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Base alumina ceramics with dispersoids: mechanical behaviour and tissue response after *in vivo* implantation

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Base alumina ceramics with dispersoids (BAC) are a new class of ceramics with improved mechanical properties as compared to pure alumina. They are obtained by dispersion of powder within an alumina matrix. Of the three new ceramics studied here, A20Z possesses the best mechanical properties as well as tribological properties superior to those of pure alumina whether it is used in ceramic–ceramic or ceramic–polyethylene combination.

Mechanical behaviour and tissue response after *in vivo* implantation were studied. Small four-point flexion bars obtained by pressureless sintering were implanted subcutaneously in the rat. The mechanical properties were unmodified even after one year from implantation.

The tissue response was studied up to one year on cylinders implanted in the paravertebral muscles of Wistar rats, and was evaluated by qualitative examination of the encapsulating membrane and measurement of its thickness in relation to pure alumina. The tissue responses were comparable for both alumina and the three tested ceramics.

1. Introduction

Total hip prosthesis implantation is becoming more and more common. This, together with the lower age at which implantations are realized, have led to the search for new friction combinations the purpose of which is to lengthen the life of these prostheses. Ceramics represent one of these lines of research.

Only alumina, introduced in the 1970s by Boutin [1] in France, then by Griss [2] in Germany, is widely used throughout the world. It has given good results in clinical practice, in alumina–polyethylene and alumina–alumina combination [3–6].

However, the progress made seems to have reached its limit with the fine grain, very highly pure aluminas which nevertheless remain brittle (low bending strength and fracture toughness), thus making it impossible to manufacture a femoral head less than 28 mm in diameter.

Various methods for increasing the bending strength and fracture toughness have led to the development of new ceramics, among which we have dispersoid base alumina ceramics. They are obtained by dispersion of another powder within the alumina matrix thereby improving its mechanical properties. For monoclinical zirconia alumina (A5Z), it is zirconia in its monoclinical crystalline form, for tetragonal zirconia alumina (A20Z or A20Z2Y), it is yttrium oxide partly stabilized tetragonal zirconia, and for aluminalon (AlON or Aa20) it is aluminium oxynitrite.

These new ceramics, not yet studied in the field of biomaterials, are produced by the classical phases of ceramization: powder attrition, drying, isostatic pressure, fretting in different conditions. The alumina and dispersoids are mixed together during the attrition phase.

Zirconia exists in three crystalline forms according to the temperature: monoclinical up to 1200 °C, tetragonal from 1200 to 2370 °C, and cubic above 2370 °C.

Monoclinical zirconia alumina (A5Z) is composed of 95% aluminium oxide (Al_2O_3) and 5% zirconium oxide (ZrO_2) or zirconia in its monoclinical crystalline form.

During the cooling phase, after fretting, zirconia is transformed from its tetragonal form into its monoclinical form, this transformation being accompanied by an increase in volume of 3–5%, which results in the appearance of micro-flaws in the alumina matrix around the zirconia particles. It is these micro-flaws, if their number and length are carefully controlled, that delay at the crack tip the propagation of the main flaws and thereby increase resistance to stress.

The tetragonal form, stabilized by yttrium oxide, is composed of 78% alumina, 20% zirconia, 2% yttrium oxide (Y_2O_3).

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TABLE I Mechanical properties of the ceramics

		σ_f (MPa)	K_{Ic} (MPa m$^{1/2}$)	E (GPa)	P	d	G_{Ic} (J m^2)
Alumina	HP	610	5	394	0.26	3.98	59
	NF	310	4.25	385	0.26		44
A5Z	HP	670	8.1	379	0.265	4.06	261
	NF	459	5.85	364	0.265		87
A20Z2Y	HP	1128	10.1	349	0.275	4.41	270
	NF	557	6.5	335	0.275		120
Aluminalon	HP	530	3.5	300	0.26	3.92	50
	NF	500	4.2	270	0.26		50

σ_f, Bending strength; K_{Ic}, fracture toughness; E, Young's modulus; P, Poisson coefficient; HP, hot pressing; NF, natural fretting; d, density.

Here, during the cooling phase, the yttrium oxide will stabilize the zirconia and maintain it in its tetragonal form up to ambient temperature. This is an unstable state. When crack propagation occurs, the tetragonal zirconia particles affected by the propagation within the alumina matrix take on their monoclinical crystalline form by absorbing energy. It is this absorption of energy that blocks the main crack, thereby improving resistance to stress. Aluminalon is composed of 80% alumina and 20% aluminium oxynitrite. Fretting is carried out under nitrogen atmosphere.

The mechanical properties of the different dispersoid aluminas are indicated in Table I [7–9]. It can be seen that A20Z is the most resistant. The toughening mechanism increases the resistance to stress by 1.8–2-fold, whatever the degree of optimization of the alumina matrix (purity, grain size).

The tribological behaviour of the ceramics tested and especially of A20Z is of particular interest. Indeed, the latter, with regard to both ceramic–ceramic and ceramic–polyethylene friction, has the same friction coefficient as alumina, but with wear rates 2–3-fold lower [10].

Among the three ceramics tested in comparison with pure alumina, A20Z represents the best compromise between improvement of mechanical and tribological properties.

The aim of the present study was to determine the tissue response to these materials and the evolution of their mechanical properties after *in vivo* implantation because of the little decrease shown for pure alumina [11–14]. Throughout our study, pure alumina was the reference material.

2. Material and methods

2.1. Mechanical behaviour after *in vivo* implantation

The test pieces were small bars (28 mm × 5 mm × 3 mm) cut out from blocks obtained by natural fretting for the determination of the bending strength (σ_f). For the determination of the fracture toughness (K_{Ic}), they had been previously nicked. The alumina matrix was less well optimized than during the first studies of mechanical characterization, which explains why none of the ceramics, have figures as high at t = 0 as in Table I. However, the efficacy of the toughening mechanism remained the same and the ratio between alumina and A20Z with regard to σ_f and K_{Ic} was equivalent. The average roughness was 0.1 μm.

After gamma ray sterilization, the bars were implanted subcutaneously in the rat, thus in non-loaded conditions. The tests were carried out on non-implanted sterilized bars and after one week, 1, 2, 3 and 6 months, and one year of implantation.

They were evaluated in four-point bending tests in comparison with pure alumina by a deforming machine (Schenck-Trebel, RM 25 T, 25 KN). The width was 7 mm for the mid axis, 24 mm for the two end points. The travelling speed was constant (0.1 mm min^{-1}).

2.2. Tissue response

The study of biocompatibility was performed according to a protocol designed after the recommendations given by ASTM [15] and the literature [16–18]. Alumina was the reference material.

The implanted cylinders (2 × 12 mm^2) presented an average roughness of 0.3 μm. A 3 cm midline dorsal cutaneous incision was made under general anesthesia and aseptic conditions, in male Wistar rats weighing about 250 g. Using a trocar the implants were placed in the paravertebral muscles. Each rat received implants: the reference alumina on the right side, the tested ceramic on the left.

The skin was then closed. The animals were sacrificed at 1, 4, 8, 12, 26 and 52 weeks. At each time and for each ceramic four rats were sacrificed.

Under general anesthesia, the paravertebral muscles were removed together with the implant and fixed with 2% glutaraldehyde in 0.2 M cacodylate buffer. They were then rinsed, dehydrated in methanol and embedded in polymethylmethacrylate. A 3 mm thick slice was cut out with a diamond saw at midlength and perpendicular to the axis [19]. The cylinders were then pushed out after freezing. The 5 mm sections were cut out on a Polycut microtome (Reichert Jung) and stained with Masson's trichrome.

The slides were then used for a qualitative assessment of the cellular and fibrous reaction within the encapsulating membrane and for measurement of the membrane thickness, obtained from the mean of the measurements made along the periphery every

300 μm (i.e. 20 measurements per sample), and compared with an unpaired Student *t*-test.

3. Results

3.1. Mechanical behaviour after *in vivo* implantation

Table II and Fig. 1 summarize the results obtained according to the duration of implantation. It clearly appears that the bending strength (σ_f) was stable for zirconia alumina (A5Z and A20Z2Y) but not for pure alumina and aluminalon for which a slight diminution was observed. On the other hand, fracture toughness (K_{Ic}) was stable over time.

3.2. Tissue response

3.2.1. Qualitative study

3.2.1.1. Sacrifice at 8 days (Fig. 2)

3.2.1.1.1. Pure alumina. The implants were surrounded by a membrane exhibiting bipolarity, i.e. one pole normal, the other thicker and more cellular. Areas where the encapsulating membrane extended deep into the muscle were also noted.

We noted a moderate cell density and cell muscular infiltration; four or five layers of macrophages were present on the surface, with fibroblasts in the intermediate layer, and then fibroblasts or monocytes + fibroblasts in the deep layer. A few neovessels and some giant cells were involved in this tissular reaction.

3.2.1.1.2. 5% monoclinical zirconia alumina. The membrane surrounding the implants showed a roughly annular form. Triangular zones of reactional tissue penetrating the muscle were noted.

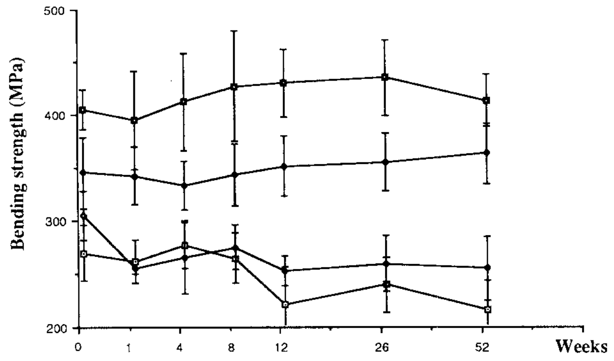

Figure 1 Evolution of bending strength (σ_f) (MPa) (mean values ± S.D. of at least four determinations). (—⊡—) Al_2O_3, (—◆—) A5Z, (—■—) A20Z2Y, (—◇—) Aa20.

TABLE II Evolution of fracture toughness (K_{Ic}) (MPa $m^{1/2}$)

Weeks	Al_2O_3	A5Z	A20Z2Y	Aa20
0	4.9 ± 0.32	5.5 ± 0.72	5.85 ± 0.53	4.1 ± 0.15
1	4.8 ± 0.16	5.05 ± 0.09	5.6 ± 0.31	4.02 ± 0.46
4	4.92 ± 0.15	5.4 ± 0.2	5.65 ± 0.14	4.50 ± 0.6
8	4.7 ± 0.51	5.01 ± 0.05	6.8 ± 0.35	4 ± 0.2
12	4.9 ± 0.13	5.4 ± 0.13	5.85 ± 0.2	3.85 ± 0.18
26	4.92 ± 0.21	5.3 ± 0.18	6.1 ± 0.23	4.2 ± 0.3
52	4.9 ± 0.18	5.2 ± 0.21	6 ± 0.35	4.3 ± 0.28

The surface of the material was associated with some layers of macrophages on the surface, the macrophages were mostly transformed into fibroblasts in the intermediate layer, and in myofibroblasts in the external membrane. Some polynuclears and neovessels were also present.

3.2.1.1.3. 20% tetragonal zirconia alumina. Around the material a membrane displaying bipolarity with slight muscular infiltration was again noted.

At the tissue–material interface several layers of macrophages were observed with some fibroblastic transformations in the intermediate layer; there were monocytes and a few lymphocytes in the deepest layer.

3.2.1.1.4. Aluminalon. Membrane bipolarity was also observed with some triangular zones and average cell density. We found some macrophages on the surface layer and some well-differentiated fibroblasts in the intermediate layer.

For one animal the cellular reaction was stronger, very cellular but also stronger for the controlateral alumina control.

3.2.1.2. Sacrifice at 30 days (Fig. 3a, b)

3.2.1.2.1. Pure alumina. A fibrocellular reaction with low cell density and well-differentiated fibroblasts was found; on some specimens, there were a few macrophages on the surface without any definite active zone.

3.2.1.2.2. 5% monoclinical zirconia alumina. The tissue reaction was weak: fibrocellular reaction, four to five fibrocellular layers with well-differentiated fibroblasts were observed whereas there were some macrophages in the deep layer.

3.2.1.2.3. 20% tetragonal zirconia alumina. Although the tissue reaction was weak and there was a fibrocellular reaction, we noted for one animal the persistence of a strong cellular reaction with membrane bipolarity, the whole remaining active. The cellular density was high, with muscle infiltration. There were macrophages and some giant cells on the surface layer, some fibroblasts in the intermediate layers with some neovessels and mitotic cells.

3.2.1.2.4. Aluminalon. A fibrocellular reaction with low cell density, well-differentiated fibroblasts, and in some places a deep layer of macrophages evolving towards fibroblasts was observed.

3.2.1.3. Sacrifice at 60 days (Fig. 3c, d)

3.2.1.3.1. Pure alumina. An almost acellular fibrous reaction was noted with fibroblasts in the deep layer, sometimes a few differentiating macrophages and some neoformed muscle cells. There was an active pole on one slide with giant cells.

3.2.1.3.2. 5% monoclinical zirconia alumina. An almost acellular fibrous reaction was present with

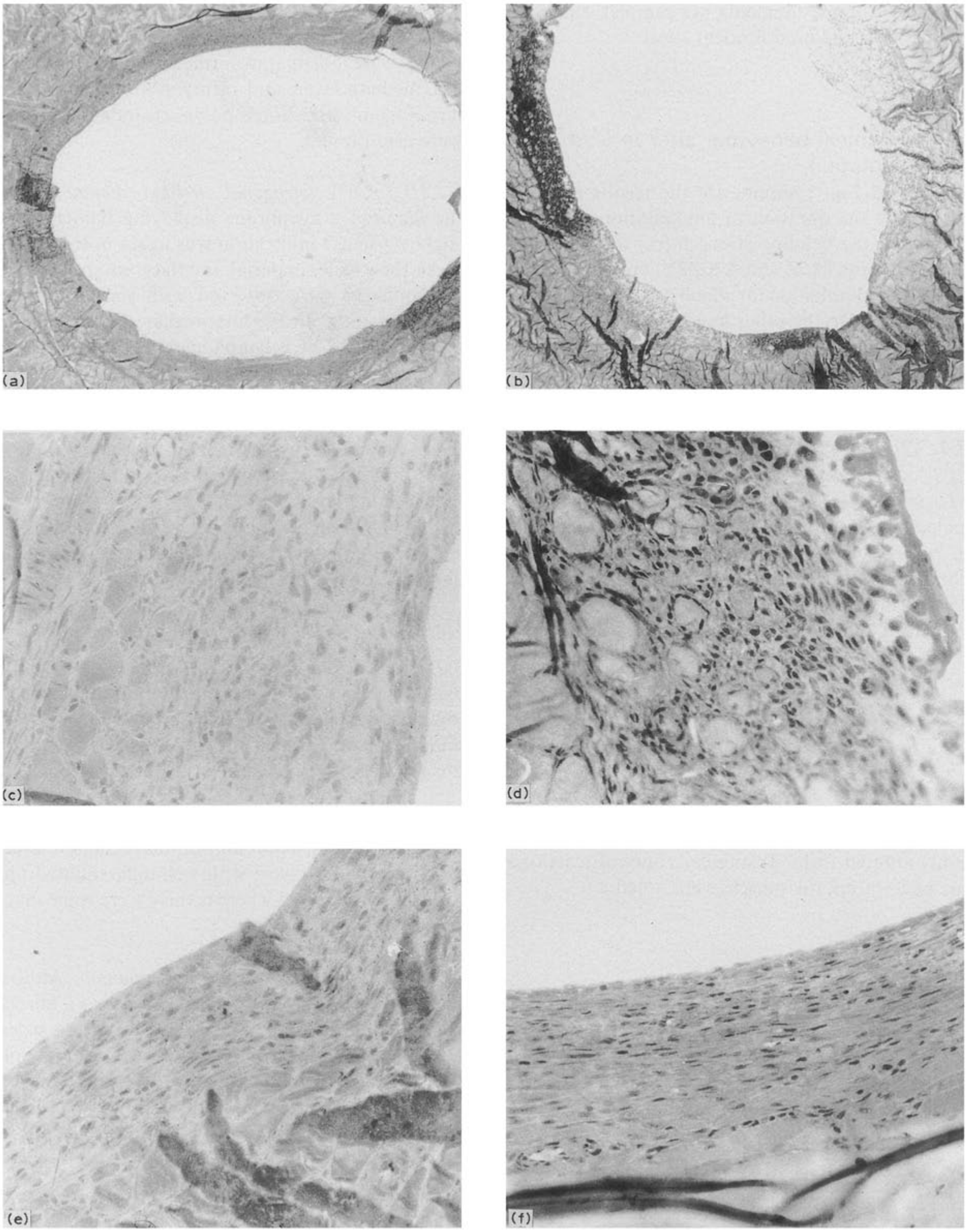

Figure 2 Histological sections one week after implantation. (a), (b) Ph. 1: Al_2O_3–Ph. 2.: Aa20. Encapsulating membrane and surrounding muscle at low magnification (OM = 44). (c) Al_2O_3. Strong tissue reaction: four or five layers of macrophages on the surface near the implant, fibroblasts in the intermediate layer, and fibroblasts or macrophages + fibroblasts in the deepest layer. Presence of neovessels and some giant cells (OM = 280). (d) Aa20. Plasma cells on the surface, macrophages + fibroblasts in the intermediate layer. Evidence of neovessels and some giant cells (OM = 280). (e) A20Z. At the tissue–material interface, presence of two layers of macrophages and then mainly fibroblasts (OM = 280). (f) A5Z. One layer of macrophages on the surface and then mainly fibroblasts. One neovessel (OM = 280).

fibroblasts in involution and some macrophages evolving towards fibroblasts in the deep layer.

3.2.1.3.3. 20% tetragonal zirconia alumina. An almost acellular fibrous reaction was found in the superficial and intermediate layers with more numerous fibroblasts in the deep layer. On one slide there were some macrophages and a small zone of giant cells.

3.2.1.3.4. Aluminalon. A very slight fibrous reaction was observed with fibroblasts in involution in the deep layer, occasionally a few macrophages and an active pole with giant cells on one slide.

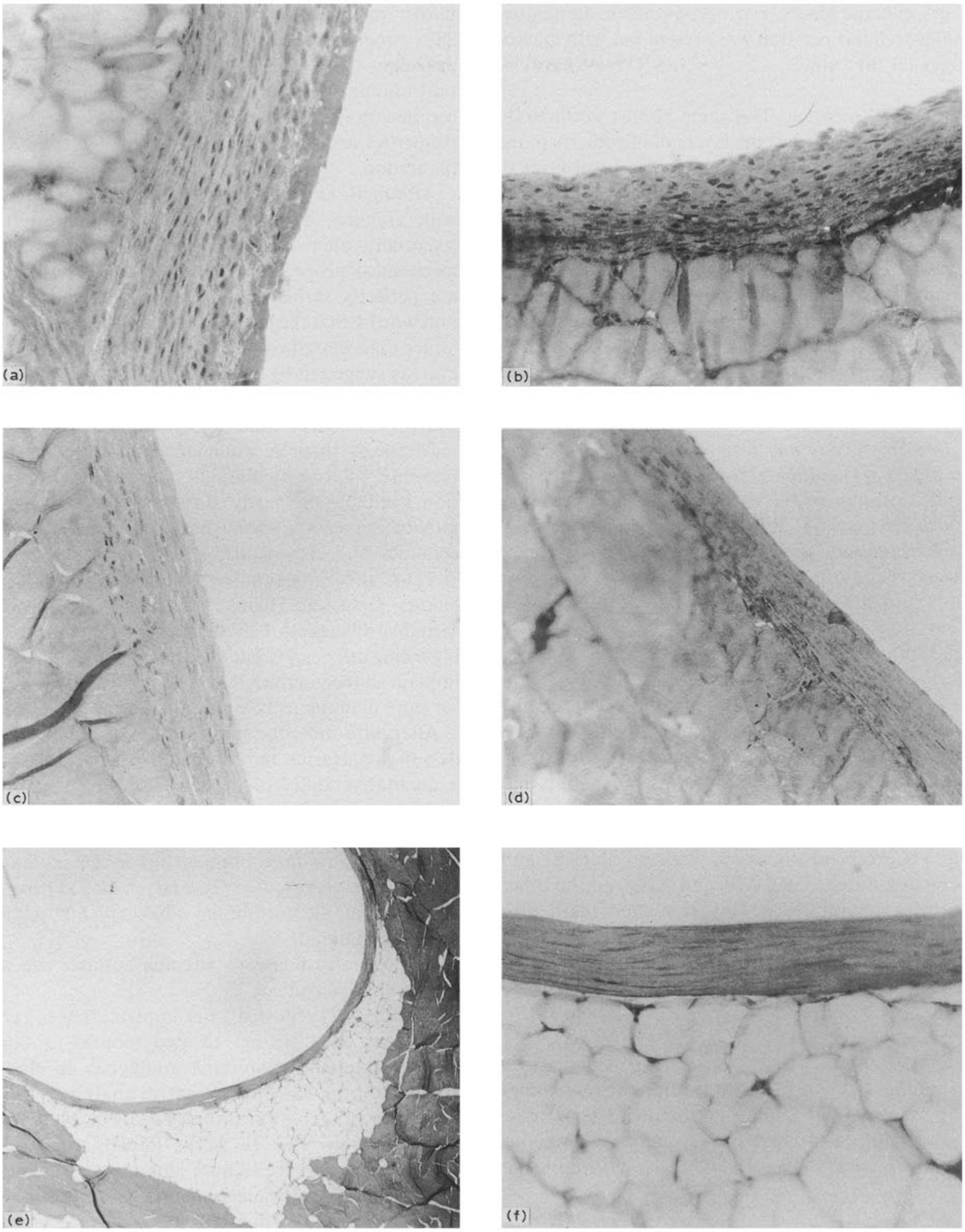

Figure 3 Histological sections of the different materials. (a) A20Z (4 weeks). Macrophages at the tissue–material interface, and macrophages + fibroblasts in the intermediate layer (OM = 280). (b) Al_2O_3 (4 weeks). Thin membrane, few macrophages present at the interface, well-differentiated fibroblasts underneath (OM = 280). (c) Aa20 (8 weeks). Fibro-cellular reaction with well differentiated fibroblasts (OM = 280). (d) A20Z (8 weeks). Low cellular fibrous reaction with a few fibroblasts in the deepest layer (OM = 280). (e), (f) A5Z (52 weeks). (e) At low magnification, almost acellular fibrous reaction with some areas of adipocytes between the membrane and the muscle (OM = 44). (f). At higher magnification, almost acellular fibrous reaction with a few cells (only fibroblasts in complete involution) (OM = 280).

3.2.1.4. Sacrifice at 90 days

3.2.1.4.1. Pure alumina. A very slight cellular fibrosis was found. The fibroblasts were hardly active or in complete involution in the deep layers.

3.2.1.4.2. 5% monoclinical zirconia alumina. A very slight cellular fibrosis was present. The fibroblasts were hardly active in the deep layer, with sometimes a few macrophages and neovessels in involution. In one animal, there were macrophages on the surface but with an analogous controlateral reaction for the alumina cylinder.

3.2.1.4.3. 20% tetragonal zirconia alumina. A very slight cellular fibrosis was observed with barely active fibroblasts. In the deep layer, there were a few macrophages in some places. For one specimen, an analogous fibrocellular reaction was present but with macrophages on the surface.

3.2.1.4.4. Aluminalon. The same almost acellular fibrosis was noted with some layers of fibroblasts in the deepest layer and, for one specimen, a basal layer of macrophages.

3.2.1.5. Sacrifice at 180 days

For all the materials studied, the tissular reaction was almost acellular with the persistence of a few involutive fibroblasts in the deep layer. There was no difference between the four materials.

3.2.1.6. Sacrifice at one year (Fig. 3e, f)

The aspect was comparable with merely a decreased overall thickness of the encapsulating membrane. In some cases a layer of adipocytes was present between the membrane and the muscle. There was no difference between the four materials.

3.2.2. Study of the thickness of the encapsulating membrane

The evolution of the thickness of the encapsulating membrane showed a considerable reduction during the first month, a plateau phase persisting up to six months and a slight decrease between six months and one year.

There was no significant difference between the four materials except at one week, between alumina and aluminalon on one side, A5Z and A20Z on the other side (these quantitative results were concordant with the qualitative findings); and at one month for A20Z when in one animal there was a strong tissular reaction (Fig. 4).

4. Discussion

The findings of the present study and previous studies [7–10] suggest that dispersoid aluminas may represent a solution to increase the resistance of pure alumina to stress. Among these aluminas, yttrium oxide partly stabilized tetragonal zirconia alumina (with 20% zirconia) presents the best mechanical properties as well as tribological properties superior to those of pure alumina whether it is used in ceramic–ceramic or ceramic–polyethylene combination. These mechanical properties are not modified by unloaded *in vivo* implantation.

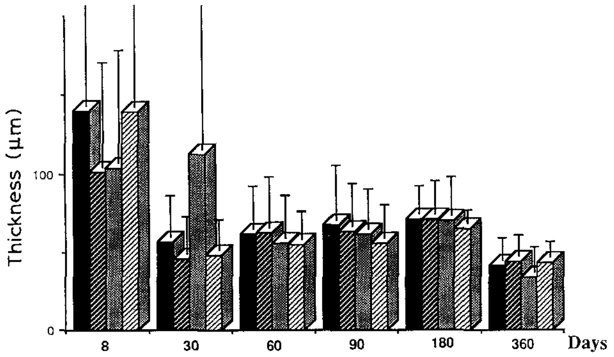

Figure 4 Evolution of the thickness of the encapsulating membrane; (■) Al_2O_3, (▨) A5, (▩) A20, (▨) AlON.

Although, as previously reported in the literature with alumina, a lowering of the bending strength (especially after three months) was obtained, the mechanical properties of the two zirconia aluminas are perfectly stable after *in vivo* implantation. It is noteworthy that the lowering of pure alumina (10%) is larger than described by Osterholm (5%) [11]. However, as suggested by Dalgleish [12], it is not unlikely that the pure alumina used in the present study was less well optimized than in Osterholm's study.

Although there is abundant literature on tissue response induced by alumina, there is little information available on partly stabilized zirconia and no publication on the biomedical use of base alumina ceramics with dispersoids.

Thus, after implantation of parallelepipeds in rat femurs, Griss and Heimke [6] did not find any discernable differences between pure alumina and steel regarding cell density but a membrane thickness at the implant–bone interface that was significantly less than for pure alumina as compared to steel.

After intra-muscular implantation of alumina cylinders in rats, Harms and Maussle [20] concluded from a qualitative study of the encapsulating membrane and measurement of its thickness that pure alumina exhibits good biocompatibility properties. They obtained the same intra-bone results as Griss. Similar results were reported by Escalas *et al.* [21] for the evolution of the membrane thickness but without reference material.

The tissue response to zirconia surfaces are also now well documented.

Oonishi [22] reported, after implantation in rabbit tibias and sacrifices up to two months, a bone–ceramic interface membrane analogous to that of alumina on the basis of qualitative analysis.

Wagner [23] confirmed these results by a quantitative evaluation after 12 weeks implantation in rat femurs with reference to pure alumina.

In the absence of reference material included in their study, Shiraishi did not find a significant tissue response after implantation of cubes of zirconia in rabbit femurs and after intra-muscular, intra-articular or intra-medullar injections of powders [24].

Garvie *et al.* [25], after implanting magnesium oxide partly stabilized zirconia cylinders in the paravertebral muscles of rabbits, found a good biocompatibility after semi-quantitative examination, but in their study, again, there was no reference material.

Recently, Christel *et al.* [26], after intra-muscular implantation of cylinders in the rat, found on histomorphometric and quantitative criteria, a tissue response induced by the three types of partly stabilized zirconia that was less marked than for pure alumina. They related this difference on a difference in roughness.

Our observations on the course of membrane thickness corroborate Escalas's [21] and Christel's [26] studies.

These findings concerning the tissue response suggest the absence of ion diffusion around the zirconia implants. This has been previously demonstrated, after intra-muscular implantation in the rabbit, by Laing [27], who showed by spectrometric analysis, the complete absence of diffusion of zirconium ions.

Ion diffusion has also been studied by microradioanalysis after implantation of zirconia in the tibia of a rabbit by Oonishi *et al.* [22] and Soumiya *et al.* [28]. They found no ion diffusion around the implants and in particular of zirconium or yttrium.

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