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Granuloma Reaction: a Complication of Dermal Filler: A Review from an Immunological Perspective

Ali Haider Khalaf*[1], and Hind Mizhir Mousa[2]

[1,2] *Department of Pathological Analysis, University of ThiQar, College of Science, Iraq.*

***Corresponding Author Email:** * ali.haider@utq.edu.iq, hindmousa_pa@sci.utq.edu.iq

ABSTRACT

***Background**: Granuloma is one of the most common complications that appear very late after injection of filler material. Due to the multiplicity of filler materials and the increase in the rate of cosmetic procedures with filler injections, we have witnessed an increase in the rate of occurrence of granuloma. **Objectives:** This review was conducted to shed light on the causes of these complications and why they appear in some products and procedures but not others, with the specific aim of identifying the safest materials and those least likely to cause granulomas. **Methodology**: A narrative review of the literature was conducted using Google Scholar, ResearchGate, PubMed, and the US National Institutes of Health. Search terms included "dermal fillers," "granuloma," and "complications." Twelve studies were selected based on their direct relevance to the topic. **Results**: Granuloma formation is influenced by particle size, surface shape, and injection duration. Particles smaller than 20 µm are more easily ingested, which may delay granuloma formation. Irregular or coarse particles elicit stronger inflammatory responses than smooth, spherical particles. Among the materials reviewed, polymethyl methacrylate (PMMA) showed the highest rate of immune cell infiltration, while hyaluronic acid (HA) showed the lowest. Calcium carboxymethyl cellulose hydroxylapatite (CaHA-CMC) had the lowest reported rate of granuloma formation. Permanent fillers carry a higher long-term risk of granuloma formation compared to temporary fillers. **Conclusion**: The risk of granuloma formation depends primarily on particle size, surface regularity, and duration of tissue retention. Fillers composed of medium- to large-sized, fine, well-purified particles with a limited duration of tissue retention appear to be the safest. Clinically, the selection of appropriate fillers should be guided by these findings.*

Keywords: Dermal filler, Granuloma, Complication, Immune response.

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INTRODUCTION

Human interest in physical appearance and aesthetic features is not a recent phenomenon. History records the first cosmetic procedure in ancient India, performed by the physician Sushruta around 600 BC. With the advancement of civilizations and the development of new techniques and methods in this field, we have arrived at the current range of procedures that are quick to produce results, inexpensive, easily accessible, and, as some claim, relatively safe. One such procedure is dermal filler, which is the focus of this review. This term applies to substances injected into the dermis tissue to increase its volume, enhance its appearance, or even treat certain scars. These substances vary in whether they are natural or synthetic, temporary in effect, or permanent [1]. The filler procedure cannot be considered absolutely safe, as the injected materials are foreign to the body, despite their similarity in structure in the case of hyaluronic acid, and therefore the body naturally has an immune response to them. In order to highlight the inherent risk of such cosmetic procedures, granuloma was chosen for this review because it is the most common late complication of dermal filler procedures, Granulomas are essentially the result of long-term inflammation brought on by foreign objects and persistent infections [2], which may not appear

until years after the procedure, thus diverting suspicion from the primary cause, which is the cosmetic procedure itself.

METHOD

This study is a narrative review of the literature, Search engines, namely Google, Re-search Gate, NIH and PubMed, were used to obtain relevant studies and reviews. The following keywords were used in the search: (Dermal filler, granuloma, complications). Excessive keyword usage was avoided to maintain focus. We did not filter the results based on the last 5 years because there are few studies on this topic and because most of the studies selected for review are recent. Twelve research papers and studies were reviewed, as shown in Table 1. This review is classified as a narrative review. A PRISMA flowchart was not used due to the non-systematic nature of the research methodology.

Material classification

Fillers are usually divided into reversible and irreversible; in the first group are included temporary fillers (collagens and hyaluronic acid), long-term (HA with dextranomer beads, poly-L-lactic acid [PLL] and calcium hydroxyl apatite), and permanent fillers as irreversible (paraffin, silicon preparations, polymethyl methacrylate microspheres, hydroxyethyl-methacrylate fragments, polyalkylimide gel, polyacrylamide hydrogel, polyvinyl hydroxide microspheres in polyacrylamide gel).[3]

At present, the Food and Drug Administration (FDA) has approved polymethyl-methacrylate as the only permanent filler; it consists of polymethyl-methacrylate beads suspended in a bovine collagen solution.[4]

Another type of filler material that naturally occurs is Autologous fat that can be used as an implant material that is adaptable in practice and is typically nonallergenic and well tolerated. In Western middle-aged and older adults, a common cosmetic approach to facial rejuvenation is autogenous fat injection (AFI) into the periorbital or midface region.[5]

Calcium hydroxylapatite–carboxymethyl cellulose (CaHA-CMC), which is used as a filler material, has been associated with several types of immunogenic reactions. Examples include activation of neutrophils and macrophages, along with lymphocyte infiltration and the presence of foreign body giant cells (FBGCs). Across commonly used filler materials, CaHA-CMC shows the lowest reported rate of granuloma formation. In most cases, Ca-HA-related nodule formation is not due to intrinsic immunogenicity but is linked to the injection technique or the specific injection site.[6]

The use of hyaluronic acid as one of the most widespread types of filler globally is not without reason. This acid is considered the safest and most well-tolerated by tissues due to its natural composition, its ability to break down in the future and be absorbed or metabolized by immune cells, and the possibility of eliminating it in case of complications by injecting it with the hyaluronidase enzyme. [3]. HA is a linear polysaccharide composed of repeating disaccharide units of glucuronic acid and N-acetyl-glucosamine. Over the past few decades, a variety of HA fillers have been developed. Skin bioavailability, total HA content, extrusion force, and type and degree of cross-linking are some of the ways they differ [7].

Many manufacturers of these materials (hyaluronic acid) claim that they are safe and do not cause an immune response. [8,9]. However, despite this claim, many complications, especially those related to the immune response, have been recorded after these procedures. [10,11]. These fillers have been used to increase soft tissue volume around the lips and the nasolabial region and to treat soft tissue irregularities. Dermal fillers should be biocompatible, safe, and remain stable at the site of implantation. They should retain their volume, remain pliable, cause minimal foreign body reactions, and not lead to foreign body granuloma[5,6]

Table (1): Summary of studies included in this review.

Source Name	Authors	Study Type	Year of Publication	DOI
Delayed sclerosing granulomatous reaction to dermal filler injection of poly-hydroxyethyl-methacrylate suspended in hyaluronic acid: Histochemical and confocal laser scanning microscopical analysis	Capodiferro S, et al.	Case Report	2019	10.1002/ccr3.2478
Foreign Body Granuloma after Nasolabial Folds Injected with a New Generation Hyaluronic Filler	Kantardjiev V, et al.	Case Report	2019	10.9734/JSRR/2019/v22i2
Foreign body reaction to polyamide filling in the face	Meyer TN, et al.	Case Report	2015	10.5935/2177-1235.2016RBCP0071
Foreign body reactions related to orofacial aesthetic fillers: a systematic review	Santos LG, et al.	Systematic Review	2021	-
Histopathological characterization of adverse reactions to aesthetic filling materials in the oral and maxillofacial region: a multicenter cross-sectional study	Tetzner AC	Dissertation	2024	-
Polymethylmethacrylate-induced foreign body granuloma in the left lower lip	Wu YH, et al.	Case Report	2025	doi.org/10.1016/j.jds.2025.02.001
Upper eyelid granuloma: a rare delayed-onset complication secondary to cosmetic filler injection on forehead	Pao SI, et al.	Case Report	2016	dx.doi.org/10.2147/IMCRJ.S97356
Complications of Collagen Fillers	Lucey P, Goldberg DJ	Review Article	2014	dx.doi.org/10.1055/s-0034-1396904.
Filler augmentation, safe or unsafe: A case series of severe complications of fillers	Omranifard M, Taheri S	Case Series	2011	-
Mesotherapy-Induced Cutaneous Foreign Body-Type Granulomatous Reaction in the Face Treated with Minocycline: Case Report and Literature Review	Zhang Q, et al.	Case Series	2023	doi.org/10.2147/CCID.S403601
Biocompatibility of Injectable Microspheres	Lemperle G	Review Article	2018	10.26717/BJSTR.2018.02.000682
Calcium Hydroxylapatite in Regenerative Aesthetics: Mechanistic Insights and Mode of Action	van Loghem J	Review Article	2024	doi.org/10.1093/asj/sjae196

Complication

As we explained previously, despite claims about the safety of these materials, many complications have been recorded. These complications can be classified by cause into three types: first is due to an error in applying the procedure, the second is due to the material itself, and the third is due to factors specific to the person being injected. The out-come of these complications can also be classified as immediate, delayed, late, temporary, permanent, inflammatory, or non- inflammatory [7].

In general, temporary fillers are considered safer than permanent fillers because they break down and dissolve over time. However, this only applies in the long term. In the short term, side effects are similar for both temporary and permanent fillers because they are all foreign substances that the body generally reacts to [3].

Immediate complications following filler injections include erythema, edema, allergic reactions, lumps, bumps, bruises and possibly necrosis if the filler is injected into arteries. Early-onset reactions may include Staphylococcus or Streptococcus infections, non-inflammatory nodules, hypersensitivity reactions (often type I), changes in skin pigmentation, vascular occlusion, uneven surface contours, and soft-tissue necrosis. Late complications, occurring weeks or even years later, include chronic inflammation, granulomatous nodular lesions, delayed allergic reactions, malar edema, infections related to Mycobacterium species or biofilm and hypertrophic scarring, filler migration, chronic discoloration. [3,12].

Granuloma reaction

A foreign body granuloma is a persistent inflammatory response that encapsulates a foreign material, preventing its migration. This reaction occurs when the immune system cannot phagocytose or enzymatically degrade the foreign particles. The underlying pathophysiology remains unclear. Granulomatous reactions typically develop gradually. True granulomas may arise between 6 and 24 months following hyaluronic acid injection, while simple nodules or lumps may appear earlier than 6 months or as late as 24 months post-injection [7,13]. These lesions present as firm, red papules, plaques, or nodules and may ultimately result in fibrosis. The clinical and histological characteristics of foreign body granulomas vary depending on the type of filler used. Three principal histologic types have been identified: cystic granulomas, which may progress to sterile abscesses and are associated with collagen and hyaluronic acid products; edematous granulomas, linked to silicone and other permanent injectable fluids; and sclerosing granulomas, which are related to particulate injectables such as Sculptra or Artecoll. Acute inflammation is indicated by the presence of neutrophils, epithelioid cells, and multinucleated giant cells [2].

Following biomaterial transplantation, some patients may experience immune or inflammatory responses known as foreign body reactions (FBR). Clinical manifestations include redness, tenderness, pruritus, swelling, and nodule formation at the site, often resulting in a prolonged clinical course [12]. In 87.1% of cases, foreign body granuloma was the most common histologic pattern of inflammation seen in adverse reactions to cosmetic fillers in the face and neck [4].

Morphological properties

Clinically, this complication most often manifests as a well-defined, nodular lesion characterized by slow and progressive enlargement. On examination, the lesion is typically firm to hard in consistency and may be accompanied by erythema or localized skin discoloration without surface ulceration. The lesion can be either tender or asymptomatic, reflecting variability in the underlying inflammatory response. In most cases, the presentation remains confined to the injection site and demonstrates a stable, non-ulcerated morphology, as illustrated in Figure (1) [3,14].

Histological properties

Histologically, these lesions appear under the microscope as distinct polygonal spaces surrounded by fibrous collagen, lymphocytes, macrophages, multinucleated giant cells, and neutrophils around amorphous mucinous artificial material. [3,7].

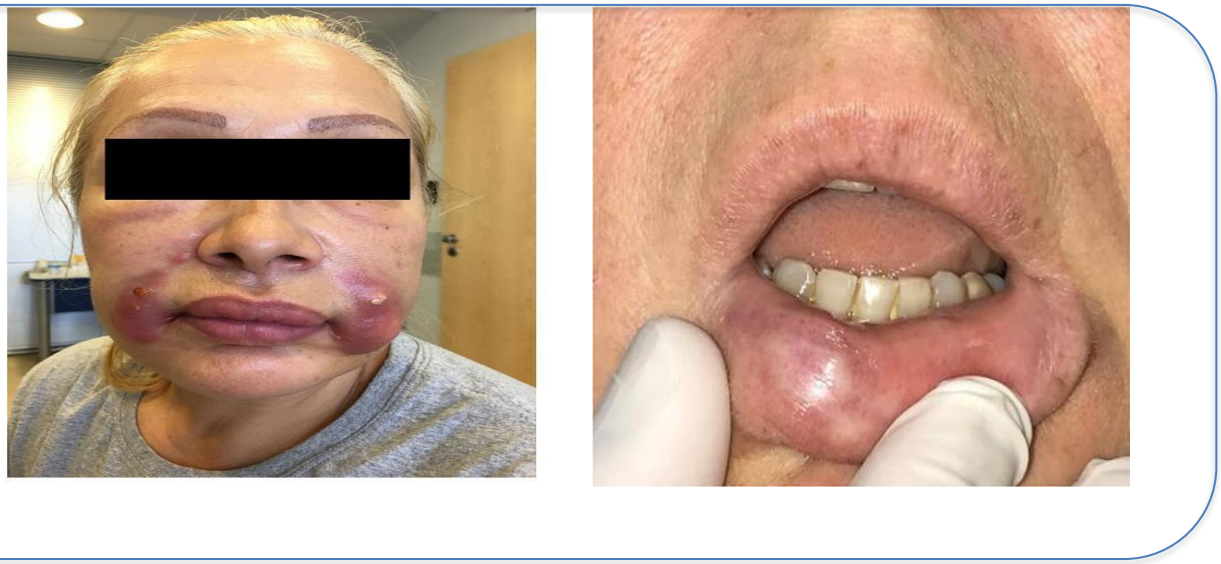

Figure (1) Left: a slow-growing, hard, nodular lesion on the inner surface of the lower lip, right: tender, fluctuating erythematous nodules in the nasolabial folds reproduced from [3,7].

In some cases, they observed the formation of granulomas amidst lympho-mono-histiocytic inflammatory infiltrate, as well as some micro-abscesses in the dermis.[14]. The histological characteristics of granulomas are not at all constant; they vary depending on the injected substance causing the reaction, such as, lipogranulomas linked to long-lasting artificial materials such as silicone fluids often contain vacuoles of different sizes, with a surrounding inflammatory infiltrate that includes lymphocytes, plasma cells, eosinophils, and scattered giant cells. In contrast, foreign body granulomas related to biological fillers such as hyaluronic acid or collagen more often show palisaded granulomatous tis-sue formed mainly by macrophages and giant cells [13].In the long term, the main cells involved in the biological response to uneven surfaces and irregularly shaped particles are macrophages and multinucleated giant cells [15].Hyaluronic acid showed the lowest infiltration of mast cells, eosinophils, and lymphocytes, likely because its composition match-es components naturally present in human tissues [4]

Influencing factors

Late-onset foreign body granulomas after dermal filler injection result from several interacting factors, including the filler's chemical makeup, the patient's immune status, and the size and surface properties of the injected particles. Poly (2-hydroxyethyl methacrylate) (HEMA) suspended in hyaluronic acid (HA) has been reported to be linked with the late development of foreign body granulomas. Although HEMA is added to improve the stability of HA, it has been reported to increase fibroblast growth and to stimulate macro-phages and multinucleated giant cells, which may lead to a foreign body reaction [1].

Beyond material composition, a range of biological, mechanical and immune factors in-fluence granuloma formation in both the early and later stages. These factors include the amount of filler injected, injection site, irregularities, repeated injection of filler at the same site, contamination of the filler that can lead to biofilm formation Biofilms are com-munities of microorganisms that attach to surfaces and can persist while avoiding detection by the immune system. They are generally considered to be about 100 times more resistant to antibiotics. Granuloma formation may be delayed in part because biofilms can slow or alter the local immune response. Also, nearby infections not directly related to the injection site, and systemic infections that may alter immune function.

The physical characteristics of filler particles are also important determinants of granuloma

formation. Phagocytosis efficiency depends on particle concentration as well as particle surface charge, size and morphology. When the total volume of particles is greater than what the recruited macrophages can ingest, these cells tend to cluster together, which can lead to a foreign body reaction. polymethyl-methacrylate is a synthetic filler material composed of medium to large microspheres. Larger particles of this material can activate macrophages and other cellular immune responses, which can lead to stronger inflammatory reactions, such as foreign-body granulomas because size and shape of the implant exceed the diameter of phagocytosable particles. Macrophages, also called histiocytes or phagocytes, typically have an average diameter of about 15 to 20 μm. Particles smaller than 5 μm can be taken up by phagocytosis in both living tissue and tissue culture systems. In clinical settings, macrophages are able to phagocytose particles and microspheres that are up to 15 μm in diameter, and in some cases larger. In some cases, instead of phagocytosing large particles, multinucleated giant cells may form when individual cells cannot engulf the foreign material on their own.

These macrophages, altered by the process, are likely to die from this excessive uptake, which leads to the release of intracellular enzymes. Impurities, especially particles smaller than 20 μm, are more likely than larger particles to induce phagocytosis and immune memory, which may increase the risk of late granuloma formation. Particle size can have two distinct, context-dependent effects on the formation and progression of foreign body granulomas. Particles smaller than 20 μm are more likely to be taken up by macrophages, which can support the development of immune memory and may increase the risk of delayed, chronic granulomatous inflammation. By contrast, medium to large microspheres, including those found in polymethyl-methacrylate (PMMA) fillers, are less likely to be taken up by phagocytic cells and can remain at the injection site for long periods. Their persistence can keep macrophages and other immune cells activated, which may lead to local foreign body reactions and, in some cases, granuloma formation. Also, Surface irregularities, including sharp edges and angular defects, may intensify this process by sustaining a chronic inflammatory response [2,3,4,12,15]. Examples of materials used in filler injections, along with brand names and particle sizes, are shown in Table 2.

Macrophages attach faster to rough surfaces than to smooth, spherical microspheres. Particles with smooth surfaces were mostly covered by fibrous tissue, while particles with rough surfaces were covered by foreign body giant cells [15] .as show in figure (2) In case of autogenous fat injection Adipose tissue collected for AFI is usually stored frozen at -20°C.Many adipocytes do not remain viable during cryopreservation because ice crystals form inside the cells. Injecting nonviable adipose tissue may increase the risk of inflammation due to a foreign body reaction [5].

Mechanism

The infiltration of neutrophils and macrophages, along with the immediate adsorption of various host proteins onto the implanted biomaterial, constitutes key aspects of the etiopathogenesis associated with foreign body response (FBR). The adsorbed proteins regulate both the healing response and the host inflammatory process [12].

One of the most important processes associated with the formation of granulomas is phagocytosis, Phagocytosis is a key part of host defense in which macrophages recognize injected biomaterials and then remove or clear it. The body reacts to these particles based on their surface charge and chemical composition, either by trying to engulf them through phagocytosis or by binding proteins to their surface and enclosing them in fibrous tissue [16].

After the particles are implanted, mononuclear blood cells move into the area around the foreign material. Macrophages and histiocytes infiltrate the tissue after mitotic proliferation of cells in the blood vessel walls. These cells can engulf suitable particles and bacteria within minutes, and they typically survive for only a few hours before they are replaced.

Cells that contain particulate matter do not divide; instead, when these cells die, other histiocytes take up the cytoplasmic inclusions they leave behind.[15].

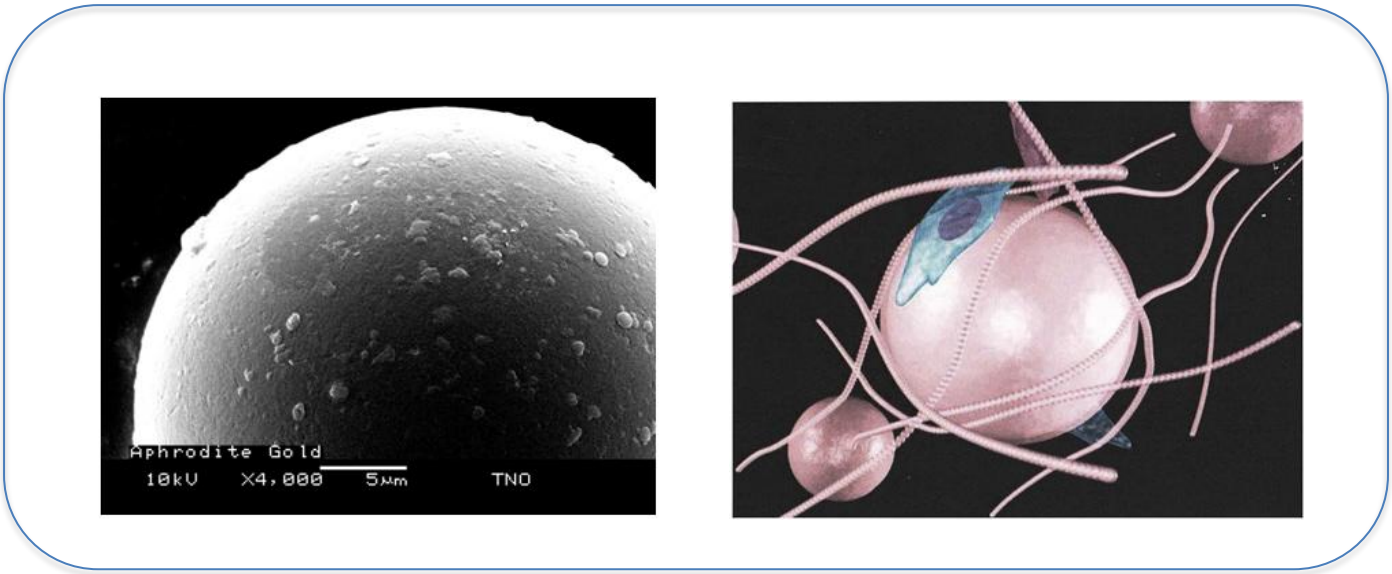

Figure (2) Left: surface shows many irregularities and attached small particles, which are the secret of macrophage stimulation and encapsulation. Right: A microsphere with an absolutely smooth surface absorbs proteins and becomes slowly covered with collagen fibers reproduced from [15].

In case of small particles, hypotheses suggest that phagocytic cells first engulf the small molecules of filler after its breakdown at the end of its life cycle. However, macrophages remain dormant until a new activation process occurs, such as through injury, infection, or even a new cosmetic procedure. This reactivation causes these cells to fuse together, forming multinucleated giant cells and thus creating a granuloma reaction [3,5]. This hypothesis answers the question: why might this type of complication appear so long after filler injections?

Peritoneal macrophages released interleukin-1 only when they were exposed to PMMA particles that could be phagocytosed. Therefore, some granulomatous reactions take so long to appear because their particles can't to be phagocytosed by macrophage and proinflammatory interleukins not secreted.

When large particles such as filler molecules, trigger phagocytosis, a macrophage can fuse into a multinucleated giant cell, typically enlarging from about 40 µm to 150 µm and containing as many as 40 nuclei because in most cases, macrophages cannot phagocytose biomaterial particles with rough surfaces or particles larger than 20 µm in diameter. Instead, they trigger the formation of a foreign body granuloma.

Treatment

The management of foreign body granulomas mainly focuses on reducing the infiltration and proliferation of inflammatory cells so that the lesion can resolve. Initial treatment of-ten starts with systemic corticosteroids and antibiotics, especially when there is clinical concern for infection or possible biofilm formation. If systemic treatment does not pro-vide adequate control, intralesional corticosteroid injections or hyaluronidase may be considered; hyaluronidase is restricted to granulomas related to hyaluronic acid–based fillers [2]. Clinical reports suggest that surgical excision remains the treatment used most often. In one case study, most patients underwent surgical excision of granulomatous lesions (n = 53, 35.8%), and it is often followed

by systemic therapy given as an adjuvant treatment. Postoperative drug treatment mainly involved systemic corticosteroids (n = 37, 25%). antibiotics were given to 9 participants (6%). Nonsteroidal anti-inflammatory drugs were reported in four cases (2%). Enzymatic degradation using hyaluronidase was performed in only a small subset of cases (n = 6). The rate was 4.1% and occurred only in patients who received hyaluronic acid fillers, which suggests that the effect is linked to the specific properties of that material. Taken together, these findings suggest that conservative, minimally invasive approaches can be appropriate in selected patients, but surgical treatment remains central for established or treatment-resistant foreign body granulomas [7].

Table 2: **Materials used in filler injections, brand names, and particle sizes [15].**

Chemical Name	Trademark	Particle Size	Particle Range	Carrier
Permanent Fillers				
Polymethylmethacrylate (PMMA) Microspheres	Artecoll	40 µm	32–48 µm	Bovine collagen
	Bellafill	40 µm	32–48 µm	Bovine collagen
	Permafill (G125, U125)	125 µm	120–130 µm	—
	Metacrill	50 µm	20–80 µm	Carboxymethylcellulose
Hydroxyethylmethacrylate (HEMA)	Dermalive	55 µm	10–130 µm	Hyaluronic acid
Temporary Fillers				
Calcium hydroxylapatite	Radiesse, Coaptite	100 µm	75–125 µm	Methylcellulose
Polylactic acid (PLLA)	Sculptra	46 µm	10–80 µm	Carboxymethylcellulose
Dextran	Deflux	100 µm	80–120 µm	Hyaluronic acid
Hyaluronic acid (HA gel)	Restylane, Juvederm, etc.	Variable	10–100 µm	Hyaluronic acid

DISCUSSION

The inflammatory response to filler material in example of polymethylmethacrylate (PMMA) microspheres depends largely on particle size, particle shape, and surface properties. Several experimental studies report that small PMMA particles, especially those un-der 20 µm, are readily taken up by macrophages and are followed by higher expression of pro-inflammatory mediators, including tumor necrosis factor (TNF) and interleukins [17]. This pattern has been reported across several biological models, including synovium-like settings, suggesting that particle size is an important factor in triggering immune activation. Particle morphology also appears to influence biocompatibility. Particles with irregular shapes tend to trigger a stronger inflammatory response, with higher expression of TNF and prostaglandin E2 (PGE2),

than spherical particles of the same size Macrophages preferentially respond to irregular and rough-surfaced particles because such sur-faces promote protein adsorption, enhance cell adhesion, induce frustrated phagocytosis, and activate pro-inflammatory signaling pathways, thereby increasing the likelihood of foreign body giant cell formation and granulomatous reactions [18,19]. By contrast, larger PMMA microspheres, especially those about 30 to 50 µm or larger, are less likely to be taken up by phagocytosis and tend to trigger only limited inflammatory responses. Particles measuring 32–40 µm generally trigger a mild foreign body response. This response is marked by early formation of a fibrous capsule, with little cytokine release and no observed movement of particles to lymph nodes or to organs elsewhere in the body [20,21,22]. When microspheres have a smooth surface and are well purified, foreign body reactions are uncommon, and the host response tends to favor tissue integration rather than inflammation. With time, implanted PMMA microspheres are enclosed by fibroblasts and collagen fibers, and capillaries grow into the area, so the injected material be-comes a vascularized living implant. This process describes a shift from the early foreign body response toward long-term biostability and compatibility with surrounding tissue [23,24]. Taken together, these results suggest that PMMA designs that favor a spherical shape, smooth surfaces, and particle sizes above the phagocytosis threshold are less likely to cause inflammatory complications, supporting improved long-term safety and clinical outcomes [15].

Finally, when filler injections are necessary, the doctor must choose a type of filler characterized by medium to large particle size and, of course, a smooth surface. In addition, the injection technique is a significant factor in the formation of granulomas; the larger the amount injected or the more injections are administered in the same area, the higher the likelihood of granuloma formation. As for the patient, they should be aware that these procedures can cause delayed complications.

CONCLUSION

Among the materials reviewed, polymethylmethacrylate was associated with the highest infiltration of mast cells, eosinophils, and lymphocytes, while hyaluronic acid showed the lowest levels likely because its composition matches components naturally present in hu-man tissues therefor HA represent safer one, although a study has shown that CaHA-CMC filler has the lowest potential to cause granuloma as a late complication of the cosmetic procedure. The larger the filler particles (above 20 micrometers) and the more uniform their structure, the less immune stimulation they receive, thus reducing the incidence of granulomatous reactions.

The greater the amount of irregularly shaped particles in the filler material, the greater its ability to stimulate the immune system and form a granulomatous reaction.

The results suggest that materials containing medium-sized microspheres may yield the best tissue augmentation, as shown by collagen fibers and fibroblasts forming a ring around the microspheres.

Fillers that consist of medium-large, smooth molecules and do not remain in the tis-sues for long periods are the safest according to our review; this should be taken in-to account when choosing a particular filler for cosmetic injections.

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