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Ceramics for medical applications: A picture for the next 20 years

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Abstract

High-tech ceramics have always been associated to medical devices: they are used today as femoral heads and acetabular cups for total hip replacement, dental implants and restorations, bone fillers and scaffolds for tissue engineering. Here, we describe their current clinical use and propose a picture of their evolutions for the next 20 years. The need for tough, strong and stable bioinert ceramics should be met by either nano-structured, alumina and zirconia based ceramics and composites or by non-oxide ceramics. Nano-structured calcium phosphate ceramics and porous bioactive glasses, possibly combined with an organic phase should present the desired properties for bone substitution and tissue engineering. The position of ceramics in a gradual medical approach, from tissue regeneration to conventional implants, is discussed.

Keywords: Biomedical applications; Toughness and toughening; Nano-composites; Composites; Lifetime

1. Introduction: clinical use of ceramics, historical highlights and current solutions

Ceramics are generally defined as ‘inorganic, non-metallic materials’. Biomaterials are now defined as ‘natural or synthetic materials suitable for introduction into living tissue especially as part of a medical device’. Considering these definitions, we may argue that ceramics have been used as biomaterials for millenia. In 1972, indeed, Amadeo Bobbio discovered Mayan skulls, some of then more than 4000 years old, in which missing teeth had been replaced by nacre substitutes.[1] Nacre is a natural composite consisting of 95–98 wt.% of calcium carbonate (aragonite, the ‘ceramic’ phase) and 2–5 wt.% of organic matter (fibrous proteins, polysaccharides). In clinical practice, the controlled implantation of bioceramics started late 18th century in dentals with the use of porcelain for crowns and late 19th in orthopedics with the use of Plaster of Paris, or gypsum (calcium sulfate dihydrate) for bone filling.[2] With the advances in the ceramic technology, the 20th century saw more and more ‘high-tech’ ceramics available for medical purpose.[3] Tricalcium phosphate was first proposed in 1920 as a bioresorbable substance to fill bone gaps. However, tricalcium phosphate (TCP) and plaster are weak ceramics, unable to sustain significant loading. The need for tough and strong ceramics was not met before 1965, when the first alumina (Al_2O_3) material dedicated to hip joints was patented.[4] Synthetic calcium phosphate ceramics (together with calcium and/or phosphorus containing ceramics and glasses) and zirconia were then proposed as alternatives to TCP and alumina, respectively. After roughly 100 years of clinical use, we come to the conclusion that there is, so far, no tough and strong ceramic able to create a strong, biologically relevant interface with bone. On the other hand, ceramics and glasses able to promote direct bone-implant adhesion without fibrous soft tissue interlayer are all unable to be used as loaded devices. Bioceramics are therefore generally separated in two families, so-called ‘bioinert’ and ‘bioactive’.

Alumina (and zirconia) ceramics are most often considered as ‘bioinert’ (although a material should never be considered as totally inert), since no direct bone–material interface is created. A soft tissue interlayer always shields the bone from the implant. This biological shielding unfortunately leads to mechanical (stress) shielding, known to promote micro-motion and subsequent aseptic implant loosening. Only under compression, with a porous structure and with a good fit with bone cavity (avoiding relative micro-motion), the fibrous tissue at the interface is thin enough and a successfull bone ingrowth is achieved. Given these restrictions, ‘bioinert’ ceramics are hardly used as bone fillers.

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Table 1
Mechanical properties of different ceramics

Material	Toughness (K_{IC}, MPa m$^{1/2}$)	Threshold (K_{I0}, MPa m$^{1/2}$)	Strength (MPa)	Vickers hardness
Alumina	4.2	2.4	400–600	1800–2000
Zirconia	5.4	3.5	1000	1200–1300
A10Z0Y	5.8	4	700–900	1800
Hydroxyapatite	0.9	0.6	50–60	500
Tricalcium phosphate	1.3	0.8	50–60	900
Mg-PSZ	8	6	600	1000
12Ce-TZP	7.8	5.1	700	1000–1100
Micro-nano-alumina–zirconia	6	5	600	1800
Nano-nano-Ce-TZP–alumina	8.4	4.6	900	1300
Silicon nitride	10*	?	1000*	2500

Toughness (K_{IC}) and threshold stress intensity factor (K_{I0}) were measured by the Double Torsion method (except for values with *, extracted from Ref. 23) and strength by four point bending.

Their major application in orthopedics concerns total hip and knee replacement. The use of bioceramic materials reduces wear rates of bearing components and produces negligible amount of ion release. The clinical success associated to the use of ceramics led to the implantation of more than 3.5 millions alumina components and more than 600,000 zirconia femoral heads worldwide since 1990. There are many reports on fracture rates associated with ceramics, since their intrinsic brittleness is their major drawback.[5] If, in the pioneering days, the fracture rate was quite high (up to 13% for some series), the *in vivo* failure rate reported by the producer of Biolox® alumina is today below 0.01%.[6] A comparable failure rate was claimed by the producer of Prozyr® zirconia heads[7] before the critical event of 2001, discussed below. The current fracture rate of ceramics is therefore negligible when compared to the overall failure rate of implants (mainly due to aseptic loosening resulting from particles release). If the clinical follow up with current alumina ceramics is very good, it must be kept in mind that their use has been restricted so far to a limited number of designs for which the mechanical loading is less demanding. This is related to their modest mechanical properties (Table 1). In the 1990s, yttria-stabilised zirconia (Y-TZP) became a popular alternative to alumina as structural ceramic because of substantially higher fracture toughness and strength. The use of Y-TZP has opened the way towards new implant designs that were not possible with alumina, more brittle. Examples are 22 mm Y-TZP femoral heads, and the development of Y-TZP knees. Biomedical grade Y-TZP exhibits the best mechanical properties of single phase oxide ceramics: this is the consequence of phase transformation toughening, which increases its crack propagation resistance. The stress-induced phase transformation involves the transformation of metastable tetragonal grains to the monoclinic phase at the crack tip. It is accompanied by volume expansion and induces compressive stresses which hinder crack propagation. On the other hand, due to this meta-stability, Y-TZP is prone to low temperature degradation (sometimes referred to as aging) in the presence of water.[8] Aging occurs by a progressive tetragonal to monoclinic transformation at the surface triggered by water molecules, which results in surface roughening and micro-cracking. This inevitably impacts the wear performance of hip joint heads, as roughening increases the wear rate of the antagonist part of the prosthesis, while the coupled effects of micro-cracking and wear generate pull-out of zirconia grains. The extension of the micro-cracked, transformed zone also generates defects, that may grow with the transformed zone and lead to delayed failure. Y-TZP manufacturers considered this problem as a minor issue until 2001, when hundreds of failures of Y-TZP heads were reported within a very short period. Even if limited in time and number, and clearly identified to be process controlled, these events have had a negative impact for the use of zirconia in orthopedics. More important, some clinical reports show that yttria-stabilised zirconia can exhibit a progressive ageing degradation even under 'normal' situation, which limits its long-term stability. Orthopedic community now faces the need for tough, strong and stable ceramics as alternatives to alumina and Y-TZP.

Dental applications add aesthetic requirements (colour, translucency) to the mechanical specifications. White to ivory colour gives a clear advantage for oxide ceramics versus metals, which is the reason why research and development are nowadays directed towards metal-free dental prosthetic restorations. Indeed, metal-free restorations preserve soft tissue colour more similar to the natural one than porcelain fused to metal restorations. Moreover, ceramics do not suffer corrosion and/or galvanic coupling as it can be observed for metals. The clinical demand for all-ceramic restoration is increasing and ceramics are becoming important restorative materials in dentistry. Pioneers like Duchateau had only access to conventional porcelain (or more precisely mixture of kaolin, feldspar and quartz), which were later replaced by more translucent feldspathic glasses reinforced by silica inclusions. However, these porcelain based materials still lacked mechanical strength. Therefore, during the last 200 years, a global approach has been to increase the content of ceramic: from silica to alumina reinforced porcelain (in 1960), to glass-infiltrated high strength ceramics (alumina or zirconia) and finally to monolithic ceramics. Translucency of technical ceramics may be achieved with a very fine (submicron) grain size and low porosity content (less than 1%). Fully dense, translucent (yttria-stabilised) zirconia ceramics can be processed with grain size less than 0.5 μm and meet the demand for both natural-teeth-looking restoration and high mechanical strength. For the last 10 years Y-TZP has been considered as the ideal solution for most dental applications. However, long-term *in vivo* studies on its stability in oral environment are still lacking and few reports on *in vitro* stability show that aging could also be an issue. As well as for orthopedic applications, alternatives to Y-TZP shall be needed shortly.

Unlike bioinert ceramics, the requirements for bioactive ceramics are to provide favorable surfaces for bone adhesion and bone ingrowth.[9] On the other hand, the specifications in terms of load-bearing capability are less demanding. Most bioactive ceramics are thus based on calcium phosphate materials (mainly hydroxyapatite, HAP, and tricalcium phosphate, TCP), because their compositions are close to the mineral part of bone.

Since the early 1980s, the most important application of bioactive ceramics has been the coating of orthopedic metal implants, at locations where a strong interface with bone is required (i.e. femoral stems and acetabular metal-backs for the hip joints and tibial and femoral components for the knee joints). These systems represent successful alternatives to cemented prostheses, especially for young and active patients, and are therefore generally associated to ceramic–ceramic couplings. In the mid 1980s, the osteo-conductive properties of calcium phosphate led to their use as synthetic bone grafts, as an alternative to auto-grafts and allo-grafts.[9] Indeed, as compared to auto-grafts, synthetic bone substitute involve less invasive surgery (a two step operation is necessary for the former) and are available in large quantities. As compared to allo-grafts, the risk of rejection is much less important, and the transmission of diseases is avoided. Most of current bone substitutes are porous pieces of biphasic calcium phosphates, i.e. HAP-TCP composites.[10] A careful control of the architecture (volume and morphology of the macro- and micro-porosities) is a key issue for a successful implant, as the macro-porosity controls the access of the tissues and biological fluids to the volume of the substitute, and the micro-porosity the adhesion of the cells and the resorption rate of the calcium phosphate (thus the availability of Ca and P ions for bone reconstruction). The fast *in vivo* resorption rate of TCP, as compared to HAP, allows controlling the overall degradation rate of the HAP-TCP composite, and thus adapting the material to the patient (faster resorption for patients with faster bone reconstruction). Current synthetic bone substitutes market is about 40 million € in Europe, with an expected 12% yearly increase (www.frost.com).

However, current calcium phosphate bone substitutes do not give full satisfaction. Micro- and macro-porosities and their effect on biological properties are not always taken into account, which results in a large variability of physico-chemical properties among current commercial substitutes. Another strong limitation is their brittleness associated to low crack resistance[11] (Table 1), which restricts their use to non-load-bearing applications, and makes them difficult to handle during surgery. Last but not least, their bioactivity should be increased in order to promote a faster and better bone reconstruction. We should keep in mind that natural HAP crystals are nano-sized while most synthetic bone substitutes in clinical use are still constituted of micro-sized grains.

2. Advances on ceramics: options for the next 20 years

2.1. The need for tough, strong and stable bioinert ceramics

2.1.1. Next 5 years: clinical use of alternative zirconia based ceramics and composites

Yttria-stabilised zirconia was the ceramic gold standard in terms of strength and toughness (see Table 1), but its lack of long-term stability is a major issue for medical use. Current research aims at developing zirconia based ceramics and composites that should benefit from phase transformation toughening without suffering surface degradation in the presence of water or body fluid. Before discussing these new materials, a synthetic description of aging is necessary. Detailed analysis is given in Chevalier et al.[12] Aging occurs experimentally in zirconia samples mostly in humid atmosphere or in water. Therefore, today, there are several models that attempt to explain how the presence of water could promote tetragonal to monoclinic transformation in zirconia. Several experimental results show that water radicals penetrate inside the zirconia lattice during exposure to humid atmosphere. Most probably, the oxygen of environmental water is located on vacancy sites and the hydrogen is placed on adjacent interstitial site.[13] This emphasizes the primary role of oxygen vacancies initially present in zirconia on water diffusion rate. In Y-TZP, the presence of numerous vacancies due to the trivalent character of yttrium makes the diffusion rate of water higher than in other zirconia ceramics (i.e. CeO_2 doped ZrO_2). After Schubert and Frey,[13] the penetration of water radicals leads to a lattice contraction, which results in the formation of tensile stresses in the surface grains that destabilise the tetragonal phase. Martensitic transformation of some grains (or part of grains) at the surface can then take place. This nucleation of the transformation leads then to a cascade of events occurring neighbour to neighbour: the transformation of one grain leads to a volume increase stressing up the neighbouring grains and to micro-cracking. This offers a path for the water to penetrate down into the specimen. The transformation occurs therefore by a nucleation and growth process.

In addition to the current improvement of Y-TZP powders (i.e. TZ3Y-E, with a very small – less than 0.5 wt.% – alumina content, which exhibits improved aging resistance), more efficient answers to the aging issue lie in stabilisation mechanisms minimizing the quantity of oxygen vacancies and/or minimizing nucleation and growth kinetics by avoiding contact between zirconia grains. Two kinds of materials are under development today and may be used clinically at large scale within the next 5–10 years:

- Alumina-zirconia composites (referred to as zirconia-toughened alumina, ZTA). The stabilisation of zirconia grains in such composites is achieved thanks to the presence of a stiff alumina matrix. Doping zirconia grains with yttria is not necessary, thus no oxygen vacancy is created. Diffusion of water radicals into the zirconia lattice is therefore strongly reduced. Moreover, for sufficiently low zirconia content (below the percolation threshold) and sufficiently good dispersion, zirconia grains are isolated and propagation of the transformation from one grain to another is avoided. Some alumina–zirconia composites are already implanted or developed by companies (Biolox delta® by Ceramtec being an improved version of these composites, with SrO and Cr_2O_3 additions and alumina grains with platelet-like morphology). They show significant improvement in aging resistance as compared to Y-TZP, and excellent crack resistance. However, there is room for further optimization. Indeed, in these commercial composites, the zirconia content is slightly above the percolation threshold and stabilisation is achieved partly by yttria addition, which lowers the benefits described above. Some composites in which zirconia is the major phase are also under development (sometimes referred as ATZ). However, these composites clearly show significant degree of aging since the major phase is a Y-TZP.

- Ceria and magnesia doped zirconia (respectively Ce-TZP and Mg-PSZ). During the first stage of zirconia development, in the 1980s, different systems, with different dopants, were proposed and characterized. Among them, Ce-TZP, Mg-PSZ and Y-TZP were the most promising. At that period, Y-TZP was preferred for orthopedic applications thanks to its excellent strength (Table 1). A posteriori, considering only strength gave a too narrow picture of the potential of the different options for long lasting implants. First, strength gives only a partial input on the crack resistance of a given ceramic: fracture toughness, K_{IC}, or even better crack propagation threshold (K_{I0}, stress intensity factor below which no crack propagation occurs) give a more intrinsic insight on ceramics crack resistance. We have to remember that strength is always measured on very small samples, well prepared and polished, while real implants contain inevitably extrinsic defects (such as machining defects). Table 1 shows that under the best processing conditions, with optimized stabiliser content, Mg-PSZ[14] and particularly Ce-TZP[15] may be more than competitive versus Y-TZP in terms of toughness. Second, the consequences of aging were also underestimated during the first developments of zirconia. Knowing the critical consequences of low temperature degradation on implants, the choice of aging resistant zirconia ceramics such as Mg-PSZ[16] and Ce-TZP[17] is obvious.

Fig. 1 compares the aging resistance of alumina, 3Y-TZP, ZTA with roughly 20 vol.% Y-TZP, ZTA with 10 vol.% yttria-free zirconia, ATZ with 80% Y-TZP and 10 mol.% ceria stabilised zirconia. When available, crack resistance curves of these materials are plotted in Fig. 2.

Although ZTA materials are becoming more and more widely used in clinical practice, Ce-TZP and Mg-PSZ may be viewed as competitive materials. Mg-PSZ is now developed for femoral heads in total hip replacement.[16]

2.1.2. Next 10 years: clinical use of nano-structured ceramics and composites

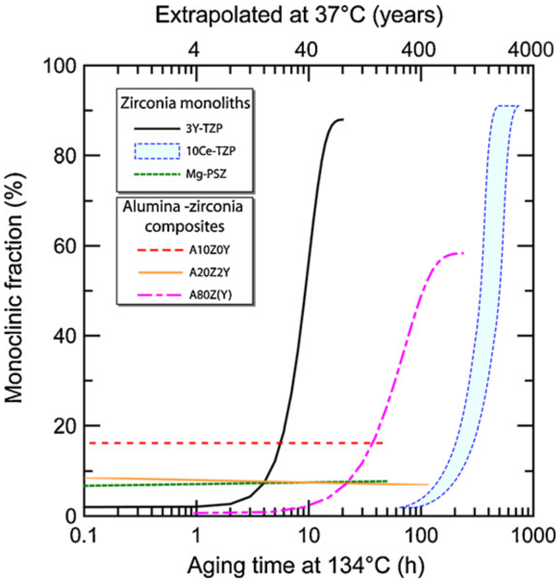


Fig. 1. Aging resistance of 3 mol.% yttria-stabilised zirconia (3Y-TZP), 10 mol.% ceria stabilised zirconia (10Ce-TZP) (12Ce-TZP is even more resistant), magnesia-stabilised zirconia (MgPSZ), zirconia-toughened alumina with 10 vol.% yttria-free zirconia (A10Z0Y), zirconia-toughened alumina with roughly 20 vol.% Y-TZP (A20Z2Y) and alumina-toughened zirconia with 80% Y-TZP [A80Z(Y)]. Note that for Ce-TZP, Mg-PSZ, A10Z0Y and A20Z2Y, aging does not occur in the timeframe of orthopedic applications.

Nowadays it is difficult to avoid the word "nano" in a scientific paper. However, disregarding this somewhat despicable consideration, one must admit that nano-structured ceramics may offer some specific improvements versus micro-structured ones. Considering inert ceramics biomedical devices, we can expect higher hardness resulting in better wear behaviour, specific toughening mechanisms that may in some cases improve crack resistance, and better translucency (potentially interesting for dental restorations).

According to us, wear behaviour of ceramic devices is already better than sufficient, thus its improvement can be considered as secondary. The improvement of wear properties does not justify by itself the risks (mainly possible health hazards due to the strong reactivity of small particles exhibiting large specific surface areas) and difficulties (larger efforts for ceramic processing in terms of disaggregation and sintering) inherent to the

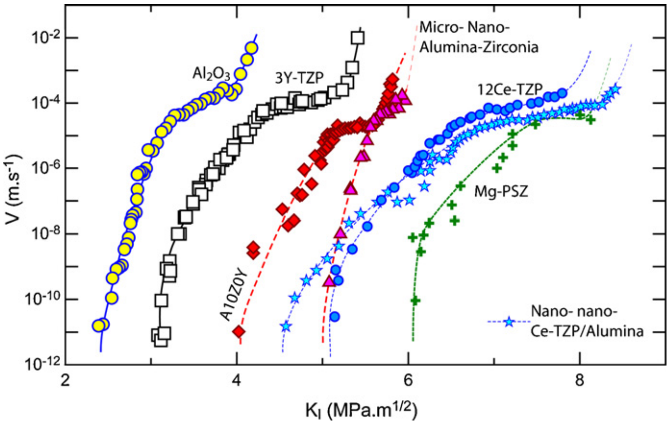


Fig. 2. Crack propagation resistance of alumina, 3Y-TZP, 12Ce-TZP,[15] Mg-PSZ,[14] A10Z0Y, micro-nano-alumina–zirconia composite,[19] Nano-nano-Ce-TZP–alumina composite.

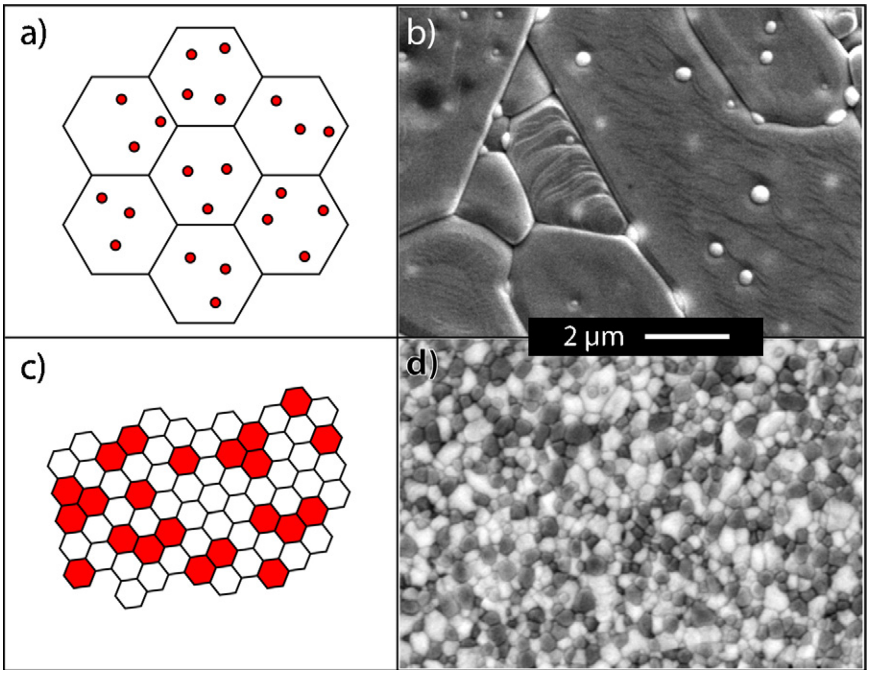


Fig. 3. (a) Schematic drawing of micro-nano-composite, (b) example of such micro-alumina–nano-zirconia composite (from Ref. 17), (c) schematic drawing of nano-nano-composite, and (d) nano-nano-composite (Matsushita Electric Works alumina–zirconia).

development of nano-structured ceramics. On the other hand, improving the mechanical properties, which gives access to new implants designs, is highly desirable. From their introduction around 20 years ago, the mechanical properties of nano-ceramics have been subject to controversies. The pioneering work of Niihara,[18] describing high potential benefits in terms of strength and to a lower extent of toughness, was followed by a general frustration in the 1990s mainly due to the impossibility to repeat his experiments at the time. New progresses in powder synthesis, forming and sintering allow a validation of his insights on a larger range of data obtained on different materials (oxide, non-oxides) systems and different types of microstructures. From the large variety of systems proposed today by ceramic researchers, we will extract the case of nano-composites processed from alumina and zirconia, since they are the most advanced in terms of process control and since the biocompatibility of each constituent is well established. Two strategies are currently explored: alumina rich nano-composites in which zirconia nanoparticles are evenly dispersed in micronic alumina grains (referred to as 'micro-nano-composites') and zirconia rich nano-composites in which both phases are below 500 nm (referred to as 'nano-nano-composites'). Fig. 3 shows a schematic drawing of each type of nano-composite, together with two examples of microstructures. Both strategies aim at increasing crack propagation threshold, tensile strength and materials stability as compared to the micro-scale ceramics and composites:

- Micro-nano-alumina–zirconia composites (*increasing crack propagation threshold of alumina*). In micron size alumina–zirconia composites, the increase in crack resistance is mainly due to phase transformation toughening and to a lower extent to crack bridging. In micro-nano-composites, we shift to another toughening mechanism associated to the presence of large residual compressive stresses around the zirconia nanoparticles (up to 150 MPa compressive stress in the alumina grains, reported in the nano-composite shown in Fig. 3, with only 1.7 vol.% zirconia intragranular particles).[19] Residual stresses are a function of the volume fraction, the size and the location of the zirconia particles. Zirconia particles at grain boundaries would not give rise to such high residual stresses. Therefore, the main challenge lies in the difficulty to confine zirconia nano-particles inside alumina grains. This may be achieved by modified colloidal routes. An example is described in details in Ref. 20 Briefly, the method consists in grafting a zirconia precursor at the surface of micron-sized alumina grains dispersed in a liquid medium. The modified powder is then dried and thermally treated so as to obtain a composite powder with zirconia nanoparticles strongly attached to alumina grains, as it is shown in Fig. 4. A strong benefit of this processing route is that it avoids the manipulation of any nano-powder: zirconia particles, when created, are bound to alumina, without risk of contamination of the atmosphere and health issues.
- Nano-nano-ceria doped zirconia–alumina composites (*increasing strength of Ce-TZP*). Standard Ce-TZP exhibits the largest crack resistance of oxide ceramics but moderate strength and hardness compared to Y-TZP. This is mainly a consequence of larger grain coarsening during sintering. The mobility of grain boundaries is indeed much higher in Ce-TZP than in Y-TZP. It is therefore difficult to obtain a fine-grained, fully dense Ce-TZP. With the aim of developing ultrafine Ce-TZP based ceramics, Nawa[21] has developed a 10 mol.% Ce-TZP–alumina nano-composite. In this compos-

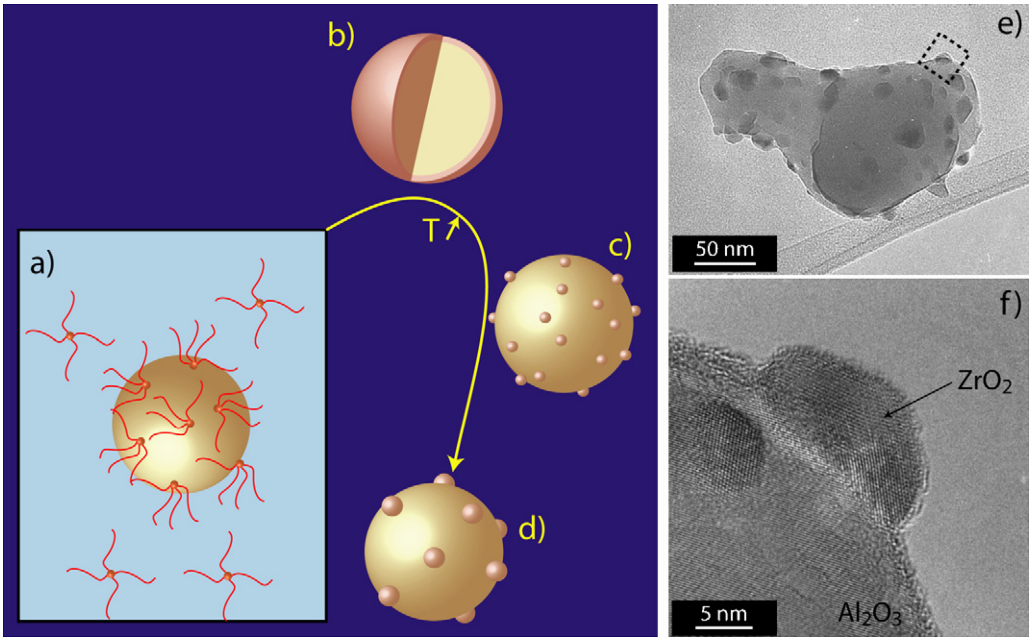


Fig. 4. Alumina–zirconia composite via modified colloidal route: (a) zirconium precursor and alumina powder dispersed in liquid medium; (b) after drying, alumina powder is coated by a zirconium precursor layer; (c and d) during thermal treatments, the layer discomposes and zirconia nanoparticles nucleate and grow on the surface of the alumina grains; (e) conventional TEM image of such a powder after thermal treatments, showing zirconia nanoparticles on the surface an alumina grain; (f) high resolution TEM of a zirconia grain on the surface of an alumina particle.

ite the Ce-TZP is further doped by small amount of yttria. The sintered material exhibits a grain size around 250 nm for both phases.

Table 1 summarizes mechanical properties available for the two nano-composites, as compared to alumina and Y-TZP. Toughening by residual compressive stresses, associated to the presence of only 1.7 vol.% zirconia nano-particles, increases both toughness and strength as compared to alumina. More important, the micro-nano-composite presents the best slow crack growth resistance (ratio of K_{I0} to K_{IC}) among oxide ceramics. On the other hand, Ce-TZP–alumina nano-composites offer the best balance between toughness and strength. Only wear and fatigue testing on real implants followed by long-term clinical studies will allow a fine tuning of each material for a given application.

Nano-structured ceramics, more than nano-composites (usually opaque, as it is the case of both previous materials), may meet the need for translucency of dental restoration. Translucency is driven by grain size and porosity content and size. It is generally assumed that a grain size well below 1 μm and a porosity content much lower than 1% are absolutely necessary. New fast sintering techniques, such as Spark Plasma and Microwave Sintering or even fast heating rate furnaces, open an avenue to the processing of ultrafine, fully dense ceramic materials offering alternatives to Y-TZP. Examples of transparent or highly translucent ceramics (alumina, YAG, etc.) are already published, but not dedicated to biomedical application.[22] Most of them unfortunately offer poor crack resistance. Research should focus on the development of translucent monolithic ceramics able to resist crack propagation.

2.1.3. *Next 10 years: on the use of non-oxide ceramics in orthopedics?*

Non-oxide ceramics, such as silicon carbide or silicon nitride, are considered to be almost not sensitive to slow crack growth (K_{I0} and K_{IC} being roughly the same), which leads to a better reliability of structural pieces (lower risk of delayed failure). They also possess the best wear properties among ceramics, which makes them preferred candidates for bearings in industry. Best mechanical properties are reached for microstructures containing elongated grains able to bridge a propagating crack. These materials are often referred to as *in situ toughened*, since no secondary phase is necessary to enhance crack resistance. Table 1 summarizes the optimal strength and toughness data for Si_3N_4. Si_3N_4 implants for Total Hip Arthroplasty are currently developed by Amedica Corp., Salt Lake City, UT. They are under clinical trials.[23]

With such interesting characteristics, one may wonder why non-oxide ceramics were not introduced sooner in orthopedics. First, we have to remind that validation of a new material by sanitary authorities is long and costly and that Y-TZP seemed to be the ultimate choice in the 1990s. Second, non-oxide ceramics require more effort during processing: they must be sintered at higher temperatures than oxides and under inert atmosphere. Being harder, they are also more difficult to machine.

Silicon nitride is now approved in terms of biocompatibility, and Y-TZP has shown its limitation. The use of nano-powders, together with the use of innovative fast sintering routes will allow to sinter these materials under moderate temperatures and to develop near net shape sintering to overcome existing technological barriers. As a consequence, we expect the development of silicon nitride in orthopedics within the next 10 years.

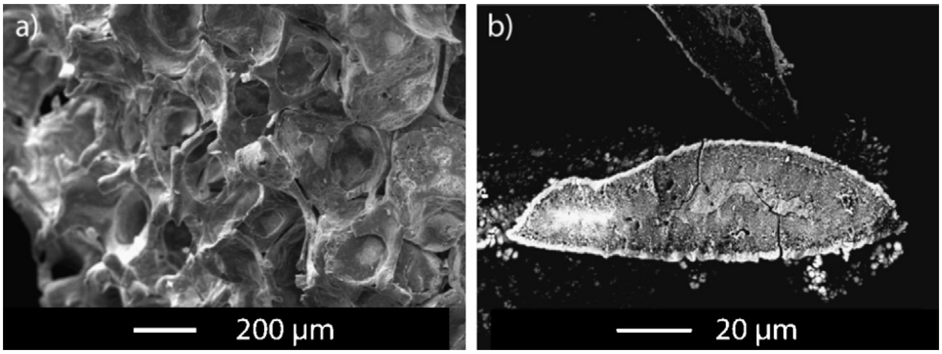


Fig. 5. (a) 45S5 scaffold processed by the polymer foam replication technique; (b) cross section of a strut of the same scaffold after exposure to simulated body fluid: the white outer layer is calcium phosphate; the dark grey layer is a silica-rich, calcium and sodium depleted glass, the inner, light grey part has the composition of the original 45S5 glass.

2.2. The need for tunable bioactive ceramics

2.2.1. Next 5 years: playing with the nano-scale structure of calcium phosphate ceramics

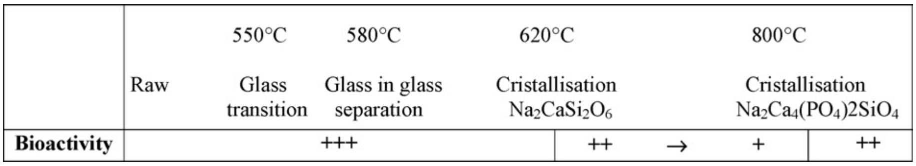
Current calcium phosphate ceramics are typically processed via sintering of submicron powders, and exhibit for most of them a final grain size of more than 1 μm, i.e. one to two orders of magnitude larger than natural crystallites in bone. Nanostructuration is therefore essential for better ion exchange, larger protein adsorption and better cell response. For the same overall porosity, it has been shown recently that nano-structured calcium phosphate bone substitutes (with 200 nm grains) processed using Spark Plasma Sintering exhibited strength and Young's modulus up to twice higher than their microstructured counterparts.[24] Calcium phosphate bioceramics being already approved by sanitary authorities, clinical applications of their nanostructured version may be expected within 5 years.

2.2.2. Next 5 years: clinical use of porous bioactive glasses bone substitutes

As an alternative to biphasic calcium phosphates, there is a renewed interest on the use of bioactive glasses.[25] Bioactive glasses are biocompatible and exhibit an early strong interfacial bonding with bone. Their bioactivity is attributed to the formation on their surface of a hydroxycarbonated apatite (HCA) layer similar to a large extent to the mineral part of bone. This apatite is characterized by nanometer size, non-stoichiometric and partially amorphous grains. The rate of tissue bonding appears to depend on the rate of HCA formation, which follows a well described sequence of reactions between the implanted material and the surrounding tissues and physiologic fluids.[26] The study of different compositions in the ternary Na_2O, SiO_2, CaO system with 6 wt.% P_2O_5 showed that the 45S5 Bioglass® (45 wt.% SiO_2, 24.5 wt.% Na_2O, 24.5 wt.% CaO, 6 wt.% P_2O_5) is the most bioactive glass. Bioglass® is believed to have the ability to promote stem cells differentiation into osteoblasts, the cells which create bone matrix.[27] Moreover it has been shown that dissolution products of Bioglass® have a direct effect on gene expression of osteoblast cells leading to enhanced bone growth.[28] In addition recent work has shown that Bioglass® can also induce a neovascularisation effect promoting the formation of blood vessels *in vitro*.[29] It is nowadays used successfully as middle ear and dental implants[9] but has the potential to be used in many more clinical applications, such as porous architectures for bone substitution and tissue engineering (see Fig. 5). In addition to the possible modification of micro-porosity via sintering temperatures and macro-porosity via forming methods, bioactive glasses offer the opportunity to tailor their bio-activity and mechanical properties via crystallisation process. Indeed, from room to melting temperature, Bioglass® undergoes a series of phase transformation presented in Table 2. Sintered Bioglass® porous structures may then exhibit different crystallinity ratios, grains sizes (from some nanometers to microns) and even crystalline phases. The effect of crystallisation processes on bioactivity are schematically depicted in Table 2.

Phase transformations occurring during thermal treatments lead to a high versatility of final component which is not reached with standard calcium phosphate ceramics. They however make the control of processing much more complex. Indeed, glass transition, immediately followed by glass in glass separation and crystallisation occur at temperatures necessary to release organic compounds generally necessary to process porous architectures. Sophisticated processing routes able to create porous architec-

Table 2
Phase transformation occurring in Bioglass® versus temperature up to 800 °C and their effect on bioactivity



	Raw	550°C Glass transition	580°C Glass in glass separation	620°C Cristallisation $Na_2CaSi_2O_6$		800°C Cristallisation $Na_2Ca_4(PO_4)2SiO_4$	
Bioactivity	+++			++	→	+	++

tures without the need for the critical step of debinding, as it is the case of freeze casting[30] should make the fine tuning of these materials easier.

There is still no clinical use of porous bioactive glasses in orthopedics. *In vivo* evaluation of their expected superiority versus calcium phosphate ceramics bone substitutes is still necessary and time consuming.

2.2.3. Next 10 years: clinical use of organic–inorganic bone substitutes

Calcium phosphate ceramics and bioactive glasses have proven good biological properties and clinical successes in some specific applications and will certainly be improved to a certain extent. However, calcium phosphates and bioactive glasses will always remain brittle, impairing their use for load-bearing applications and making difficult the handling by the surgeon. Since high porosity is absolutely needed for osseointegration, the only way to achieve less brittle bone substitutes is to use intrinsically tougher materials, for example using ceramic–polymer composites. Ideally, taking advantage of both polymer and ceramics qualities allows the processing of materials with stiffness and toughness similar to the bone to be replaced, in order to avoid stress shielding. Such composites can be based either on a polymer or a ceramic matrix.

The polymer matrix approach is the most widely studied. Recent research focus on resorbable porous composite scaffolds constituted of PCL, PLA, polysulfone or their copolymers with additions of inorganic particles or fibres (mainly bioactive glass or hydroxyapatite).[31–36] Each of them presents different biological and mechanical properties, allowing a choice of the right polymer for the right application. However, polymers usually present low modulus (below a few GPa for dense materials) and creep resistance compared to bone. This is the major reason that limits their clinical use for bone substitution.

Sintered ceramic scaffolds will exhibit higher stiffness and creep resistance than ceramic-filled polymers of equivalent porosity. Nevertheless, the ceramic matrix route is much less studied. So far, it consists in infiltrating a sintered ceramic scaffold with a polymer.[37–39] This approach is inspired by the fact that nearly 60 wt.% of dry bone is constituted by an inorganic phase (HAP). We believe that a mineral/organic ratio close that of natural bone will bring better integration of the bone substitute. Thus a material with high inorganic content may be preferred. The addition of a polymer phase to a ceramic scaffold enhances the resilience of the composite[40] (Fig. 6) and allows the functionalization of the surface.[41]

We must keep in mind that the research on organic–inorganic systems (especially ceramic based strategy) is just starting and large effort is needed before clinical use. Sophisticated approaches to incorporate the organic phase to the mineral part are necessary to avoid the use of solvents (latex with bio-polymer nano-particles would be an option) or to improve the contact between the bioactive mineral phase and biological fluids (in this regard, a simple impregnation of a ceramic scaffold by a polymer is still insufficient). The incorporation of water-soluble polymers into a cement paste during setting may be a promising strategy.[42]

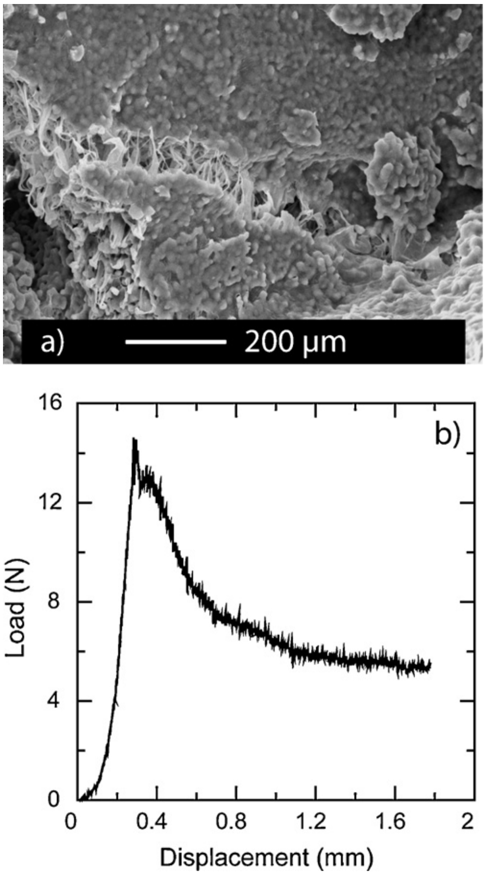


Fig. 6. Polycaprolactone (PCL) coated calcium phosphate porous composite. (a) SEM micrographs showing the presence of PCL fibrils bridging a crack and (b) load–displacement curve, showing a very controlled fracture of the composite, mainly due to the bridging by PCL fibrils.

2.3. New materials and concepts through biomimetic approach

It is noticeable that natural materials range from very simple ones (simple silica beads in the sand for example) to highly complex, multi-scaled materials. Most of these complex materials are originating from living organisms, and some of them show outstanding properties. We may think about the tough spider silk, the strong, lightweight bamboo wood, or the hydrophobic lotus leaf to mention well known examples. However we will focus on bone and nacre. In either materials the interesting mechanical properties arise not only from the association of a polymer (organic) phase with a ceramic (mineral) phase, but also from the complex structural organization.[43,44] To achieve synthetic composites with properties matching these of bone or nacre, one has to take care of both these aspects.

According to Weiner and Wagner,[45] “bone refers to a family of materials each with a somewhat different structural pattern, but all having in common the basic building block, the mineralized collagen fibril”. This basic block can be arranged in different structures, giving among others bone, dentin, cementum and mineralized tendons. Either form of bone present mechanical strength and toughness out of reach from its constituent materials.

Numerous attempts have been made to mimic the structure of bone. Porous calcium phosphate ceramic scaffolds are typical of this approach, but beside their chemical composition, their only common point with bone is their porosity designed to allow bone ingrowth. They offer none of the structural feature of bone at smaller scales, and present no organic second phase. They do however meet clinical success. The next step toward mimicking bone structure is to use organic–inorganic composites. However, the bottom-up approach (such as self-assembled mineralized collagen[46]) gives rise to structures well organized only at the nano-scale (no macroscopic pieces can be obtained yet), while the top-down approach (structures made of polymer coated porous ceramic[40,47] or polymers with ceramic charges) reproduces the macroscopic features of bone without the microscopic ones. An interesting way is to mix these two approaches by mineralizing macroscopic structures in a biomimetic way, as it was proposed by Song et al.[48] who mineralized hydrogels using the change of pH induced by urea decomposition.

Constituted of wavy, sub-micrometric aragonite platelets glued together by a 5–20 nm thick organic biopolymer interlayer, nacre is a lamellar composite exhibiting a twofold increase in strength and a 10-fold increase in toughness over its constituent materials.[49]

Several synthetic nacres have been successfully designed and constructed. For example, Tang et al. managed to deposit successive layers of polymer and montmorillonite platelets, giving rise to micrometer-thick nacre-like structures with tensile strength similar to nacre and a deformation mode dominated by the sliding of layers on one another.[50] However, this sequential deposition technique does not allow the processing of large pieces. More recently, Deville et al. used directional freezing of ceramic slurries to pile up the particles in suspension between the growing columnar ice crystals,[51] resulting in lamellar green ceramics. After sintering, the structure can be infiltrated with a softer material (polymer or metal). Excellent mechanical properties are obtained, mainly through toughening by crack deflection. However some toughening mechanisms of nacre cannot be reproduced yet, such as the collective sliding of the aragonite platelets.[43]

Both bone-like and nacre-like materials may be used for bone substitution, with the hope to replace bone in loaded sites.

Biomimetism as well as tissue engineering are probably more advanced for cartilage reconstruction. A striking example is proposed by Tampieri et al.[52] who developed a tri-layered composite to attach to bone and trigger the development of chondrocytes. The first layer is a hydroxyapatite–collagen composite mimicking bone macrostructure and composition, topped with a collagen–hydroxyapatite interlayer above which a collagen containing hyaluronic acid mimics the cartilage structure. The material greatly helps the cartilage reconstruction, and may represent a significant improvement over the "all-polymer" solutions generally considered for cartilage tissue engineering[53,54] by improving the integration between the cartilage and its supporting bone.[55]

3. The future: the position of ceramics in a gradual surgical approach

So far, regenerative medicine, tissue engineering and synthetic implants are often treated separately by different communities of researchers. They are even sometimes viewed

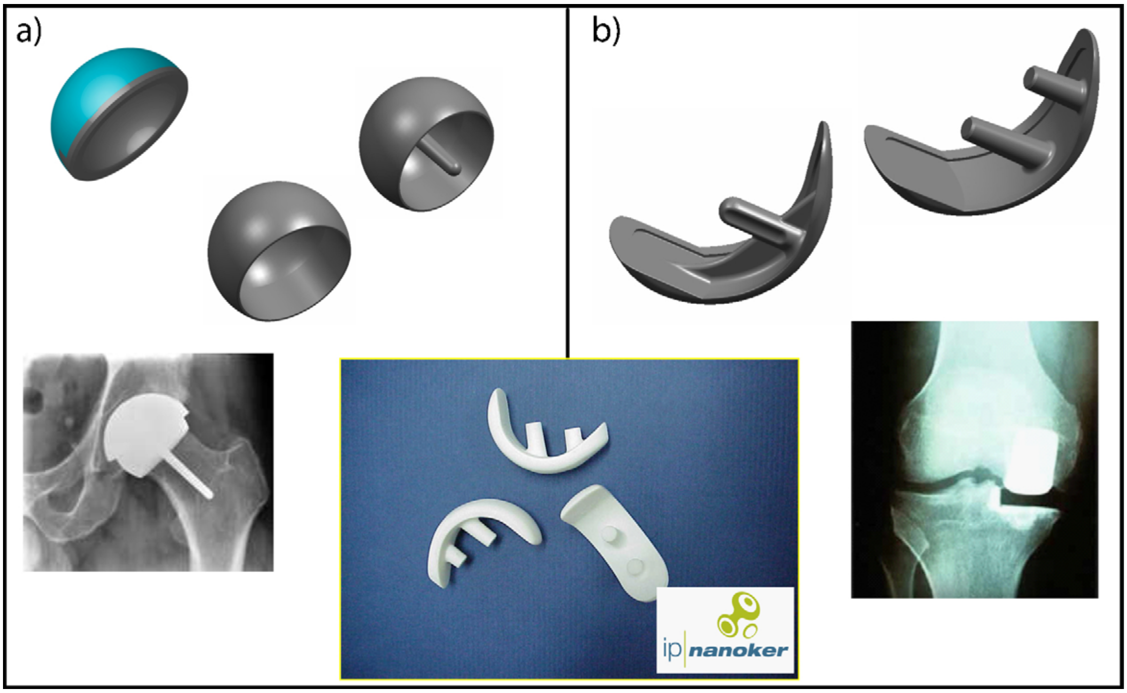


Fig. 7. Design of minimally invasive implants: (a) hip resurfacing and (b) unicondylar knee prostheses. Courtesy Wright Medical Italy and Ceramica Industriale Mongatina. Ceramic resurfacing implants are under the scope of IP Nanoker project.

as competitive approaches. Fortunately, inter-relations between biologists, clinicians and materials scientist are steeply growing and the three strategies are bound to merge in a single, gradual approach. By gradual approach, we mean a progressive treatment of a given tissue disease using at each step the right answer with the least invasive procedure. Concerning orthopedics and dental applications, for which ceramics are used today, the gradual approach may be the following:

1. Tissue regeneration without biomaterial.
2. Tissue engineering assisted by bioactive scaffolds.
3. Minimally invasive implants.
4. Conventional implants and prostheses.

Great advances have been made in development of biology, genetic engineering and synthetic drugs. Tissue regeneration may therefore be applied, when possible, with drugs able to promote tissue restoration and/or limit the functional consequences of tissue damage. This is the first answer to consider, since no surgery is needed. Tissue engineering may be viewed as the next step, when the damage is too extensive: current concept of tissue engineering lies in the belief that tissues can be regenerated *in vitro* and implanted. The striking example of skin tissue engineering demonstrates this concept. Bone, teeth and cartilage tissue engineering are still far from being applied clinically at large scale to human: in our opinion, this should take from 5 years to cartilage, for which the technique is mastered at laboratory scale to at least 10 years for bone, for which only few reports are available. The concept of nano-scale composites by self assembly for teeth reconstruction has been proposed recently[56] and the culture of dental derived stem cells has been validated in mice.[57] Further effort is needed to apply the technique for human tooth. Bone (and teeth) develop 3D architectures. Therefore 3D scaffolds are required to guide the *in vitro* cell cultures. Moreover, applied stresses and/or strains promote bone cells response. Thus, the ideal scaffolds should be able to sustain mechanical loading and transmit it to the cells. This is the case of next generation of scaffolds described above. Tissue engineering may show its limits when the organ is too damaged or the body unable to repair itself. New implants, designed to minimize the surgical trauma and preserve as much tissue as possible, should then be the next answer, especially for orthopedics. The benefit arising from alumina–zirconia composites and nano-structured materials described in the paper will permit to develop new implant designs that are in the scope of orthopedic surgeons today:

- Hip resurfacing implants, making surgery much less invasive than today;
- Unicondylar knee component, specially designed for Minimally Invasive Surgery. Unicondylar femoral replacement (UKR) should be seen as real resurfacing of the knee joint.

Examples of minimally invasive, resurfacing ceramic orthopedic implants currently developed in the framework of the Nanoker European integrated project are shown in Fig. 7. Conventional implants, such as the Charnley based total hip prosthesis will remain a widely used solution for the next 20 years. In our gradual approach, they will represent in the future the solution to use when tissue engineering and minimally invasive implant are not appropriate. This is for example the case of old patients and/or in the case of revision surgery. These standard implants will also benefit from the new progresses in ceramic materials. They will be safer (risk of failure approaching zero), less bulky (less matter to sustain *in vivo* loading) and longer lasting (lower wear rate and lower risk of aseptic loosening). Dental applications will also benefit from these new ceramic materials, who will certainly meet the demand in terms of stability, mechanical resistance and aesthetic.

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