samples tested was controlled by defects more than by phase transitions.

Shimizu et al. [46] tested TZP samples (grain size 0.25 μm , density 6 g cm^{-3}) in vitro and in vivo. In vitro tests were performed in saline at 37, 50, 95°C for 36 months, and in an autoclave at 121°C for 960 h. Samples were tested in vivo in subcutaneous tissue and in the tibial marrow of JW rabbits for 30 months. Three-point bending tests were performed on 8 mm gauge samples. Alumina was used as a control. Samples tested at 37°C in vitro and in vivo did not show significant differences. The development of the monoclinic phase on the surface of the samples was only observed 90 d after the beginning of the test, reaching approximately 2 and 5 mol% after 12 and 30 months, respectively (Fig. 5). In correspondence with the T–M surface transformation, an increase in the bending strength of samples was observed, but the starting value was recovered after 30 months. In samples tested at 50°C, 16 mol% of the surface underwent a T–M transition after 3 yr. The corresponding increase in bending strength was about 10%.

The monoclinic phase was 69 mol% in samples aged at 95°C after 27 months, while in samples aged in an autoclave at 121°C the monoclinic phase was about 50 mol% after 500 h only, being 80 mol% after 1000 h.

Zr–OH bonds were identified by FTIR in samples aged for 960 h in water at 121°C. This suggests that the phase transition in the material tested depends on mechanisms similar to the ones proposed by Sato and Shimada [31, 32] or by Yoshimura et al. [34], the formation of Zr–OH bonds being the transition initiator. Nevertheless, no microcracks were observed by SEM in identical material samples aged 1920 h in saline at 121°C. The activation energy of the transition process in the material tested was calculated to be about 21.5 kcal mol^{-1} . This result allowed the authors to predict that the bending strength of the material will maintain for 80 yr a value higher than 800 MPa.

Results of ageing tests in water for three years were recently reported [47]. The activation energy of the T–M transformation process was calculated according to the Sato and Shimada model [31, 32] to be 25.2 kcal mol^{-1} . On this basis authors can calculate that the flexural strength of the material maintained for 50 yr in water at 37°C will be more than adequate for orthopaedic or dental implants. Recently Chevalier et al. [4] reported the results of a study on the T–M transformation kinetics

Table 5
Summary of some results of ageing tests on zirconia ceramics

Ref.	Material	Medium	T (°C)	Time	% MOR variation	Remarks
[25]	TZP	Ringer's	37	6 w 12 w 24 w 52 w	Roughly + 10% after 52 weeks	
[36]	Ca-PSZ	Ringer's	37	1 w 2 w 4 w	- 16.1 -17.4 -18.5	ZrO ₂ + 4%CaO, 1% SiO ₂ , 1% Al ₂ O ₃ . Presence of TiO ₂ and Fe ₂ O ₃
		Rabbit dorsa	—	3 m	-25.8	
[37]	Mg-PSZ	Saline	100	1000 h 7 d	-6.5 a -13.7 b	a: ground; b: polished Samples characteristics: Grain size: 50 µm porosity: 2%
		Rabbit muscles		1 m 3 m 6 m	—	M-phase 12–30%
[38]	TZP	Ringer's	37	3 m 6 m 12 m	0 + 19.5 +22	M-phase increase was less than 2% in all samples at 12 m
		Bone marrow		3 m 6 m 12 m	0 + 17 +9.8	
		Subcutis		3 m 6 m 12 m	0 +22 +5	
[39, 40]	Y-PSZ	Ringer's	37	1 d 7 d 50 d 100 d	—	Fracture toughness K_{IC} : -7.4% -6.6% -6.6% + 3.1%
[41]	ZrO ₂ + 3% Y ₂ O ₃	HCl sol.	37	up to 12 m	No variations	T-phase > 90%
		Subcutis				
[42]	Y-PSZ	Ringer's	37	140 d 304 d 453 d	0 -12.9 -22	6.6% mol Y ₂ O ₃ at test start
		Saline		140 d 304 d 453 d	0 -19 -19.5	
		Water		140 d 304 d 453 d	- 1.7 - 15.5 -17.3	
[43]	Mg-PSZ	Air (*)	37	6 m 12 m 18 m	-1 -4.9 -2.5	MOR for crosshead speed 0.1 mm min ⁻¹ * Autoclaved at 121°C in water prior to ageing
		Water (*)		6 m 12 m 18 m	-8 -3.6 -2.5	
		Air seal		6 m 12 m 18 m	0 0 -3	
[44]	TZP	Ringer's	37	19 m	-16.4	5% M phase at test start 14% M phase at test end
[45]	TZP	Bone marrow		30 m	-5	Average increase M phase 2 mol% per year
[28]	TZP A	Steam	140	24 h 48 h 120 h	-15 -21 -25	5 vol% M phase at test start > 80 vol% M phase at test end
	TZP B			24 h 48 h 120 h	-6.5 -6.5 -11.5	11 vol% M phase at test start 60 vol% M phase at test end
[50]	TZP	Ringer's	37	783 d	No change	

Time units: h—hour, d—day, w—week, m—month.

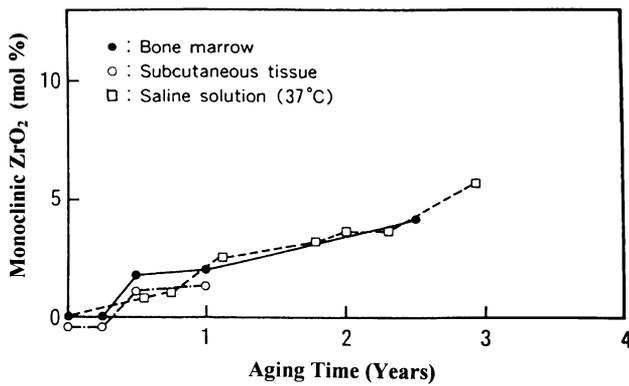


Fig. 5. Tetragonal to monoclinic transformation of TZP in vivo and in saline (Reprint with permission from Shimizu K, Oka M, Kumar P et al., Time-dependent changes in the mechanical properties of zirconia ceramic. *J Biomed Mat Res* 1993;27:729–34.).

in TZP obtained from coprecipitated powders. These results allow to predict a 25 yr ageing period at 37°C to reach 20% monoclinic content in their samples. The activation energy measured ($\log \text{kJ mol}^{-1}$) is of the same order of the one measured by Shimizu et al. [46].

Not only the yttria content but also the yttria distribution plays a role on T–M phase transition in TZP materials. The stabilizing oxide is introduced in zirconia during the early steps of the powder manufacturing process, i.e. coprecipitation of yttrium and zirconium salts. A different approach to the introduction of stabilizing oxide in ceramic powders consists a coating zirconia grains with yttria, thus obtaining an yttria gradient in the material. The effects of this yttria distribution on TZP hydrothermal stability was investigated by Richter et al. [29]. Samples obtained by coprecipitated and coated powders following the same preparation and sintering schedule were treated in an autoclave in the presence of water vapour at 140°C up to 120 h. The development of M-phase in the samples made out of the two materials follow a quite different evolution: in ‘coprecipitated’ samples one can observe a fast increase in M-phase content, reaching 80 vol% after 24 h. The successive evolution of the transformation is slower, the amount of M-phase reaching 90 vol% after 120 h of treatment. In ‘coated’ samples, the evolution of the M-phase appears to be progressive, reaching 60 vol% after 120 h of treatment.

The thickness of the monoclinic layer after 120 h approximately 120 μm in TZP made out of coprecipitated powder, and around 5 μm when made out of coated powder. This result was achieved using precursors sintered to full density at a relatively low temperature without glassy additives, resulting in a TZP completely tetragonal with grains less than 0.5 μm in size [48, 49].

Calès et al. [50] reported the first results on mechanical behaviour of THR zirconia ball heads after clinical use. Tests were performed on four ball heads retrieved

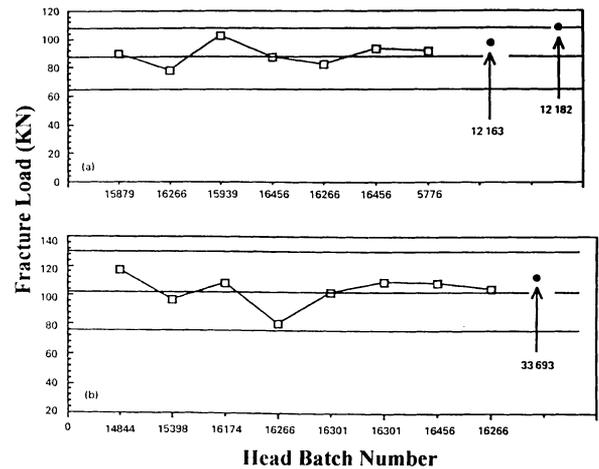


Fig. 6. TZP ball heads ultimate compression load after clinical use, in comparison to the acceptance values of production batches (Reprint with permission from Calès B, Stefani Y, Mechanical properties and surface analysis of retrieved zirconia femoral hip joint heads after an implantation time of two to of two to three years. *J Mat Sci Mater Med* 1994;5:376–80.).

from patients after 22, 24, 27, 39 months. The results obtained are very relevant as the ball heads were subjected not only to the action of the body environment, but also to the physiological cyclic loading.

Three out of the retrieved ball heads were subjected to static compression tests, while bar samples for the bending test were obtained from the ball retrieved after 22 months. The UCL of the retrieved ball heads was within the acceptance values characteristic of each production batch (Fig. 6). The experimental values obtained from the bending tests performed on test bars obtained from the 22 months implanted ball head, as well as results of tests performed on test bars machined from current production TZP ball heads aged in Ringer’s solution and in animals at 37°C for 2 yr [23] did not show significant differences, the bending strength remaining unchanged.

The effects of the combination of stress and a wet environment on TZP stability were also reported [5]. TZP ball heads, $\emptyset 32 \text{ mm}$, were maintained in Ringer’s solution for 3, 6 and 12 months under static loads of 10, 20 and 30 kN fitted in Ti6Al4V tapers. An axial bore in tapers allowed Ringer’s solution to reach the top of the conical bore in the ball head. Compression tests did not show significant variations in UCL. Whatever the time in Ringer’s solution and the applied load, the average UCL is $(129.5 \pm 6.5) \text{ kN}$, which corresponds to the average UCL measured before the test (132 kN). XRD analysis did not show variations in the contents of the monoclinic phase up to 12 months. Ageing of samples of the same material for 2 yr was performed by implanting then in muscles of rats and rabbits, and in the femur of rabbits and sheeps. Fracture toughness measured by the micro-indentation do not show significant variations, K_{IC}

ranging (9 ± 1) MPa $m^{-1/2}$ whatever the site or time of implantation. Neither differences in the finish of outer and inner bearing surfaces between virgin and retrieved TZP ball heads, nor in density or hardness were observed after 18 months of clinical use. Similarly no differences were observed in the average bending strength of TZP bars aged for 300 d in SBF at 37°C and 60°C. In these samples the formation of monoclinic phase ($<1\%$) in the predominant tetragonal structure [52, 53] was observed.

The above results presented by different authors, confirm the conclusions of the work by Swab [33] reported at the beginning of this section. The extent of strength degradation of TZPs in wet environments depends on the material microstructure, and can be controlled by acting on the material manufacturing process and on the precursors selected for ceramic manufacture. One can observe that there is experimental evidence that TZP ceramic is able to maintain good mechanical properties in wet environments for expected implant lifetimes, but general conclusions about the stability of TZP must be avoided, as this behaviour is peculiar to each material and of its manufacturing technology.

3.3. Impact tests

Impact test constitutes a useful assay to evaluate the ability of a component to dissipate shock energy, i.e. its toughness. There is very limited information in this field: up to now the only results presented on this topic are due to Tateishi and Yunoki [28]. Bodies growing in weight were dropped from a 0.5 m height onto a ball head inserted in its spigot. $\varnothing 22.2$ mm TZP ball heads (on Ti alloy spigot) failed under an impact of some 78 J, while $\varnothing 28$ mm Alumina ball heads (on CoCr spigot) failed under some 15 J impact. The role exerted by the spigot material due to the differences in elastic properties of the two alloys and its influence on the results reported was not clarified.

3.4. Fatigue resistance

Tests in Pseudo Extra Cellular Fluid (PECF) and in saline solution, with loads cycled from 1 to 12 kN and from 5 to 10 kN at 30 Hz are reported by Tateishi et al. [27, 28]. Tests were performed up to 10 million cycles on $\varnothing 22.2$ mm TZP ball heads without failure. More interesting results are reported by Calès [54]. The number of cycles-to-rupture increase as the maximum load decreases from 15 to 90 kN, and shows a tendency to increase to infinity for loads less than 28 kN. It was observed experimentally that TZP $\varnothing 22.2$ mm ball heads can withstand up to 50 million cycles with load cycled from 2.8 to 28 kN.

4. Wear

4.1. Zirconia on zirconia

There is clear experimental evidence that the wear rate of the couple zirconia/zirconia is too high to use this ceramic couple in prosthetic joints. Early studies performed by Murakami and Ohtsuki [55], Sudanese et al. [56, 57], show the disastrous amounts of wear of this ceramic couple, up to 5000 times the wear of the alumina/alumina one. Recently TZP/TZP wear was the object of new interest, probably due to the improvements in TZP ceramics processing (reported after the previous studies). The TZP/TZP couple was investigated taking into account the effects of environment, sliding speed, and load on wear properties, using the ball on ring (pin on disk) method [58], by the ring on disk test in conformity to the standard ISO 6474 [59, 60], and on hip simulator [61]. These authors confirmed the results obtained previously.

Sliding of a pair made of low thermal conductivity materials leads to an increase in surface temperature. For zirconia/zirconia pair the temperature may rise up to more than 100°C [58], enhancing the T–M phase transition in the wet environment. This process may lead to cracking, grain pullout and catastrophic abrasive wear. Nevertheless, the work recently published by Chevalier et al. [165] opens again the research in this field. In pin-on-disc tests performed using water as a lubricant, they observed zirconia/zirconia or zirconia/alumina wear rates one order of magnitude lower than the wear rate of alumina/alumina pair. These results were not replicated using bovine serum as lubricant.

4.2. Zirconia/UHMWPE

The wear of the couple UHMWPE/zirconia was studied by many authors. The results obtained are summarized in Table 6. Data are scattered over several orders of magnitude.

Wear rates of UHMWPE against zirconia five times less than against alumina were observed in ring on disc tests carried out in conformity to ISO 6474 [59], due to the much finer grain size of zirconia than alumina ($8 \times$) [26]. Other authors [62] found an increase of some 65–70% in UHMWPE volume loss, depending on the number of cycles, for alumina surface roughness passing from $R_a = 0.06 \mu\text{m}$ to $R_a = 0.22 \mu\text{m}$. Low residual porosity in zirconia surface induced UHMWPE wear 40–50% less than alumina ceramics [63, 64]. Different finishing processes can have a big influence on wear. Surface roughness and porosity obtained from sample finishing may produce different wear rates. It was hypothesized that the existence of a threshold value below which surface roughness changes can influence only a little the wear rate [65].

Table 6
Summary of results of UHMWPE wear tests—(1) WRR: Wear Rate Ratio; UHMWPE/zirconia as unit

Ref.	Method	Medium	Load (N)	Stress (MPa)	Speed (m/s)	Materials	Roughness R_a (μm)	UHMWPE wear	Wear unit	WRR (1)	Notes
[25]	Ring on disc	Ringer's	—	—	—	Ti6Al4V CoCr Alumina Zirconia	—	0.019 0.015 0.0096 0.0018	$\text{mm}^3 \text{h}^{-1}$	10.6 8.3 5.3	
[66]	Pin on flat	Bovine serum	223	3.5	0.05 Av.	Ti6Al4V CoCr Alumina Zirconia	0.008 0.008–0.016 0.005–0.006 —	0.56 0.05 0.29 0.21	mg	2.4 0.2 1.4	Wear measured after 1 million cycles
[60]	Pin on disc	—	—	2–3	0.06	Ti6Al4V SS316L Alumina Zirconia	0.018 0.021 0.009 0.005	29.84 23.90 18.28 10.78	$\text{mm}^3 \text{Nm}^{-1} \times 10^{-6}$	2.8 2.2 1.7	Unidirectional motion
	Pin on flat	Bovine serum	—	3.45	0.05 Av.	Ti6Al4V SS316L Alumina Zirconia	0.018 0.021 0.009 0.005	2.81 1.88 1.25 0.54		5.2 3.5 2.3	Reciprocating motion
[79]	Pin on flat	PECF	—	3.54	0.05 Av.	Ti6Al4V + N ₂ PSZ 2 PSZ 3	0.01 < 0.01 < 0.01	0.35 0.25 0.38	mg	0.92–1.4	Reciprocating motion Zr(OH) precipitates in PECF were detected
[61]	Pin on flat	Ringer's	57	—	0.025 Av.	Alumina ZTA, 5% ZTA, 20% TZP	0.02	3.9 3.1 2.1 1.9	$\text{mm}^3 \text{Nm}^{-1} \times 10^{-5}$	2.0 1.6 1.1	Reciprocating motion
[64, 65]	Pin on disc	Ringer's + 30% calf serum	—	3.45	0.025	Alumina A Alumina B Alumina B2 Mg-PSZ Si ₃ N ₄ Ti6Al7Nb TiN Ti6Al7Nb ODH CoCr TZP	0.008–0.030 0.008–0.030 0.008–0.030 0.008–0.030	2.15 2.25 2.25 2.65 2.9 2.1 1.35 2.8 3.25	$\text{mm}^3 \text{Nm}^{-1} \times 10^{-5}$	0.7 0.7 0.69 0.8 0.9 0.7 0.4 0.9	Unidirectional motion Roughness of ceramic discs are not representative of the one of ball heads
[74]	Ring on disc	Saline + calf serum 3:1	—	5.6	0.314	Ti6Al4V-N impl. CoCr Alumina Zirconia	0.022 max 0.003–0.008 0.003–0.008 0.003–0.008	7.5 4.2 2.2 2.2	mm^3	3.4 1.9 1	Reciprocating motion Speed 0.025–0.1 m s^{-1} σ : 5.6 and 9.4 Mpa γ : sterilized PE

[62]	Pin on disc	Bovine serum	—	3.45	0.05	SS316L Alumina Zirconia SS316L Alumina Zirconia SS316L Alumina Zirconia SS316L Alumina Zirconia	0.006	27.7 18.2 10.7 90.5 32.7 7.5 37.1 11.8 8.61 1.81 1.01 0.56 3.89 0.57 0.45 1.12 0.68 0.38	$\text{mm}^3 \text{Nm}^{-1} \times 10^{-7}$	2.6 1.7 12.0 4.4 4.3 1.4	Unidirectional motion
		Saline									
		Dist. water									
	Pin on flat	Bovine serum	—	3.00	0.06	SS316L Alumina Zirconia SS316L Alumina Zirconia	0.006	8.61 1.81 1.01 0.56 3.89 0.57 0.45 1.12 0.68 0.38	3.2 1.8		Reciprocating motion
[75]	Pin on flat	Dist. water	—	27.5	0.03	Cast CoCr Wrough CoCr TZP	0.003	64 71 33	μm μm	1.9 2.2	Reciprocating motion UHMWPE flat
[73]	Pin on flat	Dist. water	225	3.5	0.084 max	SiN ₄ CoCr Alumina Zirconia	0.02 0.01 0.005 0.005	25 100 3.3 2.6	$\text{mm}^3 \text{Nm}^{-1} \times 10^{-9}$	38.5 9.6 1.26	Reciprocating motion UHMWPE γ sterilized
[63]	Pin on flat	Bovine serum	240 N (12 MPa)	Max 0.24 m s ⁻¹	Max	SS SS CoCr (w) CoCr (w) CoCr (c) CoCr (c, s) Alumina Zirconia	0.008 0.017 0.010 0.019 0.033 0.040 0.016(+) 0.005	6.1 11.5 11.3 12.6 16.5 13.8 10.8 7.4	$\text{mm}^3 \text{Nm}^{-1} \times 10^{-9}$	0.8 1.6 1.5 1.7 2.2 1.9 1.5	(+) Roughness not representative of ceramic ball heads
[71]	Hip simul.	Bovine serum	2 kN max			CoCr Alumina Zirconia	48.2 57.5 26.3		mg mg	1.8 1.2	Wear after 2 million cycles

On the other hand other authors [66, 67] did not observe correlations between surface roughness of ceramics (Al_2O_3 , TZP, Mg-PSZ) and UHMWPE wear rate: poor quality of the ceramics (residual porosity) and of their finish, (R_a and R_z twice that of medical components) can account for the large scatter of data. Mg-PSZ ceramics with big grain size ($42\ \mu\text{m}$) and high roughness show an average UHMWPE wear rate, characterized by high scatter of data ($\pm 70\%$), lower than the one of TZP and Si_3N_4 .

Differences in lubricant fluid can also modify wear test results [64, 68]. Serum quality may induce UHMWPE wear (weight loss) up to 40 times higher after 10^6 cycles [69]. Extremely low wear of UHMWPE against zirconia and alumina (wear factor in the order of $10^{-9}\ \text{mm}^3\text{Nm}^{-1}$) was found using a reciprocating pin on flat apparatus [70]. The difference observed in the average UHMWPE wear factor against alumina and zirconia (26%) was not statistically significant. UHMWPE coupled with both ceramics showed a wear approximately 30 times lower than against CoCr alloy.

Some authors [71, 72] recently remarked on the level of significance of wear tests, especially on unidirectional tests. The wear rates and wear rankings measured in unidirectional tests and multidirectional tests may differ significantly, and this may lead to a misleading conclusion on the screening of materials to be coupled to UHMWPE. Unidirectional motion may [73] lead to the orientation of the polymer surface layer, with the formation of fibrils in the sense of motion, while the motion occurring *in vivo* is multidirectional. The extremely low UHMWPE wear rates observed by several authors in unidirectional tests may be related to the surface orientation and strain hardening [72, 73]. In tests using a hip joint simulator [74] UHMWPE cups wore less against zirconia ball heads than against alumina or CoCr alloy balls. After 2 million cycles, the cups average wear was 57.7 mg against alumina, 48.2 mg against CoCr alloy and 26.3 mg against zirconia. UHMWPE wear rates in the last 0.5 million cycles against alumina and CoCr were 30% higher than against zirconia. Also frictional torque, measured at the commencement of the tests and after 1.75 million cycles, was lower for zirconia ball heads than for alumina and CoCr. In the other wear tests on a hip simulator reported till now [75], commercial UHMWPE cups were tested against experimental TZP ball heads up to five million cycles. The clinical wear rate observed were in the range $0.6\text{--}9.4\ \mu\text{m yr}^{-1}$. A higher clinical wear rate ($9.4\ \mu\text{m yr}^{-1}$) was observed in the cup tested against the ball head with a largest surface roughness ($0.014\ \mu\text{m Ra}$). Deviation from roundness, due to the hand-operated finish on the experimental ball heads, was in the range $2.8\text{--}6.4\ \mu\text{m}$, some order of magnitude higher than the one of commercial ball heads. The average wear factor reported in tests is $8 \times 10^{-8}\ \text{mm}^3\text{Nm}^{-1}$. The

average wear rate (4.1 mg per million cycles) is very much lower than the ones previously reported [74]. Frictional torque of $\emptyset 22\ \text{mm}$ TZP, $\emptyset 28\ \text{mm}$ alumina, $\emptyset 22$ stainless steel ball heads against UHMWPE sockets was tested at 37°C in PECF, under pulsating load. TZP ball heads frictional torque was lower than the Alumina one, whatever the testing conditions [76].

As it can be observed in Table 6, the spread in the wear rate observed is remarkable and can be ascribed to the different characteristic of the materials (zirconia and UHMWPE) used in the tests due to material processing, to the differences in testing methods and in testing conditions. Moreover, the samples used have different shapes, dimensions and surface roughnesses; tests were performed in different environments, with different speeds and applied loads. There is no agreement on the effects on wear of sample characteristics like roughness, lubricant fluid, speed and load.

It must be taken into account that wear is a complex behaviour of the system under study, not a material property. Not only the simple laboratory tests (pin on disk, etc.), but also the costly and time consuming tests on joint simulators may give questionable results. In the best case joint simulators can give indications only about the *in vivo* wear behaviour, because the accurate reproduction of the *in vivo* operating conditions needs the knowledge of the role that each one of the factors involved plays in controlling wear.

5. Biological safety

The use of cell cultures in the early phases of the study of biocompatibility of a would-be biomaterial is such an established research practice that it may appear odd that the first results on biocompatibility of zirconia, published in 1969 [1], were obtained *in vivo*, and that experimental data reporting cell culture results were published only in 1990 [79]. However, in this paper *in vitro* test results are reported as usual. *In vitro* biocompatibility is evaluated using cell culture which *in vivo* interacts with the biomaterial (Harmand [80]); zirconia is currently used as femoral ball head in THR and so *in vivo* will contact soft tissues and blood. Most of the authors tested this ceramic with fibroblasts or blood cells, probably for the reasons above.

5.1. *In vitro* tests

Zirconia powders or ceramics were tested onto different cell lines (Table 7): some authors observed that zirconia has no cytotoxic effects when fibroblasts were co-cultured with it or with extracts using different methods (viability of cells and MTT assay) [81, 82]. SEM studies also reported the adhesion and spreading of 3T3 fibroblasts [79]. On the other hand higher inhibition of

Table 7
Summary of in vitro tests on zirconia ceramics and powders

Ref.	Material	Physical form	Cell type	Test	Effects	Remarks
[76]	CaPSZ	sintered ceramic (30% porosity) powder	3T3 Fibroblasts	SEM observation	Adhesion and spreading of cells	After 72 h cell monolayer onto ceramic samples
[78]	Zirconia	sintered ceramic	Human lymphocytes	Inhibition of cell mitogenesis after PHA induction	Dose dependent cytotoxicity	CaPSZ less cytotoxic than TiO ₂
[79]	YPSZ	Ceramic precursor and sintered ceramic	Fibroblast Human oral fibroblasts	Cell viability-MTT Colony forming efficiency, MTT, dissolution test	No Cytotoxic effect Powders more toxic than crushed and milled ceramic	Toxicity related to specific surfaces and ion release
[80]	YPSZ	Wear particles of UHMWPE	L929 fibroblasts	Cell growth in presence of PECEFs	Wear product of UHMWPE vs. YPSZ more cytotoxic than UHMWPE vs. Ti6Al4V	Toxicity is related to the presence of particles of Zirconium hydroxides
[81]	YPSZ	Powder	Human lymphocyte	Inhibition of cell mitogenesis after PHA induction	Dose dependent cytotoxicity	Toxic effect of YPSZ similar to alumina and lower than the ones of titania
[82]	ZrO ₂	Particles	Macrophages	Cytotoxicity at 24 hours	Zirconia less toxic than polyethylene	Higher phagocytosis of zirconia than PE
[84]	YPSZ	Powder	Balb 3T3 and human osteoblasts	Cell viability, MTT	No cytotoxic effects	Different levels of sensitivity among the tests used

cellular growth using zirconia and TCP powders in comparison to alumina or HA was observed in the direct contact test, cell viability and MTT assay [82]. In particular, cytotoxicity of zirconia powders (ceramic precursors) was higher than cytotoxicity of powders obtained by the crushing and the milling of sintered zirconia ceramics: this effect was related to different reactive surfaces and yttria ions release. Ion release was tested in saline solution at 37°C of temperature (to 0.12 µg cm⁻²) from plates of high density sintered material (HIP, 160 MPa, 1225°C, 2 h). In acid solution (lactic acid 0.02 M at 37°C) yttrium and zirconium ions increased (to 3 µg cm⁻²), leading to the conclusion that zirconia ceramics cannot be used in an acid environment as the oral cavity.

Cytotoxic effects on L929 fibroblasts co-cultured in the presence of PECEF (Pseudo Extra Cellular Fluid) used as a lubricant in wear tests were analyzed by Ito et al. [83]. The cytotoxicity of wear products obtained by the friction of UHMWPE against YPSZ was higher than the cytotoxicity of UHMWPE/Ti-6Al-4V wear products. The cytocompatibility of PECEF was improved using a 0.22 µm pore size filter. Since toxic effects could be related neither to ion release, nor to polyethylene particles less than 0.22 µm in diameter because of the presence of floats on the surface of culture medium, amorphous particles of Zr(OH)₄, coming from friction in alkaline PECEF, may be considered as one of the causes of the cytotoxicity. The presence of zirconium hydroxide may indicate—at least to the opinion of the authors—a lack of stability in the PSZ material tested. One can remark that when PECEF was used as a lubricant, semi-angular particles of the size range 4–20 µm were observed.

Dion et al. [81], in the presence of ZrO₂/Y₂O₃ extracts tested the indirect contact, cell viability and MTT assay of 3T3 fibroblasts and HUVEC, in order to detect the possible effects of products released by ceramic powders. The conclusion drawn by the authors was that both ceramics and their products have no toxic effects on cell cultures also when in contact with blood cells.

Toxic effects of CaPSZ powders of different grain sizes (30–106 µm) on human lymphocyte mitogenesis after PHA proliferative induction, were evaluated in comparison with TiO₂ powders [79]. The inhibitory effect was dose dependent (from 0.06 to 12 mg ml⁻¹). At all the concentrations used, CaPSZ powders showed inhibitory effects lower than TiO₂ (rutile) powders. Even at higher concentrations the inhibitory effect never exceeded 50% (LD 50%). These observations were confirmed successively [84], when the cytotoxicity of ZrO₂-Y₂O₃ on human lymphocyte mitogenesis was compared with the one observed in cultures with alumina and titania powders. All the materials tested (Grain size ≤ 44 µm) showed a dose dependent lymphocyte mitogenesis inhibition. Alumina and zirconia cytotoxicity were similar and both were lower than the one of TiO₂ rutile.

The effects of wear products of alumina and zirconia ceramics were evaluated using flow cytofluorimetry analysis [85]. Alumina and zirconia ceramics were tested in comparison with high density polyethylene on macrophages J774 and RAW267.5. Polyethylene particles were more cytotoxic than ceramic particles, even if a quantity of polyethylene less than ceramic particles were phagocytosed by macrophages. The lack of toxic effects of $ZrO_2 + 2 \text{ mol\% } Y_2O_3$, hydroxyapatite (HAP) and alumina on a macrophage cell culture was also observed by other authors [86]. The absence of cytotoxic effects on Balb 3T3 fibroblasts and human osteoblasts of $ZrO_2/8 \text{ wt\% } Y_2O_3$ and HAP was reported [87]. The authors observed different levels of sensitivity among tests (in particular direct contact was more sensitive than indirect contact).

In vitro carcinogenicity tests (Ames test) and teratogenicity tests (cellular chromosome aberrations) in the presence of $ZrO_2 + Y_2O_3$ additive with 0.5 ppm UO_2 were performed by Satoh and Niwa [88], who reported negative results in both tests. In genotoxicity tests the absence of aberration in chromosomal patterns in cells cocultured on Zirconia plates was also reported [89].

Only few papers have analyzed the in vitro toxicity of zirconia. The limit of cell cultures is that by this method it is possible to analyse only single aspects of cell–material interaction. It is not possible to establish the biological safety of a material only by this method. Moreover, it can be remarked that the results of in vitro assays are influenced by several material characteristics, like the physical form, reactive surface, chemical composition, impurity content and distribution. Also the cell conditions during the test plays a major role (fibroblasts vs. PHA induced lymphocytes).

In a round-robin test performed within the confines of the VAMAS Project on various biomaterials, including zirconia, significant differences were reported by different research institutes using the same test (with the same cells) onto the same material [90].

5.2. In vivo tests

Biocompatibility of zirconia ceramics was investigated in vivo by implanting them in bone and in soft tissues several years before the first in vitro studies. In the first in vivo study, performed by Helmer and Driskell [1], the absence of adverse tissue reactions related to dense zirconia + 6% Y_2O_3 implanted in a monkey's femur was reported. Hulbert et al. [91] implanted discs and tubes of $CaO + Al_2O_3$, $CaO + TiO_2$, $CaO + ZrO_2$, as porous materials with a pore size in the range 45–150 μm and as nonporous materials, into rabbit muscles. Histological analysis of all the materials tested 9 months after operation did not reveal signs of toxic, immune or carcinogenic effects.

Another early study on zirconia as a candidate biomaterial was performed by Bortz and Onesto [92], who introduced ZrO_2 tubular elements in rabbits and dogs in order to develop tracheal prostheses. Serious problems of heavy fibrinous growth within the lumen of the tube, which sometimes closed it off, was observed. Bacterial infections were observed always in rabbits, but never in dogs; nevertheless prostheses were firmly attached to the trachea, even when infection was present.

Successive in vivo long term effects after implantation of Magnesia Partially Stabilized Zirconia (Mg–PSZ) in the paraspinal muscle of rabbits were investigated by Garvie et al. [38]. 1 week, 1, 3, 6 months post-operatively, animals were sacrificed. The authors did not observe adverse tissue reactions.

The promising results obtained in the first studies on biological reactions to zirconia, coupled with the first positive results on wear tests and mechanical properties, caused several research laboratories direct their interest on zirconia. In vivo biocompatibility tests were performed using alumina as reference 'bioinert' ceramic and HA. The first results of this comparison were contradictory: after the implantation of alumina and zirconia ceramics into femur of rats, no differences in bone reaction were observed [93], while differences in new bone formation after insertion of YTZP, alumina and hydroxyapatite in rabbit femur were reported [39]. Neither phlogosis nor osteolysis were observed but bone apposition on YZTP was less than on alumina (ratio 1 : 10, when samples were inserted into the medullary cavity; 2 : 10 when samples were in direct contact with the cortical bone; 4 : 10 when implants were transcortical). The authors remarked the critical role exerted by the site of implant on bone response, due to the different stress levels and distributions inducing osteogenesis around inert materials [39]. In 1989 Christel et al. [40] published an important study on in vivo effects of zirconia ceramics. YPSZ cylinders were implanted into paraspinal muscles of rat in comparison to alumina. From 1 to 12 weeks after operation, no significant differences were observed between materials. Comparable results were obtained after the implantation into rats and rabbits bone [41].

In vivo reactions to Ca–PSZ ceramics were also analyzed [94]. Cylinders were inserted in the proximal tibial metaphysis of rabbits. One month after surgery, connective tissue was present at the bone ceramic interface; nevertheless 1 yr after the operation direct bone ceramic contact was observed [95]. Neither local or systemic adverse reaction nor carcinogenesis were observed after intraperitoneal injection of Ca-PSZ powders in mice [94].

One can observe from the results summarized in Table 8, that there is general agreement on the absence of local or systemic toxic effects after the implantation of zirconia ceramics into muscles or bones of different animals, neither after powder injection in mice. During tests,

Table 8
Summary of in vivo tests on zirconia ceramics

Ref.	Material	Physical form	Site of implant	Tissue response	Remarks
[1]	Zirconia (6% Y_2O_3)	Pellets	Monkeys femur	No adverse response	Apparent bone ingrowth
[71]	ZrO_2CaO	Porous and non porous Tubes	Rabbit muscle Rabbit and dog's trachea	No adverse response Fibrinos growth in lumen	Faster tissue healing around porous Stability of implants, even when infection occurs
[72]	Flame sprayed ZrO_2 -stainless steel composite				
[73]	Mg-PSZ	Bars	Paraspinal muscle	No adverse response	No differences in bone reaction between alumina and zirconia
[74]		Bars	Rats femur	No adverse response	Differences in bone formation related to site of implant
[75]	YTZP	Bars	Rabbits femur	No phlogosis neither osteolysis	No differences between alumina and zirconia A connective tissue present at the interface in early phase
[29]	YPSZ	Cylinders	Rats paraspinal muscles and Rabbit's bone	No adverse response	No differences among zirconia alumina or titania powders
[76]	CaPSZ	Cylinders	Rabbits tibiae	Direct bone contact 1 yr after surgery	Absence of carcinogenic effects No differences in affinity index with alumina or SUS-316L
[77]	YPSZ	Powder	Intraperitoneal in mice	No local or systemic toxicity	Dense fibrous capsule involved material Osteogenesis related to material's osteoconductivity and tissue osteogenetic capacity
[78]	$ZrO_2 + 5\% Y_2O_3$	Cylinders and screws	Dogs femur	Direct bone contact 96 w postoperatively	
[79]	YTZP	Cylinders	Wistar rats subcutis	Absence of toxic effects	
[80]	Dense zirconia	Bars	Rabbits tibiae (into medullary cavity and transcortically)	New bone formation around implant	

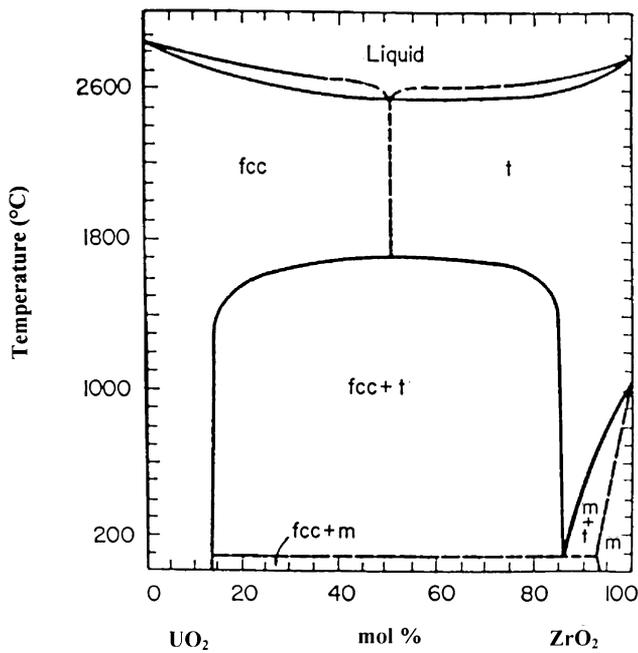


Fig. 7. System UO₂-ZrO₂. Note the wide field of miscibility. (Reprint with permission from Voronov NM, Voitekhova EA, Dalinin AS. Proc. 2nd U.N. Intern. Conf. on Peaceful Uses of Atomic Energy, 1958;6:223. In: Levin EM, Robbins CR, McMurdie HF, editors. Phase diagrams for ceramists. The American Ceramic Society, 1964, Columbus, OH, USA, 70.)

especially in the early postoperative phase, connective tissue is frequently observed at the bone-ceramic interface.

6. Radioactive impurities

Zirconium does not occur in nature in a pure state. It can be found as oxide (ZrO₂ or Baddeleyite) or as silicate (ZrSiO₄ or Zircon) in association with rutile, ilmenite and monazite with significant concentrations of natural radionuclides of the secular chain U-235, U-238, Th-232. Zirconia and uranium dioxide have a wide field of miscibility [99] (Fig. 7). Uranium concentrations up to 3% were observed in some Brazilian baddeleyite [100], and urania and thoria were found associated to zircon in granite rocks [101].

Zirconia powder production processes operate an effective separation of such elements. Nevertheless, uranium, thorium and their decay products can be present at impurity levels in some zirconia powders, their concentrations depending on the powder production process and on the purification level attained. The presence of such impurities can be disregarded in ceramics to be used as refractories or as combustion engine parts, but it has to be carefully assessed in ceramic biomaterials.

The radiation protection aspects linked to the handling of huge quantities of zircon bearing materials, like zircon sands, are well known to people concerned with the safety of workers in the refractory industry [102–104].

In the biomedical field, the attention on the presence of radioactive impurities in zirconia was stimulated by reports [105, 106] concerning high concentration of gamma emitters (up to 11,500 Bq/kg specific activity) in ZrO₂ powders used as radiopacifier in PMMA cements.

In TZP powders and ball heads specific activities were measured some orders of magnitude lower [107] than in radio-pacifiers. The doses to tissues from TZP and Cr-Co alloy ball heads were in the same range, only 1 to 3 times natural background. On the other hand very high levels of gamma activity, approximately 20,000 Bq/kg, in association with alpha emission of about 25 s⁻¹ [108, 109] were detected in Mg-PSZ materials. It is a matter of fact that differences exist among zirconia powders, depending on the chemicals used and on the manufacturing process. High levels of radioactive impurities can be present, but purified materials to be used as precursors for TZP ceramics can reach specific activities lower than that of human bone [110, 111].

Gamma specific activity of about 40 Bq/kg in TZP and 42,500 Bq/kg in a PSZ was found [112]. Depending on the powder used it is possible to calculate the activity of a Ø28 mm zirconia ball head in the range from 2–2100 Bq. This result is to be put in comparison with the human body total gamma radioactivity (about 3700 Bq) mainly due to ⁴⁰K natural abundance.

It was also remarked [113] that although TZPs have specific activities higher than alumina, titanium or Cr-Co alloys, the use of TZP ball heads does not entail doses higher than 1 mSyr⁻¹ which is the dose to the general public due to natural background, conforming to the International Commission for Radiation Protection (ICRP) recommendations [114, 115]. Such results are in agreement with recently published papers [47] which state that the effective dose from zirconia ceramics made out by high purified powders is far below the dose due to natural background.

7. Other zirconia applications in biomaterials

The term Zirconia Toughened Ceramics (ZTC) represent a wide class of materials and microstructures [116]. Besides TZP and PSZ, another ceramic appears promising in biomedical application, Zirconia Toughened Alumina (ZTA). Very little was published on ZTA as a ceramic biomaterial although the results obtained in the development of a manufacturing process of ZTA ceramic ball heads by slip casting were recently reported [117].

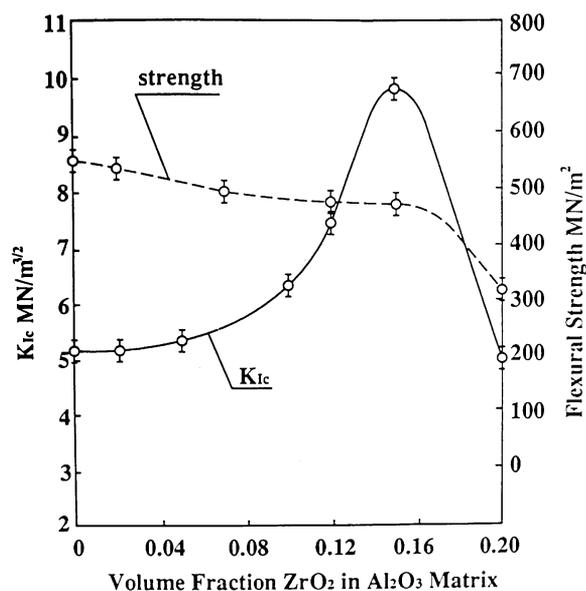


Fig. 8. Fracture toughness and flexural strength of ZTA vs. zirconia content in alumina matrix (Reprint with permission from Clausen N, Fracture toughness of alumina with an unstable zirconia dispersed phase. *J Amer Ceram Soc* 1976;59:49–51).

ZTA structures can be formed by a fine and uniform dispersion of T-phase zirconia in the alumina matrix [118, 119]. The energy of the advancing crack induces a phase transformation of the dispersed zirconia grains, that due to their volume expansion in the T–M transition stresses the brittle alumina matrix, creating a microcrack network around the transformed particle. The fracture energy is dissipated in the phase transformation and in the increase of the crack surface into many microcracks, enhancing toughness. ZTA structures can also be obtained by introducing metastable zirconia polycrystals agglomerates in the alumina matrix [120]. Toughening is due to the cracks that will preferentially cross in their progress the zirconia particles with their Young's modulus lower than the one of the matrix. Stress induced phase transformation of the agglomerates will stop the advancing crack.

In both cases the zirconia concentration in the alumina matrix has to be controlled so that the stresses due to phase transformation of zirconia do not compromise the strength of the ceramic (Fig. 8).

ZTA cylinders were implanted in the femur of monkeys [121] for eight months, in paraspinal muscles of Wistar rats for twelve months [122, 123], in subcutis and in femoral condyles of JW rabbits [88]. In no case were adverse tissue reactions reported. The results of ageing tests are contradictory, probably due to the differences in materials and methods. Bending strength of ZTA containing 5 vol% and 20 vol% Y-TZP after 12 months in vivo ageing do not show variation [122, 123], the same

as the case for samples aged in vivo for 18 months [88]. According to other authors the samples maintained in Ringer's solutions for 19 months show 20% decrease in bending strength [45].

In wear tests, the UHMWPE/ZTA pair show behaviour similar to the one of UHMWPE/TZP [62].

To enhance wear performance of joints in knee prostheses the effectiveness of ZrO₂ layers on zirconium–niobium alloys obtained by high temperature oxidation on metallic femoral condyles was investigated [124, 125]. In wear tests for PMMA pins no wear tracks were evident on the zirconium alloy treated surface [126].

This surface treated zirconium–niobium alloy was tested also in view of its use in hemiarthroplasty [126]. The wear of pins obtained from the osteochondral tissue of the bovine cartilage was tested including CoCr alloy as reference. Against oxidized zirconium–niobium alloy, cartilage pins show wear performance better than against cast or wrought CoCr alloy, wear being more than 50% lower.

A sol gel process based on polymeric alkoxides to obtain zirconia coatings on Ti–6Al–4V alloys was presented by Filiaggi et al. [127]. After treatment at 500°C the film was partially crystalline, with tetragonal and cubic phase. The paper also gives a review of the results obtained by other authors on zirconia coatings.

To complete the overview on the uses of zirconia in biomaterials, it is worthwhile to mention the studies performed on composites formed by hydroxyapatite ceramic (HA) as matrix and zirconia as second phase [128, 129]. Depending the precursors used, on the sintering temperature and on the final density and porosity it was demonstrated that in sintered hydroxyapatite it was possible to reach maximum bending strength ranging from 100 to 150 MPa [130, 131]. Notwithstanding these bending strength values, HA ceramics show fracture toughness relatively low. Fracture toughness as high as 1 MPa m^{1/2} were measured in HA ceramics showing bending strength of 115 MPa. In a wet environment such values drop to 75% of the starting 'dry' values [132]. To obtain a ceramic biomaterial that associates the bone bonding properties of HA to an enhanced toughness, some studies were carried out on HA–zirconia composites.

There is enough experimental evidence that during sintering of HA/zirconia composites, the diffusion of CaO in ZrO₂ takes place, originating the transition from metastable tetragonal to stable cubic phase, for which the transformation toughening is not expected. Also the formation of resorbable phases CaZrO₃, α -TCP and β -TCP takes place.

This behaviour is reported by Wu and Yeh [133] who observed the decomposition of HA in β -TCP and CaO at sintering temperatures over 1150°C. Due to the following CaO–ZrO₂ reaction, the formation of CaZrO₃ took place.

Also Tamari et al. [134] observed the T–C transformation of zirconia after sintering at 1300–1400°C, but they observed the formation of α -TCP phase rather than β -TCP. The composite made out of HA-50 vol% $\text{ZrO}_2 + 2 \text{ mol}\% \text{ Y}_2\text{O}_3$ showed a bending strength of about 400 MPa, and fracture toughness of $3.0 \text{ MPa m}^{1/2}$.

Ioku et al. [135] did not observe tetragonal to cubic phase transition after hot pressing followed by HIP post-sintering at 1050°C, and after the decomposition of HA in β -TCP. The maximum fracture toughness of the composite was $2.8 \text{ MPa m}^{1/2}$, vs. $1.1 \text{ MPa m}^{1/2}$ measured on pure HA sintered at 1050°C and HIP post sintered in the same conditions. Caetano-Zurita et al. [136], reported the increase of toughness in HA-zirconia composites formed by HA, 30 wt% zirconia fibres and 10 to 30 wt% of zirconia powder. In the range 1100–1200°C toughness increased with sintering temperature and apparent density. Above this temperature, the toughness decreased besides the growing density. The higher toughness was obtained with 10% zirconia powder. They explained their results on the basis of a mechanism based on the formation of a reaction layer of CaZrO_3 limiting the diffusion of CaO and then the decomposition rate of HA. Takagi et al. [137], using a process based on colloidal pressing followed by HIP at 1150°C obtained full density composite ceramics with 26.8 wt% zirconia. The XRD of the composites show only the tetragonal zirconia and the HA peaks. The toughness was $2.3 \text{ MPa m}^{1/2}$, twice that of the samples obtained by the same method ($1.2 \text{ MPa m}^{1/2}$). Also the bending strength (3 points – $3 \times 3 \times 10 \text{ mm}$, span 5.5 mm) was about 19% higher than that of pure HA samples. Bending strength up to 380 MPa, more than twice than in pure HA samples (3 points, $5 \times 5 \times 30 \text{ mm}$, span 25 mm) were also obtained. The toughness of the composite was $2.4 \text{ MPa m}^{1/2}$ vs. $0.8 \text{ MPa m}^{1/2}$ of the HA samples [138].

Also small zirconia concentrations may enhance mechanical properties of HA. Bending strength from 61.2 MPa were measured on HA-1 wt% zirconia composites (96.3% TD), vs. 27.2 MPa measured on pure HA (92.4% TD). It must be taken into account that these results were obtained in concentric ring tests ($\emptyset 4 \text{ mm}$ load, $\emptyset 15 \text{ mm}$ support spans) [139]. Zirconia-HA composites were also tested as plasma spray coatings. Chang et al. [140], showed an increase of the bonding strength of the coating from 28 to 35 MPa as the zirconia content in the composite increased up to 10 wt% in spite of the higher porosity due to the presence of zirconia in the HA matrix. The formation of CaZrO_3 in the coating was scarce, as a consequence of the short residence time of the powder in the high temperature plasma. The degradation in bonding strength of HA-10 wt% zirconia coating after 20 d immersion in simulated body fluid (–47% to –49%) was found lower than that of the pure HA coating (–51%) [141]. Also 50% HA-zirconia composite showed in vivo good osteogenic response at three months [142, 143].

8. Discussion

Toughening mechanisms which operate in many zirconia ceramics is the key issue for the use of these materials in structural and in biomedical applications. The studies on zirconia as a ceramic biomaterial, that were started on several zirconia ceramics are now concentrated on the improvement of the performances of TZP for THR ball heads, that were implanted in several thousands worldwide. New applications of TZP are emerging also in dentistry [144, 145, 166].

The interest in the development of Mg-PSZ for biomedical applications, which were reportedly used in THR ball heads [60] in the USA and Australia, was high in the early stages of research and now appears greatly reduced, likely due to the rather coarse grain size of such materials (30 to 40 μm) and to their high residual porosity (2–4%). On the other hand, favourable results were reported [62, 117, 121–123] by the studies performed on ZTA as ceramic biomaterials, although their development appears to be in a preliminary stage. Mechanical properties both static and dynamic of TZP ceramics depend on the control of the microstructure and of its stability in the physiological environment during implant device lifetime. These are the keypoints for the biological safety of the material and for the reliability of components in the specific application, i.e. the two components of the biocompatibility of zirconia as a ceramic biomaterial.

The stability of the microstructure of TZP depends on the stability of the metastable T-phase in a humid environment. Generalized conclusions on TZP degradation in the presence of water are not possible, as TZP ceramics made out by different precursors and different processes will have different microstructural characteristics and different behaviors.

Stable performances of TZP ceramics in a wet environment were reported by several authors [4, 33, 46–49, 146]. Hence there is experimental evidence that TZP stability can be controlled acting on several parameters, as the stabilizing oxide concentration, its distribution, grain size and residual stresses in the ceramic [147].

A relevant aspect for the stability of the material in a biological environment is the presence of glassy phases formed by SiO_2 , Al_2O_3 , TiO_2 and CaO impurities in grain boundaries. These impurities may come from the chemical precursors, from the milling bodies used in powder processing, or may be added to powders as sintering aids. Their presence leads to a loss of stability of the tetragonal phase, as it was demonstrated that aluminosilicate glassy phases in grain boundaries are able to scavenge yttrium ions from TZP grains [17]. Also mullite ($3\text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2$) pockets detected in glassy sintering aids are leading to the loss of stability of the zirconia ceramic in a wet environment.

Mechanical properties depend not only on the microstructure, but also on defects, that in turn are dependent on the characteristics of the starting powders and on the manufacturing process.

In the two cases of zirconia ball head failures reported [5], there are no data on the material microstructure, nor on the taper and bore characteristics. But in the sole ball head examined, which was of the long neck type, the failure that took place 27 months after surgery originated by a crack at the taper-bore interface; metal marks are present at the origin of the failure. The tooling of THR ball heads is the source of surface defects, that are mainly responsible for failures in nanometer size grained ceramics [148]. As the main tensile (hoop) stress is located at the bore-taper interface, flaws in the bore surface are the most critical ones. The tooling of ceramics can be minimized or avoided by using new forming processes that can allow the attainment of near-to-net shape parts.

Defects can be reduced using sintering routes different from the traditional ones, like Hot Isostatic Pressing (HIP). UCL of some 92 kN of HIP treated $\varnothing 22.22$ mm ball heads, vs. 61 kN of ball heads not HIP-treated, as well as improvements in surface finish process leading to very high MOR values in TZP ceramics [54]. UCL of $\varnothing 22.22$ mm ball heads reaching 120 kN is also reported [4].

The mechanical properties of TZP allow the use of ceramic ball heads of diameters $\varnothing 26$ and $\varnothing 22.22$ mm. Diameter reduction may induce beneficial effects on UHMWPE sockets wear. This was shown by the late Sir John Charnley [149], by Livermore et al. [150], by Clarke et al. [151], and by Hirakawa et al. [152], who observed that the ball head diameter has a significant correlation with the rate of particle production. The question is controversial: opposite results were reported [153]. Also the manner in which the stress was applied [154] influences the reduction in UHMWPE wear observed for $\varnothing 22.22$ mm ball heads [155].

The Young's modulus of TZP, of the same order as that of some metallic alloys (Table 3), contributes to limit the strain discontinuity at the bore-taper interface, avoiding taper rubbing which can be the source of metallic debris that were observed during some simulator wear tests on alumina ball heads [156]. Moreover, this is coupled with a lower hardness of TZP in comparison to alumina.

The stability of the material also is a keypoint for the successful wear performances of the joint: surface T–M transition may in the short term improve the wear performances of the joint due to the compressive layer formed onto the ball head surface, but in successive steps this can lead to excessive amounts of UHMWPE wear due to grain boundaries degradation and surface grain pullout [157, 158].

Wear constitutes a critical aspect in the clinical performance of the prosthesis. In clinical practice, TZP ball heads are coupled with UHMWPE sockets. It is possible to remark that the results of wear tests performed on the zirconia/UHMWPE couple are scattered on several orders of magnitude. The reasons for the results variability are in the differences in the materials used by the different laboratories, in their finish, in testing procedures, etc. Obviously, also UHMWPE quality and processing is to be taken into account [159, 160].

An example of variability of results due to testing conditions and materials is the high UHMWPE wear rate induced [68, 74] by the precipitation of calcium-phosphate on the surface of zirconia ball heads during wear tests in simulated body fluid (SBF). Recently, precipitation of hydroxyapatite on the surface of CaO–SiO₂ glasses containing 13 wt% ZrO₂ in SBF was reported [161]. On the basis of these findings, one can hypothesize either the presence of intragranular glassy phases in the ball heads tested or ascribe the calcium phosphate formation to SBF degradation during the test. It has to be remarked that calcium phosphate precipitation was not observed on ball heads retrieved after three years implantation [146]. Notwithstanding the scatter in test results, when looking at the set of values obtained by each laboratory it can be observed that there is almost general agreement on the fact that UHMWPE wear against zirconia is not higher than (and in most of cases lower than) against alumina, both ceramics showing better wear behaviour than metals in coupled with UHMWPE. The reduced wear is mainly due to the extremely regular surface topography of ceramics [75]. Moreover, if confirmed in clinical trials, the results obtained in laboratory tests on zirconia/zirconia or zirconia/alumina wear couple will bring new developments in artificial joints [165].

Biocompatibility of zirconia was evaluated using in vitro and in vivo tests. In vitro tests were performed on different materials (powders or compacts, different composition and impurity levels, etc.), different cell lines in different biological conditions (fibroblasts, PHA stimulated lymphocyte) with similar positive results. Negative results were observed as a consequence of the degradation phenomena in the structure of the material. Cytotoxic reactions observed on cells cocultured with PECF used as a lubricant [83] in wear tests is not specific for zirconia ceramic but is very likely due to the presence of submicron sized particles of zirconium hydroxide in the liquid. The formation of Zr–OH and Y–OH bonds at the surface of Y-TZP in water after chemical adsorption of H₂O at the surface is a clear indication of material degradation in progress [34].

Another indicator of material degradation is the release of yttrium ions observed in vitro tests [82], but not detected in vivo.

The results of *in vivo* test, performed on different animal models, never show adverse reaction in spite of the differences among materials, shape of samples, site of implantation and evaluation method selected. Several authors [38, 94–96] have observed direct bone–ceramic contact. Nevertheless at the early stages connective tissue was present at the interface. The origin of that tissue, which plays a major role in stress distribution in the early stage of bone response, is to be related to shear stresses that originate at the interface between a material and a tissue (ceramic and bone) with different Young's moduli [162]. Moreover, according to Chang et al. [163], bone metabolic response to ceramics may be influenced by the implant site, because the osteogenic activity of medullary cavity is very low in comparison to the one of the periosteum and endosteum. It is worthwhile to remark that implant sites and animal models may induce different responses related to the different stresses transmitted.

High levels of radiochemical impurities were determined on samples of powders used as radiopacifier in bone cements, or on Mg-PSZ ball heads. These results, achieved on materials completely different from the TZP used in ball head manufacture constituted for several years the obstacle to zirconia clinical use. The presence of high levels of radioactive impurities in zirconia ceramic precursors indicates an unpurified material by which it will be very difficult, say impossible, to obtain the desired microstructure, mechanical properties and wear behaviour, i.e. the expected biocompatibility of TZP ball heads. Although high purity powders used for TZP ceramics manufacture show gamma specific activity in the range of 50 Bq kg^{-1} [112], that is well below the 200 Bq kg^{-1} limit set in ISO 13356 Standard that identifies the minimal characteristics required for TZP in clinical implants, the presence and the level of radioactive impurities has to be carefully controlled by TZP ceramic biomaterials producers.

A few research groups are studying the use of zirconia as the second phase in alumina or in calcium phosphate ceramics to improve the properties of these materials. The addition of zirconia to the alumina matrix may give rise to a promising class of would-be ceramic biomaterials (ZTA-zirconia toughened alumina) due to the improved mechanical and wear properties of the composite and due to the lack of negative responses, in the biocompatibility assays performed. In the case of CPC–zirconia composites, results are still controversial. Namely, some authors [134, 138, 139] report enhancement in bending strength and in toughness. On the other hand, the decomposition of HA in TCP resorbable phases and in CaZrO_3 , and the T–C phase transition of zirconia that was observed by several authors [133–136] show different effects on the mechanical properties of the composite. These results show the need for further inves-

tigations to clarify the behaviour of CPC–zirconia composite ceramics.

9. Conclusions

Up to now, among the different zirconia ceramics, only TZP has found wide use as a biomaterial. About 300 000 TZP ball heads were implanted in THR. Breakthroughs can be expected in the future in THR joints and in TKR femoral components.

Improvements in precursors to enhance material stability, in processing to reducing flaws due to tooling of components and in forming techniques to obtain near-to-net-shape parts are fostering the expectations of future developments in biomedical applications of zirconia ceramics.

The following conclusions concerning the use of zirconia as a ceramic biomaterial, can be drawn:

(1) No local or systemic adverse reactions correlatable to the material were detected, neither were cytotoxic effects directly correlatable to the presence of zirconia ceramics or precursors observed in spite of the variety of the materials tested and test methods used (different cell lines, animal models and implant sites).

(2) Mechanical properties of TZP allows the manufacture of $\varnothing 22.22 \text{ mm}$ ball heads suitable for clinical applications. TZP properties allow a high safety factor in terms of low sensitivity to the stress risers in the bore, allowing more flexibility in modular design.

(3) Mechanical properties are dependent on the precursors and on the process selected for the manufacture of components.

(4) The production of TZP ceramic biomaterials demands the use of high chemical and radiochemical purity precursors, as high purity materials can only comply with the levels of hydrothermal stability demanded to TZP in the specific application.

(5) Wear tests show that the tribological behaviour of the UHMWPE/TZP couple are better than the ones of the UHMWPE/metal couple. Moreover, the tribological behaviour of the UHMWPE/TZP are at least similar to the UHMWPE/alumina couples. The feasibility of TZP ball heads in small diameters (down to $\varnothing 22.22 \text{ mm}$) may contribute to the reduction of volumetric wear of UHMWPE sockets.

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