

# Polyalkylimide: A Nonstable Filler Over Time

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**BACKGROUND** Polyalkylimide hydrogel is supposed to be a permanent, biocompatible implant. However, years after subcutaneous implantation clinical complications are seen.

**OBJECTIVE** To increase the understanding of the changes that occur over time in this subdermal implanted filler.

**MATERIALS AND METHODS** The extruded filler material of 34 patients was evaluated by histologic examination.

**RESULTS** In most patients who had cosmetic disturbances but no complaints, histology showed no immune cells in or around the filler material. In patients with an acute inflammatory response, giant cell invasion was seen in and around the filler material. Patients with chronic complaints showed a neutrophilic cell influx in the extruded filler. In all patients, degeneration and calcification of the material was noted. The polyalkylimide hydrogel changed over time, both macroscopically and microscopically. As in most of the patients no immune response was seen around the filler material, this may indicate that the material is biocompatible.

**CONCLUSION** The authors conclude that a dermal filler should not be judged solely on its biocompatible characteristics but also on the degradation process over time in the human body.

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Polyalkylimide (Bio-alcamid) is a nondegradable hydrogel used for soft tissue replacement. This filling substance is described as a biocompatible endoprosthesis.<sup>1</sup> Polyalkylimide has been used on a wide scale from approximately the year 2000 onward. In the Netherlands, its use has been discouraged after the publication in 2007<sup>2</sup> and a warning by governmental institutions<sup>3</sup> because of the types and rate of complications. The Dutch representative (AB Medical) stopped supplying the substance shortly afterward.

In 2007, the frequency of complications in the Netherlands was rated at 4.6%.<sup>2</sup> However, between 2007 and 2016, the authors have experienced a steady influx of new patients with complications from the substance to the outpatients' clinic. The complication rate is probably much higher than first described. In a retrospective study published in 2012 looking back

for 7 years after treatment with polyalkylimide, George and colleagues report a complication rate of 50%.<sup>6</sup> Complications described due to polyalkylimide are inflammatory reactions, hardening, dislocation, and accumulation of the product.<sup>2,4-6</sup> The last 2 are probably caused by dynamics of the underlying muscles.<sup>7</sup> Two theories have been proposed about the pathophysiology of the inflammatory reactions. Some view this as a foreign body response others regard this as a reaction to biofilm formation around the hydrophilic gel.<sup>8-10</sup>

Early tests with this substance suggested a favorable biocompatibility.<sup>11</sup> In vitro tests with the fresh product showed a very low interference with cell viability, absence of tissue necrosis,<sup>4</sup> and no involvement of neutrophilic lymphocytes, monocytes, and macrophages, such as is regularly seen in foreign body responses.<sup>12</sup> With subcutaneous injections in human

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skin, no significant changes were observed on cell proliferation and cell function 12 weeks after placement of the implant.<sup>10</sup> At the present time, 16 years after the introduction of polyalkylimide as an injectable filler, considering the high complications rate and the type of complications, it must be concluded that over a period of years, this substance is either nonbiocompatible or nonstable; maybe even both propositions apply.

To increase the understanding of the changes that occur over time in this subdermal implanted filler, the authors evaluated the material that they extruded from patients with complications years after a treatment of polyalkylimide.

## Methods

During 2012 to 2015, all patients who consulted the outpatient clinic and presented themselves with complications due to polyalkylimide were evaluated with ultrasound. Information about the amount of product used, the location and depth of injection, and the occurrence of an acute inflammatory reaction was gathered. Taking into account the degree of cosmetic disfiguration in a patient's face and complaints suggesting any (low grade) inflammatory reaction such as itching, swelling, redness, tenderness or pain, and results from the ultrasound examination, it was advised either to leave the filler at rest or to evacuate the product by 18 G needle puncture under ultrasound guidance. Filler material was evacuated from 40 patients and sent for histologic examination.

All patients gave informed consent for the material to be examined. The material was fixed in formaldehyde 4% in phosphate buffer saline. The material was stained with hematoxylin–eosin and examined by light microscopy.

## Results

A total of 41 samples of extruded materials were collected. Seven of these were not included in this study due to wrong handling or preparation of the material or when it turned out to be a different product than

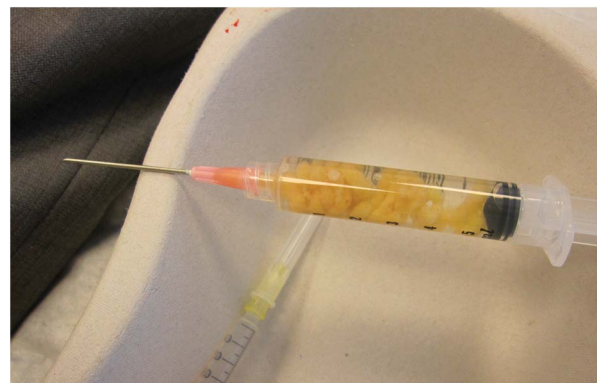
polyalkylimide. In the remaining 34 patients (7 men and 27 women), the polyalkylimide gel fillers had been injected more than 8 years before.

Macroscopically, the extruded filler has a different aspect compared with the original transparent gel that was injected years ago. None of the samples were transparent. Some were whitish and gel-like, but most of them were yellowish and creamy, much like a purulent substance (Figure 1).

The histological findings are given in Table 1. In all the polyalkylimide preparations examined, the material collected showed some degree of degradation, varying from mild to severe (Figure 2). The polyalkylimide particles become smaller and show irregular edges, making a dehydrated impression. In most samples, dehydration and calcification in the degenerated gel were seen. Calcification was not seen in the intact filler parts.

Furthermore, 3 different types of immunological reaction were seen. In all patients, the reaction toward the polyalkylimide filler corresponded with the clinical aspect of the patient in the following ways:

- (1) A total of 25 patients with accumulation of dislocation of the product and hardening of the filler. These patients had no signs of inflammation; actually, they had no physical complication at all besides a disturbing cosmetic aspect. In these patients, no immune cells were seen in or around the filler material. Calcification was seen in the degenerated, dehydrated filler parts.



**Figure 1.** Nontransparent extruded filler.

**TABLE 1. Histology Related to Type of Complication**

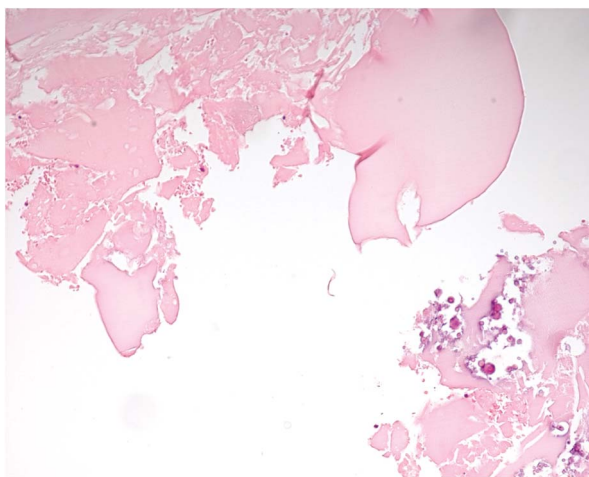
No. of Patients	Type of Complication	Histology
25	Cosmetic disfiguration	Calcification and dehydration
5	Chronic response	Neutrophils, calcification, and dehydration
4	Acute inflammatory response	Giant cells, calcification, and dehydration*

\*One of these 4 patients was HIV+ and besides giant cells, also neutrophils and bacterial influx (streptococci) were seen at histology.

- (2) A total of 4 patients with an acute inflammatory response, clinically visible as swelling, redness, and pain. The material was collected at the time of inflammation. Histologically, in and around the filler, material giant cell invasion was seen. No other immune cells were seen; calcification was noticed (Figure 3, A and B).
- (3) A total of 5 patients with physical complaints of the filler material as changing mild swelling, tingling feeling, itching, and awareness of the material when temperature drops. The extruded filler material showed a neutrophilic cell influx, and some giant cells but no other immune cells were seen (Figure 4, A and B). Calcification was seen in the material.

## Discussion

Polyalkylimide hydrogel is supposed to be a permanent, biocompatible implant. Yet, years after subcutaneous implantation clinical complications are seen, most commonly dislocation, accumulation,

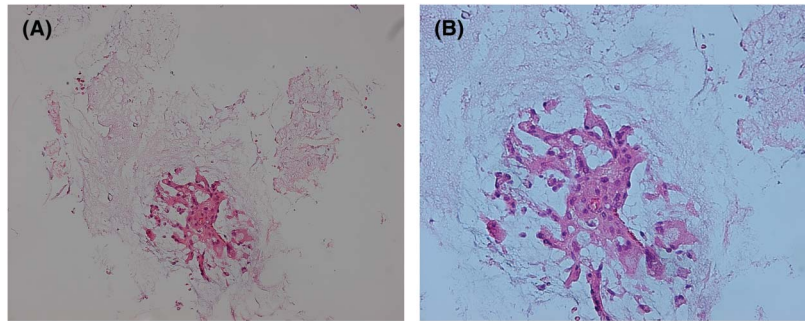


**Figure 2.** Amorphous mass (polyalkylimide) showing degeneration at the lower right site, no immune cells present.

hardening, and more rarely, an acute inflammatory response.

The former 2 the authors assume to be due to underlying muscular activity, leading to either upward movement of the filler or spherical accumulation of the filling substance at 1 central point. Today, these types of complications are considered to be the result of wrong placement of the filler. Subcutaneous injection of volumizing implants is known to lead to these kind of problems.<sup>13</sup> The extruded product of these patients showed no immune cell reaction in or around the implant. This is in concordance with the initial report about polyalkylimide implants, where none or only a very minor inflammatory response with a fibrotic layer around the material was shown.<sup>14</sup> This was found 3 months after implantation<sup>15</sup>; in this study more than 8 years.

Degeneration of the product was seen in all patients, although the degree of degeneration may vary. Even in the same patient, with all the filler material injected at the same time, different histological samples showed a different degree of degeneration. This is in accordance with the clinical aspect of the evacuated material; per patient the filler material may have a different aspect, varying from a purulent substance to a dry and powdery material. Dehydration probably accounts for the nontransparent appearance of the removed product. Polyalkylimide hydrogels have a high capacity for the exchange of water molecules with the surrounding tissue.<sup>16</sup> In vitro, dehydration and calcification of hydrogels have been described.<sup>17,18</sup> Hydrogels which are dehydrated change in structure.<sup>18–20</sup> It seems, however, that this does not automatically lead to complications because the authors observed some degree of dehydration inside the gel in the histology of all patients.



**Figure 3.** (A) Amorphous mass (polyalkylimide) degenerated surrounded with giant cells exclusively. (B) Detail of panel (A).

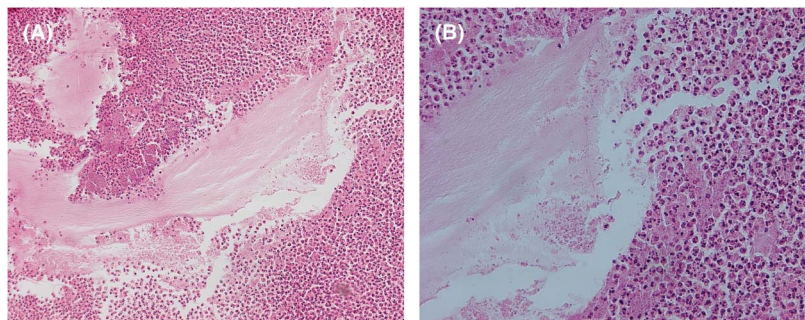
The authors also observed calcium deposits in all samples. The role of calcium in implants is unclear. In some orthopedic biomaterials, calcium deposits are appreciated for the stimulation of osteoclasts. In vitro tests with other biomaterials show that it can act as a potent stimulus of neutrophil activation, as well as causing fibroblast cytotoxicity.<sup>16</sup> Calcium phosphate can drive an inflammatory response and should be carefully monitored and controlled in biomaterials.<sup>17</sup> Although in vitro studies for biomaterials including acrylate hydrogels are available, these are not specific for dermal filler applications and in vitro studies cannot be extrapolated to an in vivo situation.<sup>20</sup>

Five patients in the group had chronic complaints. On histological examination, they showed neutrophilic influx around the filler material. As neutrophils are assumed to be involved at the first stage of a foreign body response, the authors suggest that these patients were stable for a long time and developed an immune impulse toward the filler as the result of an unknown stimulus.

Four patients who presented themselves with acute onset of inflammatory response corresponded histologically with a giant cell influx. It is known that dermal fillers will

induce a foreign body reaction where at first neutrophils and later on macrophages and foreign body giant cells may attach to the surface of the filler material.<sup>21,22,23</sup> It is described that these macrophages and foreign body giant cells may persist for the lifetime of the implant. With biocompatible materials, the composition of the foreign body reaction in the implant site may be controlled by the surface properties of the biomaterial, the form, and the volume of the implant.<sup>23,24</sup> Polyalkylimide was used subcutaneously in large volumes for facial volume loss. Size disparity between the biomaterial surface and the attached cell may induce frustrated phagocytosis.<sup>11</sup> This process does not involve engulfment of the biomaterial but does cause the extracellular release of leukocyte products in an attempt to degrade the biomaterial. The authors hypothesize that this may lead to an ongoing cell infiltration in the hydrogel noticeable as a chronic giant cell reaction. It is uncertain what causes the acute inflammatory response and if a bacterial biofilm is involved.<sup>25,26</sup> Only 1 of 4 patients had a bacterial influx, which explains the presence of neutrophils found in histology.

The authors may conclude that in all patients the polyalkylimide hydrogel filler changed over time, both



**Figure 4.** (A) Amorphous mass (polyalkylimide) surrounded by neutrophils exclusively. (B) Detail of panel (A).

macroscopically and microscopically. This indicates that the material is unstable over time. Furthermore, on histological examination, different types of immune reaction were seen corresponding to the different clinical presentations.

Why some patients do respond with (acute or chronic) inflammation and others do not, remains unclear. A possible explanation might be an immune response caused by a sterile (secondary) inflammatory response or a low grade biofilm.

In most of the patients, however, no immune response was seen around the filler material, indicating that the material is biocompatible. Other characteristics of the product may be responsible for the complications seen. The authors conclude that a dermal filler should not be judged solely on its biocompatible characteristics but also on the degradation process over time in the human body.

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