

Silicone Allergies and the Eye: Fact or Fiction?

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Objective: The purpose of this manuscript was to review the evidence concerning the role of an allergic reaction to silicone as the basis for the reported increase in contact lens-associated infiltrates in wearers of silicone hydrogel contact lenses.

Methods: A literature review was undertaken to investigate the antigenic properties of silicone and the causes of contact lens-associated inflammatory reactions.

Results: Immune cells cannot interact with silicone directly but can interact with antigens on these lenses. These antigens could be due to tear film deposits, microbial contamination, or components of care systems used with these lenses.

Conclusions: Inflammatory reactions associated with silicone hydrogel contact lens wear are not caused by an allergic reaction to silicone alone.

Key Words: Silicone—Contact lens—Allergy—Inflammation—Corneal infiltrates.

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Contact lenses are widely used biomaterials, which have an estimated worldwide market of \$7.1 billion USD annually and an estimated U.S. market of \$2.4 billion USD.¹ Over the past decade, usage of silicone hydrogel contact lenses (SiHys) have been steadily gaining ground and they now account for 50% to 70% of new lens fits and refits in many mature markets.^{1,2} Despite the improvements in oxygen availability that SiHys provide over older, conventional hydrogel lens materials, SiHys have been linked with the development of various inflammatory reactions, including giant papillary conjunctivitis,^{3–7} infiltrative keratitis,^{8–15} contact lens peripheral ulcers,^{7,16,17} and contact lens acute red eye.^{7,16,17} Of particular note are several recent reports^{8,10,18–21} showing that wearing SiHy materials results in an almost twofold increase in relative risk for infiltrative keratitis. Discomfort, which could also be associated with subclinical inflammation, remains the major reason why patients cease wearing contact lenses^{22,23} and comfort remains relatively unchanged with these new materials.²⁴

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What do patients feel is the cause of this discomfort? Review of health and health-related websites reveals that many wearers are convinced that the discomfort is caused by an “allergy to silicone,” a view shared by some clinicians.²⁵ Is there any truth to these claims that these inflammatory reactions are caused by an “allergic reaction” to the silicone components within these lenses? This review will discuss, from an immunological standpoint, whether an allergic response is plausible or whether such reactions occur due to antigens on the lenses rather than the silicone present in the materials themselves.

THE HUMAN IMMUNE SYSTEM

The human immune system comprises a complex coordination of organs, tissues, cells, and molecules that have evolved to protect against microbial infection.^{26–28} Since life on Earth is carbon based, the immune system is “wired” to only recognize molecules that have a carbon-based chemistry (such as proteins, sugars, nucleic acids), as that may signal “attack” by microorganisms. Sugars and nucleic acids serve as “danger” signals to warn that a pathogen is present, which then triggers an innate immune response, which recognizes general features of microorganisms.²⁸ In comparison, proteins from pathogens are recognized by the adaptive immune system, which uses antigen receptors that are highly specific²⁸ and subsequently targets those pathogens for destruction (Fig. 1).

Innate Immune System Receptors

Receptors of the innate immune system recognize signals derived from common features of invading microorganisms. These are usually repeating patterns of molecular structure, termed pathogen-associated molecular patterns (PAMPs).²⁷ Innate immune system cells, such as specialized antigen presenting cells (APCs) or innate responsive cells like natural killer (NK) or mast cells, can recognize unwelcome visitors via various cell surface receptors on PAMPs (Table 1). APCs also recognize damage-associated molecular patterns (DAMPs).^{29,30} Injury or damage to cells can cause the release of molecules that are not normally secreted, known as DAMPs.^{29,30} APC can activate and initiate inflammation upon recognition of these DAMPs.²⁹

Innate immune system receptors are also referred to as pattern recognition receptors (PRRs).³¹ These receptors, which bind to PAMPs, initiate cascades of internal protein activity either alone or in conjunction with a specialized signaling protein. The activated immune cell responds to the pathogen while simultaneously sending signals to activate many other immune system cells. The macrophage mannose receptor is a classic example of a PRR receptor, which binds particular and different anionic polymers (usually sugar residues found on the surface of pathogens) and initiates the phagocytosis process in which microorganisms are ingested.³²

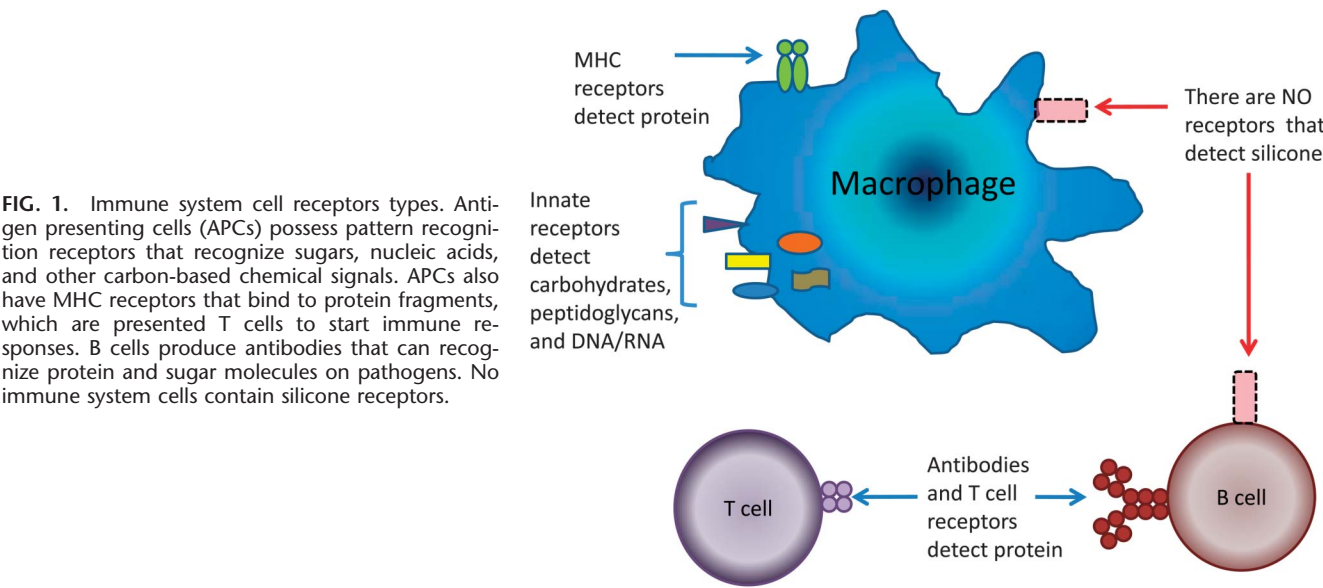


FIG. 1. Immune system cell receptors types. Antigen presenting cells (APCs) possess pattern recognition receptors that recognize sugars, nucleic acids, and other carbon-based chemical signals. APCs also have MHC receptors that bind to protein fragments, which are presented T cells to start immune responses. B cells produce antibodies that can recognize protein and sugar molecules on pathogens. No immune system cells contain silicone receptors.

One important group of signaling receptors is the Toll-like receptors (TLRs). There are 10 TLR genes in humans, encoding 10 distinct TLR proteins, each of which recognizes a particular PAMP.³³ Despite the small number of TLR proteins, they can recognize a wide variety of ligands, including lipoproteins, peptidoglycans, single- and double-stranded RNA, and flagellin.²⁶ When a TLR has bound a PAMP, downstream signaling events activate the transcription factor nuclear factor- κ B, which initiates the production of small protein signaling molecules (cytokines and

chemokines), which are important in triggering inflammatory responses.²⁶ Thus, although APC have many types of receptors capable of binding to a wide variety of organic molecules, they do not have any receptors that could bind and recognize silicone alone. The silicone incorporated into silicone hydrogels is bound to an oxygen atom (Si-O-Si), forming a siloxane functional group. APC cannot respond to the many different silicone-containing molecules in silicone hydrogel materials. The only molecules that APC could

TABLE 1. Foreign Compounds That are Recognized by the Innate Immune System (Pathogen-Associated Molecular Patterns), Their Receptors, and the Location in the Body or Cell Type That Expresses Them^{28–31}

Compound	Receptor	Location/Cell Type
Soluble proteins		
Acetylated sugars	Ficolin	Plasma protein
Bacterial and viral mannose/fucose	Mannose binding lectin	Plasma protein
Bacterial cell walls	Serum amyloid P	Plasma protein
Bacterial cell walls	Complement C3b	Plasma protein
LPS	LPS binding protein	Plasma protein
LPS	Bactericidal permeability increasing protein	Plasma protein
Phosphatidyl choline	C-reactive protein	Plasma protein
Receptors		
Bacterial ribosomal RNA sequence "CGGAAAGACC"	Toll-like receptor 13	Inside macrophage/dendritic cells
Diacyl lipopeptides	Toll-like receptor 6	Macrophage/dendritic cells/mast cells
Double-stranded RNA	Toll-like receptor 3	Inside dendritic cells/B cells
Flagellin	Toll-like receptor 5	Macrophage/dendritic cells/epithelial cells
Glycolipids, lipoproteins, lipoteichoic acid, β -glucan	Toll-like receptor 2	Macrophage/dendritic cells/mast cells
LPS	CD14	Macrophage/epithelial cells
LPS, bacterial heat shock proteins, nickel	Toll-like receptor 4	Macrophage/dendritic cells/B cells/mast cells/epithelial cells
Mannose (on terminal end of glycosylation group)	Macrophage mannose receptor	Macrophage/dendritic cells
Mannose (on terminal end of glycosylation group)	DEC 205	Macrophage/dendritic cells
N-acetylgalactosamine (GalNAc)	Macrophage C-type lectin	Macrophage/dendritic cells
Profilin	Toll-like receptor 11	Inside macrophage/liver cells/kidney cells/intestinal epithelium
Profilin	Toll-like receptor 12	Macrophage/dendritic cells/neurons
Single-stranded RNA	Toll-like receptor 7	Inside macrophage/dendritic cells/B cells
Single-stranded RNA	Toll-like receptor 8	Inside macrophage/dendritic cells/mast cells
Triacyl lipopeptides	Toll-like receptor 1	Macrophage/dendritic cells/B cells
Unmethylated CpG oligodeoxynucleotide DNA	Toll-like receptor 9	Inside macrophage/dendritic cells/B cells

LPS, lipopolysaccharide.

recognize and respond to would be proteins, sugars, and nucleic acids that were bound in some way to the lens surface.

Adaptive Immune System

The adaptive immune system exhibits a relatively delayed response compared with the innate immune system, but it is a targeted response.²⁶ The adaptive immune system has two broad types of responses: “cell-mediated response,” which, as the name suggests, involves a cellular response to intercellular pathogens, and the “humoral response,” which involves secreted antibodies in response to intracellular pathogens.

Cell-Mediated Immune Response

T lymphocytes (T cells) are involved in the cell-mediated immune response, which involves the activation of cells (such as macrophages and cytotoxic killer cells) in response to antigens. T cells recognize antigens presented on the major histocompatibility complex (MHC) II receptors of APC or MHC I receptors, which are present on nucleated cells. Upon recognizing an antigen, T cells activate into two types of effector cells, cytotoxic T cells, and helper T cells. Cytotoxic T cells recognize antigens presented on MHC I molecules of cells that are infected with intracellular pathogens and trigger the host cells to undergo apoptosis.

The majority of T cells react to peptides; however, $\gamma\delta$ T cells can recognize antigens not presented on MHC receptors, typically intact proteins or lipids,³⁴ and NK T cells can react to lipid antigens presented on CD1d molecules. There are no known T-cell receptors for silicone.

Humoral Immune Response

Helper T cells bind peptide antigens bound to MHC II molecules, but their response to stimulation is to secrete cytokine signals that induce further immune responses by effector cells, especially antibody-secreting B cells. B cells are involved in the humoral immune response, which involves secreted antibodies in response to antigens. They develop in the bone marrow and naive B cells (B cells that have not encountered antigens) populate the peripheral lymphoid organs. B cells have immobilized immunoglobulin molecules on the cell surface known as B-cell receptor (BCR) complexes. BCRs bind protein antigens, internalize them, and then present them on their cell surface complexed with MHC molecules, which T cells can bind. The T cells then secrete cytokines, which stimulate B-cell proliferation and differentiation. The products of this proliferation are plasma cells (antibody-secreting cells) and memory cells compared with naive B cells. For example, helper T cells can differentiate into T_H1 or T_H2 effector cells. T_H1 effector cells activate to cause pathogens to be phagocytosed by macrophages, whereas T_H2 effector cells are involved in immune reactions to pathogens that are too large to be phagocytosed, such as parasites, and are thought to play a role in hypersensitivity reactions (see below). Non-protein antigens, such as sugars, lipids, and nucleic acids, are bound by the BCR, but cannot be recognized by T cells, which only respond to protein antigens. Antibodies are secreted by B cells with these types of antigens, but they are mainly of the same type. Once again, B cells do not recognize or react to silicone.

Antibodies, or immunoglobulins (Igs), are synthesized by B cells and are a large family of glycoproteins with similar function and structure. They are divided into five main classes: IgA, IgG, IgD,

IgE, and IgM. These immunoglobulins, which are distributed throughout biological fluids, can recognize the majority of biological molecules. An individual can produce up to 10^9 different antibodies and these are highly specific to various antigens. Antibodies bind to and enhance the removal of remaining antigens, but again these do not include silicone.

ALLERGIES AND HYPERSENSITIVITY REACTIONS

Type I hypersensitivity reactions, commonly known as allergies, are thought to affect some 55% of people in the United States.³⁵ Type I hypersensitivity reactions occur rapidly and are typically caused by overproduction of IgE in response to environmental antigens, particularly to proteins found in pollen, dust mites, and foods.³⁶ IgE has a relatively low concentration in serum, at least 30 times less than IgG, but has a strong affinity for its receptors.³⁶ Immediate hypersensitivity reactions occur when IgE bound to the Fc ϵ RI receptor on mast cells and basophils cross-link via interactions with the same antigen. A signal cascade ultimately will cause the cells to degranulate, release stored mediators, and synthesize and release cytokines that will lure and stimulate inflammatory cells.^{36,37} To elicit an allergic response, an individual must have repeated exposure to an allergen for continuous production of the necessary IgE. There are no known structural properties of allergenic proteins that make them inherently allergenic, but they do share certain characteristics, such as low molecular weight and high solubility in body fluids. Allergic reactions are dependent on T_H2 cells, which will bind protein antigens and initiate B cells to produce IgE. In the case of non-protein allergens, the antigen must first attach to a protein before T_H2 recognition and subsequent initiation of IgE production in B cells.

In type II hypersensitivity reactions, antibodies bind to antigens on the patient's own cellular membrane. The antigen can be innately part of the cell membrane or may be foreign and adsorbed onto the cell membrane.³⁸ The cells are subsequently targeted by cytotoxic reactions.³⁹ Type III hypersensitivity reactions also involve antibodies; however, the antibodies involved form small immune complexes that can deposit in small blood vessels and joints, triggering an inflammatory response.³⁹ Type IV hypersensitivity reactions use a cell-mediated response, activating cells in response to antigens.³⁹

Examination of this information confirms that “true” allergic and other hypersensitivity reactions cannot occur in response to silicone alone but could be triggered in response to antigens found associated with silicone hydrogel materials. These could include deposits, microbial fragments, or components from solutions, which are taken up and released from SiHy lens materials.^{40,41}

WHAT HAPPENS IN THE EYE?

It is evident so far that silicone cannot elicit a response from the immune system, in general. However, the eye is a unique site immunologically and it is worth discussing the multiple layers of immunological activity in the eye in terms of allergic responses. The eye can be divided into four immunological areas: the tear film and conjunctiva, the sclera, the uvea, and the retina.⁴²

There are several layers to the tear film⁴³ that contains many immune proteins such as lysozyme and lactoferrin,⁴⁴ immunoglobulins^{44,45} such

as IgA, IgE, IgM, and IgG, and inflammatory mediators such as histamine and various cytokines.^{46,47} The conjunctiva can be divided into two layers based on histology: an epithelial layer of two to five cell layers, and a layer of substantia propria.⁴² The epithelial layer contains APCs, known as Langerhans cells,⁴⁸ and T cells, but not normally other inflammatory cells.⁴² Mast cells are normally found within the substantia propria⁴⁹ but not the epithelium. Blood circulating inflammatory cells are not generally found in the normal conjunctiva.⁴² The corneal epithelial and stroma contain macrophages and dendritic cells that mediate the initial host response to lipopolysaccharide (LPS) and flagellin.⁵⁰ Human corneal epithelial cells themselves can also respond to TLR ligands and LPS exacerbating inflammatory reactions.⁵⁰

The vitreous humor and the anterior chamber are immune privileged sites, which are areas that tolerate antigens without eliciting immune responses. Immune privilege in the eye is extremely important, as inflammatory responses could result in visual loss in many ways.⁵¹ This immune privilege arises from three broad factors: (1) structural features (such as the blood ocular barriers and absence of lymphatic vessels), (2) soluble effector, and (3) cell surface molecules. The latter two of these both suppress immune activation, such as transforming growth factor β_2 that inhibits T-cell activation.⁵¹ In the anterior chamber, exposure to certain antigens results in suppression of the cell-mediated immune response, a process known as anterior chamber-associated immune deviation.⁵² This phenomena is a result of the “immune privileged” status and redirects the immune response away from damaging IgG antibody or CD8⁺ T-cell responses to milder allergic IgE-based responses.

Despite the eye’s special immunology, the resident immune cells described do not react to silicone. Many groups that study this problem fail to account for the fact that there may be misfolded self-proteins (proteins normally produced by patients themselves) attached to the silicone, leading to erroneous results as misfolded self-proteins can cause inflammation.⁵³ Sindt et al.⁵⁴ reported that contact lens wearers seemed to have more resident corneal immune cells than nonwearers, but this difference was not statistically significant. Additionally, there was no difference between the numbers of resident immune cells between users of poly(hydroxyethyl methacrylate) lenses versus SiHy users. Thus, silicone is not inducing a large immune response and the authors did not address self-proteins deposited on the contact lenses, which may be the cause of the putative increase in immune cells.

In another study, Miro-Mur et al.⁵⁵ studied the peripheral blood mononuclear cells of 39 individuals. They showed that, based on several measures of immunity, including immune cell viability, immune cell activation, and immune cell cytokine production, silicone did not induce immune reactivity alone. They suggest that silicone is merely acting as an adjuvant rather than an antigen. No T-cell activation was seen, suggesting that the immune system is not directly recognizing the silicone. Without T-cell activation, there can be no direct response with antibodies, cytotoxic cells or allergic responses. Thus, there is no immune reaction seen to silicone, as predicted above based on the structure of the mammalian immune system.

HYPERSENSITIVITY IN THE EYE

The principal hypersensitivity reaction observed in the eye relates to allergic conjunctivitis, which can be either type I or type IV hypersensitivity.⁵⁶ Type I hypersensitivity involves activation of mast cells by IgE cross-linking an antigen (usually environmen-

tal) and subsequent release of inflammatory mediators such as histamine and polymorphonuclear leukocyte attracting chemokines, whereas type IV hypersensitivity reactions in the eye involve T_H1 activation of macrophages.⁵⁶ Following the initial allergic response (2–24 hours after exposure), late-phase allergic responses can occur. The late-phase response involves the recruitment of neutrophils, eosinophils, and macrophages. A minority of hypersensitivity reactions in the eye are caused by biocompatibility issues with biomaterials used within the ocular environment. There are a few types of biomaterials used in very different ocular immune environments: contact lenses (which interact with the tear film and the conjunctiva), intraocular lenses (which are located within the immune-privileged environment of the inner eye), and scleral buckles (which sit underneath the conjunctiva).

Contact Lens–Related Hypersensitivity

Soft contact lenses can be broken up into two broad groups: conventional hydrogels and silicone hydrogels.^{57,58} Conventional lenses are made up of primarily HEMA, whereas silicone hydrogels have siloxane groups.^{58,59} These siloxane groups greatly increase the oxygen transmissibility of the lenses but also increase their hydrophobicity.⁵⁸ These materials only deposit low levels of protein,^{60,61} but the increased surface hydrophobicity denatures a higher percent of the deposited protein compared with conventional hydrogels^{57,62} and the relatively hydrophobic surfaces also attracts a greater amount of tear film–derived lipid than conventional lenses.^{58,63,64}

Hydrogel and silicone hydrogel materials show differing uptake and release profiles of the components within care systems^{41,65} and demonstrate markedly differing corneal staining profiles following their exposure to lenses used with certain preserved care systems.^{66,67} It is plausible that any putative “allergic reaction” could be related to these interactions rather than those driven by the siloxane component of the lens material per se.

Contact Lens–Induced Papillary Conjunctivitis

Contact lens–induced papillary conjunctivitis (CLPC) (Fig. 2) is characterized by inflammation of the papillae in the upper tarsal conjunctiva^{68,69} and has the following complications for contact lens wearers: increased mucous discharge, irritation, burning, itching, redness, decreased lens tolerance, and increased lens awareness.^{7,68–70} The inflammatory responses seen in CLPC are not caused by an allergic reaction to the “silicone” in the materials but rather a reaction to the deposited lipids and protein on the lens materials and/or some degree of minor mechanical response to the reduced wetting surface of the lens.^{7,68,71} Donshik et al.⁶⁸ suggest that the tear film coating stimulates the immune system to produce IgG, IgE, and IgM and to activate the complement system. They propose that C3 anaphylatoxin and the immunoglobulins interact with basophils and mast cells, which then release vasoactive amines. The subtle mechanical trauma to the conjunctival cells releases neutrophil chemotactic factor, which attracts more mast cells, basophils, and eosinophils, which further react with C3 anaphylatoxin and the immunoglobulins, resulting in the giant papillary response seen in some wearers of silicone hydrogel materials.⁶⁸

Intraocular Lens–Related Hypersensitivity

Cataract surgery, involving intraocular lens implantation, is the most common form of ophthalmic surgery.⁷² Performing cataract

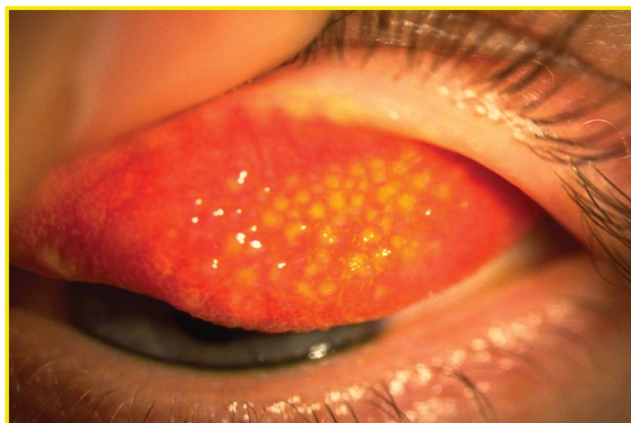


FIG. 2. An example of contact lens-induced papillary conjunctivitis.

surgery and intraocular lens implantation results in the release of proteins and cells into the anterior chamber⁷³ and these proteins can adsorb onto the surface of the implanted lenses, resulting in inflammatory reactions.⁷³ Inflammatory cells can be seen on the surface of intraocular lenses just a few days after surgery. The complement system is activated, which attracts polymorphonuclear leukocytes and monocytes and eventually macrophages and giant cells.⁷⁴ The giant cell response peaks at about 3 months and usually involves the giant cells degenerating on the surface of the intraocular lens, leaving a proteinaceous membrane that isolates the lens from the rest of the ocular tissues.⁷³

Abela-Formanek et al.⁷⁵ studied the biocompatibility of hydrophilic acrylic, hydrophobic acrylic, and hydrophobic silicone intraocular lenses. They studied 155 eyes from 131 patients and found that silicone lenses had a greater deposition of small round cells, which are involved in the foreign body reaction against intraocular lenses,⁷³ than hydrophobic acrylic lenses, while the hydrophilic acrylic had lenses with both the highest and lowest deposition of small round cells. The hydrophobic acrylic lenses showed the highest deposition of giant cells, followed by hydrophilic acrylic, and silicone lenses had the lowest deposition of giant cells. Neither small round cells nor giant cells are involved in allergic reactions. Thus, it is clear that inflammation associated with intraocular lens usage is not caused by an allergy to silicone but rather results from foreign body reactions and inflammatory responses to deposits on the lenses.

Scleral Implant–Related Hypersensitivity

Retinal detachments, which can occur due to trauma, high refractive error, after cataract surgery or due to the natural aging process, can be repaired by the use of scleral implants or “buckles.”⁷² Scleral implants have been used since the 1930s,⁷⁶ but only relatively recently have silicone materials been introduced.⁷² Since the introduction of silicone materials, there has been some limited evidence of foreign body reactions to silicone scleral implants.⁷⁷ Shaikh et al.⁷⁸ examined the serum from 25 patients who had silicone scleral buckles and found statistically significant IgG binding of silicone in only one patient (4%), and this patient had systemic connective tissue disease, which could be related to this occurrence. In comparison, Pastor et al.⁷⁹ found that 35.7% of patients with a silicone implant exhibited positive anti-silicone IgG-antibodies. Thus, information to-date concerning the ability of silicone scleral implants to induce an allergic response appears equivocal.

NON-EYE-RELATED SILICONE HYPERSENSITIVITY STUDIES

Silicone is used in a variety of biomaterial applications in body sites other than the eye. The most extensively studied of these is silicone breast implants, which are widely used and have been the focus of many biocompatibility studies.^{80–85} Some studies have suggested that anti-silicone antibodies (mainly IgG) are present in patients who have (or have previously had) silicone breast implants.^{80,84} In addition to silicone breast implants, Goldblum et al.⁸⁶ have suggested the same for ventriculoperitoneal shunts. These findings remain controversial, as other studies have reported the low likelihood of anti-silicone antibodies^{83,87} and no discernable difference in IgG binding to silicone in patients with silicone breast implants, when compared to those without.⁸¹ Levy et al.⁸⁵ performed a critical review of the literature regarding anti-silicone antibodies and concluded that most studies suggest silicone implants cause nonspecific foreign body reactions.

Recently, Petry et al.⁸⁸ investigated the skin sensitization hazard of five silicone materials and reviewed the work of other skin sensitization studies. They concluded, based on the weight of the available evidence, that the silicone materials investigated in their and other studies are not a skin sensitization hazard to humans.

CASE STUDIES OF “SILICONE ALLERGY”

Although the human immune system only recognizes carbon-based chemistry and while allergies can only be directed at proteins, there have been a limited number of case reports in the literature. These case reports, however, invariably turn out to be either not bona fide allergic reactions (as there are no IgE antibodies involved)^{89–91} or are other types of hypersensitivity reactions, which can be attributed to impurities in the silicone material, such as metals complexed to human proteins,⁹² organomercury molecules,⁹³ or silicone-protein complexes.⁹⁴

RECOMMENDATIONS TO EYE CARE PROFESSIONALS

Clinicians do a disservice to their profession, their scientific training, their patients, and to industry by invoking the phrase “silicone allergy,” as the explanation for problems their patients might encounter with silicone hydrogel lenses. Scientifically accurate and sufficiently detailed explanations will ultimately lead to improved options for correction of refractive error, less abandonment of contact lens wear, and greater numbers of satisfied patients.

Patients may experience discomfort and/or adverse events due to conditions such as contact lens peripheral ulcer and contact lens acute red eye; however, these conditions should be attributed to inflammation caused by the presence of bacteria, which has been demonstrated in a number of studies.^{7,95–98} Patients experiencing CLPC should be informed that the cause is most likely due to denatured protein on the lens and/or mechanical trauma caused by the lens design.^{7,68} Patients who experience infiltrates can be assured that this is not due to an “allergy” to the material itself but rather a response to material deposited on the lens material or care components released from it.

SUMMARY

In summary, this review has demonstrated that inflammatory reactions in the eye are not directly caused by silicone but can occur in response to antigens that can accumulate on or within these silicone biomaterials.

REFERENCES

- Nichols JJ. Contact lenses 2012. *Cont Lens Spectr* 2013;28:24–29.
- Philip BM, Woods CA, Tranoudis IG, et al. International contact lens prescribing in 2012. *Cont Lens Spectr* 2013;28:31–44.
- Sorbara L, Jones L, Williams-Lyn D. Contact lens induced papillary conjunctivitis with silicone hydrogel lenses. *Cont Lens Anterior Eye* 2009;32:93–96.
- Donshik P, Long B, Dillehay SM, et al. Inflammatory and mechanical complications associated with 3 years of up to 30 nights of continuous wear of lotrafilcon A silicone hydrogel lenses. *Eye Contact Lens* 2007;33:191–195.
- Skotnitsky CC, Naduvilath TJ, Sweeney DF, et al. Two presentations of contact lens-induced papillary conjunctivitis (CLPC) in hydrogel lens wear: Local and general. *Optom Vis Sci* 2006;83:27–36.
- Skotnitsky C, Sankaridurg PR, Sweeney DF, et al. General and local contact lens induced papillary conjunctivitis (CLPC). *Clin Exp Optom* 2002;85:193–197.
- Dumbleton K. Adverse events with silicone hydrogel continuous wear. *Cont Lens Anterior Eye* 2002;25:137–146.
- Chalmers RL, Keay L, McNally J, et al. Multicenter case-control study of the role of lens materials and care products on the development of corneal infiltrates. *Optom Vis Sci* 2012;89:316–325.
- Szczotka-Flynn L, Benetz BA, Lass J, et al. The association between mucin balls and corneal infiltrative events during extended contact lens wear. *Cornea* 2011;30:535–542.
- Chalmers RL, Wagner H, Mitchell GL, et al. Age and other risk factors for corneal infiltrative and inflammatory events in young soft contact lens wearers from the Contact Lens Assessment in Youth (CLAY) study. *Invest Ophthalmol Vis Sci* 2011;52:6690–6696.
- Szczotka-Flynn L, Lass JH, Sethi A, et al. Risk factors for corneal infiltrative events during continuous wear of silicone hydrogel contact lenses. *Invest Ophthalmol Vis Sci* 2010;51:5421–5430.
- Chalmers RL, McNally JJ, Schein OD, et al. Risk factors for corneal infiltrates with continuous wear of contact lenses. *Optom Vis Sci* 2007;84:573–579.
- Szczotka-Flynn L, Debanne SM, Cheruvu VK, et al. Predictive factors for corneal infiltrates with continuous wear of silicone hydrogel contact lenses. *Arch Ophthalmol* 2007;125:488–492.
- Papas EB, Carnt N, Willcox MDP, et al. Complications associated with care product use during silicone daily wear of hydrogel contact lens. *Eye Contact Lens* 2007;33:392–393; discussion 399–400.
- McNally JJ, Mckenney CD, Robirds S. Risk factors for corneal infiltrative events with 30-night continuous wear of silicone hydrogel lenses. *Eye Contact Lens* 2003;29:S153–S156; discussion S166, S192–S194.
- Stapleton F, Stretton S, Papas E, et al. Silicone hydrogel contact lenses and the ocular surface. *Ocul Surf* 2006;4:24–43.
- Willcox M, Sankaridurg P, Zhu H, et al. Inflammation and infection and the effects of the closed eye. In: Sweeney D, ed. *Silicone Hydrogels: Continuous Wear Contact Lenses*. Oxford, United Kingdom, Butterworth-Heinemann, 2004, pp 90–125.
- Szczotka-Flynn L, Chalmers R. Incidence and epidemiologic associations of corneal infiltrates with silicone hydrogel contact lenses. *Eye Contact Lens* 2013;39:49–52.
- Szczotka-Flynn L, Diaz M. Risk of corneal inflammatory events with silicone hydrogel and low dk hydrogel extended contact lens wear: A meta-analysis. *Optom Vis Sci* 2007;84:247–256.
- Radford CF, Minassian D, Dart JKG, et al. Risk factors for nonulcerative contact lens complications in an ophthalmic accident and emergency department: A case-control study. *Ophthalmology* 2009;116:385–392.
- Chalmers RL, Keay L, Long B, et al. Risk factors for contact lens complications in US clinical practices. *Optom Vis Sci* 2010;87:725–735.
- Sankaridurg PR, Sweeney DF, Sharma S, et al. Adverse events with extended wear of disposable hydrogels. *Ophthalmology* 1996;106:1671–1680.
- Stern J, Wong R, Naduvilath TJ, et al. Comparison of the performance of 6- or 30-night extended wear schedules with silicone hydrogel lenses over 3 Years. *Optom Vis Sci* 2004;81:398–406.
- Guillon M. Are silicone hydrogel contact lenses more comfortable than hydrogel contact lenses? *Eye Contact Lens* 2013;39:86–92.
- Papas E. Contact lens and silicone allergy. Silicone hydrogels. 2008. Available at: http://www.siliconehydrogels.org/editorials/sep_08.asp. Accessed March 1, 2012.
- Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell* 2006;124:783–801.
- Medzhitov R. Recognition of microorganisms and activation of the immune response. *Nature* 2007;449:819–826.
- Iwasaki A, Medzhitov R. Regulation of adaptive immunity by the innate immune system. *Science* 2010;327:291–295.
- Matzinger P. Tolerance, danger, and the extended family. *Annu Rev Immunol* 1994;12:991–1045.
- Seong S, Matzinger P. Hydrophobicity: An ancient damage-associated molecular pattern that initiates innate immune responses. *Nat Rev Immunol* 2004;4:469–478.
- Barton GM. A calculated response: Control of inflammation by the innate immune system. *J Clin Invest* 2008;118:413–420.
- Fraser IP, Koziel H, Ezekowitz RA. The serum mannose-binding protein and the macrophage mannose receptor are pattern recognition molecules that link innate and adaptive immunity. *Semin Immunol* 1998;10:363–372.
- Fitzner N, Clauberg S, Essmann F, et al. Human skin endothelial cells can express all 10 TLR genes and respond to respective ligands. *Clin Vaccine Immunol* 2008;15:138–146.
- Chien Y, Jores R, Crowley MP. Recognition by gamma/delta T cells. *Annu Rev Immunol* 1996;14:511–532.
- Arbes SJ Jr, Gergen PJ, Elliott L, et al. Prevalences of positive skin test responses to 10 common allergens in the US population: Results from the third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 2005;116:377–383.
- Sutton BJ, Gould HJ. The human IgE network. *Nature* 1993;366:421–428.
- Galli SJ, Gordon JR, Wershil BK. Cytokine production by mast cells and basophils. *Curr Opin Immunol* 1991;3:865–872.
- Clynes R, Ravetch JV. Cytotoxic antibodies trigger inflammation through Fc receptors. *Immunity* 1995;3:21–26.
- Butrus S, Portela R. Ocular allergy: Diagnosis and treatment. *Ophthalmol Clin North Am* 2005;18:485–492, v.
- Powell CH, Lally JM, Hoong LD, et al. Lipophilic versus hydrodynamic modes of uptake and release by contact lenses of active entities used in multipurpose solutions. *Cont Lens Anterior Eye* 2010;33:9–18.
- Jones L, Powell CH. Uptake and release phenomena in contact lens care by silicone hydrogel lenses. *Eye Contact Lens* 2013;39:29–36.
- Bielory L. Allergic and immunologic disorders of the eye. Part I: Immunology of the eye. *J Allergy Clin Immunol* 2000;106:805–816.
- Tauber S. Treating and managing dry eye. *Clin Refractive Optom* 2005;16:270–276.
- Fullard RJ, Snyder C. Protein levels in nonstimulated and stimulated tears of normal human subjects. *Invest Ophthalmol Vis Sci* 1990;31:1119–1126.
- Mimura T, Usui T, Mori M, et al. Relation between total tear IgE and specific serum IgE in seasonal allergic conjunctivitis. *Cornea* 2011;30:790–795.
- Abelson MB, Soter NA, Simon MA, et al. Histamine in human tears. *Am J Ophthalmol* 1977;83:417–418.
- Sonoda S, Uchino E, Nakao K, et al. Inflammatory cytokine of basal and reflex tears analysed by multicytokine assay. *Br J Ophthalmol* 2006;90:120–122.
- Kari O, Saari KM. Updates in the treatment of ocular allergies. *J Asthma Allergy* 2010;3:149–158.
- Morgan SJ, Williams JH, Walls AF, et al. Mast cell numbers and staining characteristics in the normal and allergic human conjunctiva. *J Allergy Clin Immunol* 1991;87(pt 1):111–116.
- Pearlman E, Sun Y, Roy S, et al. Host defense at the ocular surface. *Int Rev Immunol* 2013;32:4–18.
- Streilein JW, Okamoto S, Sano Y, et al. Neural control of ocular immune privilege. *Ann N Y Acad Sci* 2000;917:297–306.
- Streilein JW. Anterior chamber associated immune deviation: The privilege of immunity in the eye. *Surv Ophthalmol* 1990;35:67–73.
- Golde TE, Miller VM. Proteinopathy-induced neuronal senescence: A hypothesis for brain failure in Alzheimer's and other neurodegenerative diseases. *Alzheimers Res Ther* 2009;1:5.
- Sindt CW, Grout TK, Critser DB, et al. Dendritic immune cell densities in the central cornea associated with soft contact lens types and lens care solution types: A pilot study. *Clin Ophthalmol* 2012;6:511–519.
- Miro-Mur F, Hindié M, Kandhaya-Pillai R, et al. Medical-grade silicone induces release of proinflammatory cytokines in peripheral blood mononuclear cells without activating T cells. *J Biomed Mater Res B Appl Biomater* 2009;90:510–520.
- Ono SJ, Abelson MB. Allergic conjunctivitis: Update on pathophysiology and prospects for future treatment. *J Allergy Clin Immunol* 2005;115:118–122.

57. Subbaraman LN, Jones L. Kinetics of lysozyme activity recovered from conventional and silicone hydrogel contact lens materials. *J Biomater Sci Polym Ed* 2010;21:343–358.
58. Jones L, Senchyna M, Glasier MA, et al. Lysozyme and lipid deposition on silicone hydrogel contact lens materials. *Eye Contact Lens* 2003;29:S75–S79; discussion S83–S84, S192–S194.
59. Nicolson PC, Vogt J. Soft contact lens polymers: An evolution. *Biomaterials* 2001;22:3273–3283.
60. Subbaraman LN, Glasier MA, Senchyna M, et al. Kinetics of in vitro lysozyme deposition on silicone hydrogel, PMMA, and FDA groups I, II, and IV contact lens materials. *Curr Eye Res* 2006;31:787–796.
61. Luensmann D, Zhang F, Subbaraman L, et al. Localization of lysozyme sorption to conventional and silicone hydrogel contact lenses using confocal microscopy. *Curr Eye Res* 2009;34:683–697.
62. Hall B, Jones L, Forrest JA. Measuring the kinetics and activity of adsorbed proteins: In vitro lysozyme deposited onto hydrogel contact lenses over short time periods. *J Biomed Mater Res A* 2013;101:755–764.
63. Lorentz H, Jones L. Lipid deposition on hydrogel contact lenses: How history can help us today. *Optom Vis Sci* 2007;84:286–295.
64. Carney FP, Nash WL, Sentell KB. The adsorption of major tear film lipids in vitro to various silicone hydrogels over time. *Invest Ophthalmol Vis Sci* 2008;49:120–124.
65. Carnt N, Stapleton F. Silicone hydrogel lens-solution interaction and inflammation. *Eye Contact Lens* 2013;39:37–41.
66. Andrasko G, Ryen K. Corneal staining and comfort observed with traditional and silicone hydrogel lenses and multipurpose solution combinations. *Optometry* 2008;79:444–454.
67. Carnt NA, Evans VE, Naduvilath TJ, et al. Contact lens-related adverse events and the silicone hydrogel lenses and daily wear care system used. *Arch Ophthalmol* 2009;127:1616–1623.
68. Donshik PC, Ehlers WH, Ballow M. Giant papillary conjunctivitis. *Immunol Allergy Clin North Am* 2008;28:83–103, vi.
69. Allansmith MR, Korb DR, Greiner JV, et al. Giant papillary conjunctivitis in contact lens wearers. *Am J Ophthalmol* 1977;83:697–708.
70. Elhers WH, Donshik PC. Giant papillary conjunctivitis. *Curr Opin Allergy Clin Immunol* 2008;8:445–449.
71. Nichols JJ. Deposition on silicone hydrogel lenses. *Eye Contact Lens* 2013;39:20–23.
72. Lloyd AW, Faragher RG, Denyer SP. Ocular biomaterials and implants. *Biomaterials* 2001;22:769–785.
73. Werner L. Biocompatibility of intraocular lens materials. *Curr Opin Ophthalmol* 2008;19:41–49.
74. Mamalis N. Intraocular lens biocompatibility. *J Cataract Refract Surg* 2002;28:1–2.
75. Abela-Formanek C, Amon M, Schild G, et al. Uveal and capsular biocompatibility of hydrophilic acrylic, hydrophobic acrylic, and silicone intraocular lenses. *J Cataract Refract Surg* 2002;28:50–61.
76. Schepens CL, Acosta F. Scleral implants: An historical perspective. *Surv Ophthalmol* 1991;35:447–453.
77. Kalicharan D, Jongebloed WL, Veen G, et al. Cell-ingrowth in a silicone plombe. *Doc Ophthalmol* 1991;78:307–315.
78. Shaikh S, Morse LS, Goldblum RM, et al. The effect of silicone ocular surgical devices on serum IgG binding to silicones. *Am J Ophthalmol* 1998;126:798–804.
79. Pastor JC, Puente B, Telleria J, et al. Antisilicone antibodies in patients with silicone implants for retinal detachment surgery. *Ophthalmic Res* 2001;33:87–90.
80. Wolf LE, Lappé M, Peterson RD, et al. Human immune response to polydimethylsiloxane (silicone): Screening studies in a breast implant population. *FASEB J* 1993;7:1265–1268.
81. Oliver DW, Walker MS, Walters AE, et al. Anti-silicone antibodies and silicone containing breast implants. *Br J Plast Surg* 2000;53:410–414.
82. França DCC, de Castro AL, Soubhia AMP, et al. Evaluation of the biocompatibility of silicone gel implants—Histomorphometric study. *Acta Inform Med* 2013;21:93–97.
83. White KL, Klykken PC. The non-specific binding of immunoglobulins to silicone implant materials: The lack of a detectable silicone specific antibody. *Immunol Invest* 1998;27:221–235.
84. Bekerecioglu M, Onat AM, Tercan M, et al. The association between silicone implants and both antibodies and autoimmune diseases. *Clin Rheumatol* 2008;27:147–150.
85. Levy Y, Rotman-Pikielny P, Ehrenfeld M, et al. Silicone breast implantation-induced scleroderma: Description of four patients and a critical review of the literature. *Lupus* 2009;18:1226–1232.
86. Goldblum RM, Pelley RP, O'Donnell AA, et al. Antibodies to silicone elastomers and reactions to ventriculoperitoneal shunts. *Lancet* 1992;340:510–513.
87. Klykken P, Colas A, Thomas X. Antisilicone antibodies are biologically unlikely. *Clin Rheumatol* 2008;27:1077–1078.
88. Petry T, Bosch A, Coste X, et al. An assessment of the skin sensitisation hazard of a group of polyfunctional silicones using a weight of evidence approach. *Regul Toxicol Pharmacol* 2012;64:305–314.
89. Rubio A, Ponvert C, Goulet O, et al. Allergic and nonallergic hypersensitivity reactions to silicone: A report of one case. *Allergy* 2009;64:1555.
90. Hunsaker DH, Martin PJ. Allergic reaction to solid silicone implant in medial thyroplasty. *Otolaryngol Head Neck Surg* 1995;113:782–784.
91. Stuck B, Hecksteden K, Klimek L, et al. Type I hypersensitivity to a silicone tube after laryngectomy [in German]. *HNO* 2004;52:255–257.
92. Cantisani C, Cigna E, Grieco T, et al. Allergic contact dermatitis to synthetic rubber following breast augmentation. *Eur Ann Allergy Clin Immunol* 2007;39:185–188.
93. Hong J, Huang J, Liu S, et al. Stability and activity of chymotrypsin immobilized on magnetic nanogels covered with carboxyl groups. *J Appl Polym Sci* 2009;111:2844–2850.
94. Kossovsky N, Hegggers JP, Robson MC. Experimental demonstration of the immunogenicity of silicone-protein complexes. *J Biomed Mater Res* 1987;21:1125–1133.
95. Wu P, Stapleton F, Willcox MDP. The causes of and cures for contact lens-induced peripheral ulcer. *Eye Contact Lens* 2003;29(suppl 1):S63–S66; discussion S83–S84, S192–S194.
96. Sankaridurg PR, Sharma S, Willcox M, et al. Bacterial colonization of disposable soft contact lenses is greater during corneal infiltrative events than during asymptomatic extended lens wear. *J Clin Microbiol* 2000;38:4420–4424.
97. Sankaridurg PR, Vuppala N, Sreedharan A, et al. Gram negative bacteria and contact lens induced acute red eye. *Indian J Ophthalmol* 1996;44:29–32.
98. Holden BA, La Hood D, Grant T, et al. Gram-negative bacteria can induce contact lens related acute red eye (CLARE) responses. *CLAO J* 1996;22:47–52.