Getting comfortable with contact lens deposits

Johnson & Johnson INSTITUTE

KEY POINTS

- Different contact lens materials attract different amounts of protein and lipids, but more clinically relevant is the nature of the deposition.
- Proteins in the tear film are present in their natural native functional state. When they deposit on a contact lens, proteins can change from their native state to a denatured form, altering the protein's ability to perform its natural function.
- Lysozyme is a major protein deposited on contact lenses.
  The presence of denatured lysozyme has been shown *in vitro* to trigger the release of inflammatory biomarkers which may result in irritation.
- High lysozyme deposition is observed on group IV hydrogel lenses, and is greatest on etafilcon A material. The majority of deposited lysozyme is maintained in its native state which has been demonstrated to help maintain low levels of inflammatory biomarkers using a corneal epithelium construct *in vitro* model.
- Just like proteins, lipids, when deposited on contact lenses, can also change function by oxidation and degradation, and may impact comfort and vision over time.
- Further research is required to fully understand any potentially beneficial effects of selective adsorption of certain lipids and their maintenance in their native state by some silicone hydrogel materials.
- Management options for lens deposits that cause discomfort or visual symptoms include: material change, increase replacement frequency, incorporate a rub and rinse step or change solution to avoid protein denaturation.

How clinically relevant are contact lens deposits and can they actually be beneficial? The Johnson & Johnson Institute report on research findings presented at a special session at the 2015 BCLA Clinical Conference

The arrival of the first daily disposable contact lenses in 1995 seemed to spell the end of concern about lens deposits. Since the advent of frequent replacement, lenses were no longer returned to the practice for intensive cleaning, or regularly subjected to protein removal. Rubbing and rinsing reusable lenses, and replacing them to schedule, came to be seen as sufficient to keep deposits in check.

Fast forward 20 years and there is renewed interest in the subject as we gain a better understanding of the interaction between lens deposits and the eye, and differences in deposition between modern materials. The British Contact Lens Association included an education session in its 2015 Clinical Conference to report on findings that challenge our thinking on deposits.

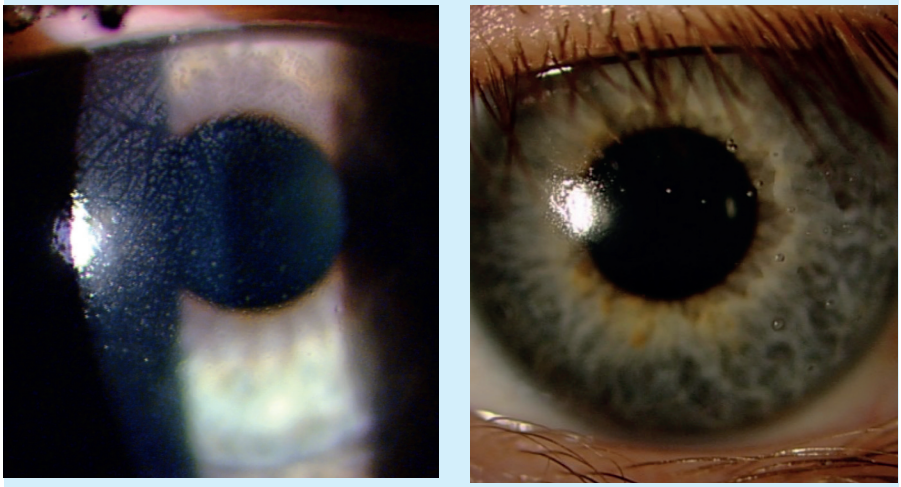

Figure 1. Deposition on soft lenses differs in appearance from a protein film (left) to discrete lipid deposits (right)

Setting the scene, **Professor Philip Morgan** (University of Manchester) said contact lens deposits showed a range of clinical presentations from discrete and bumpy to filmy (Figure 1). The two major categories were protein and lipids.

Proteins were abundant in the tear film and were essentially strings of amino acids that could interact with other strings of amino acids and take up complex three-dimensional forms (Figure 2). Understanding these forms helped to understand what was happening clinically.

Importantly, the shape and structure of proteins could change, in the tear film and on the contact lens, and in doing so proteins moved from a 'native' and/or 'active' state to a 'denatured' and/or 'inactive' form. As a protein denatures, its ability to perform its natural functions alters.

The tear protein that was best understood was lysozyme which – along with lipocalin, lactoferrin and secretory IgA – was abundant in the tear film, with a concentration of approximately 2mg/ml. Many other tear film proteins had been identified, but at much lower concentrations (<0.1mg/ml).

It was important to appreciate the effect that introducing a contact lens to the tear film had on proteins. Many contact lenses became 'soaked full of protein' within a few minutes of wear, said Morgan, but most proteins were transparent and only became visible once they became denatured and changed their structure to become translucent.

Lysozyme is an antibacterial protein which can interact with bacterial cell walls to hydrolyse them and kill the bacteria. The shape of the protein was critical to allow this to happen.

There were two particular amino acid sequences in lysozyme that, when in its native form, were ideally placed for this interaction to take place. As the protein denatured, these amino acids were no longer in the right place and the lysozyme was no longer as effective at killing bacteria.

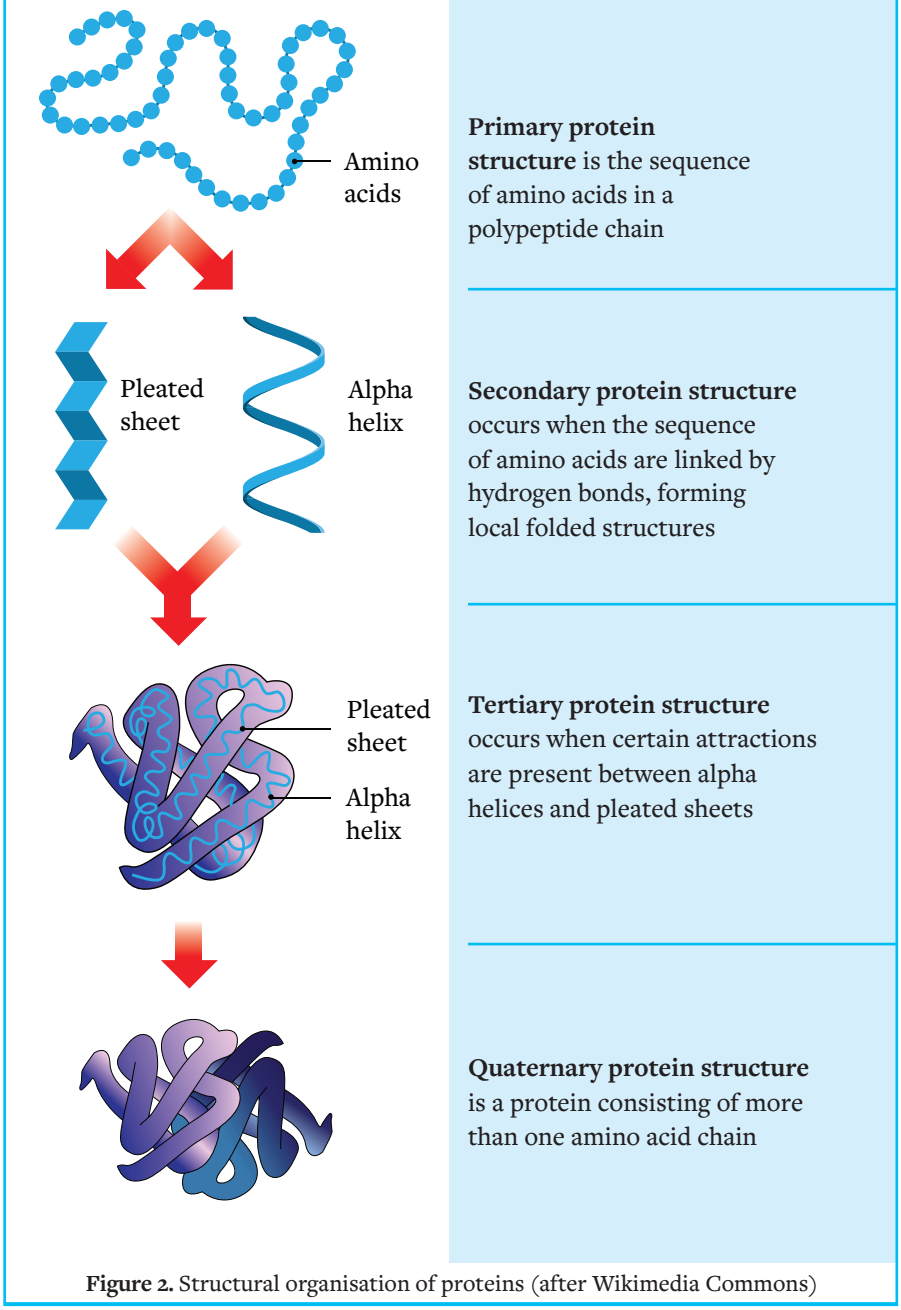

Figure 2. Structural organisation of proteins (after Wikimedia Commons)

Material differences

Another key point was that different materials attracted different amounts of protein. Group IV materials (mid/higher water and ionic), such as etafilcon A (Johnson & Johnson Vision Care Companies), attracted a relatively high level of protein, but more clinically relevant was the nature of the deposition.

With etafilcon A, much more of the protein (>90 per cent with ACUVUE® 2) was in its native form after it had deposited onto (and into) the lens. With some materials, such as lotrafilcon B (AIR OPTIX® AQUA, Alcon), although they deposit less protein, only a very small proportion retains its activity (<10 per cent).

The range of lysozyme activity was surprisingly wide and there were clear differences between materials that could be important clinically, said Morgan.

Moving on to lipid deposits (sometimes termed 'jelly bumps' when they occur as discrete deposits rather than a lipid film), while there were hundreds or perhaps thousands of different proteins in the tear film, there were far fewer types of lipid. These included steroids such as cholesterol, saturated and unsaturated fatty acids, glycerides and polar lipids. Lipids could also change their function, but by oxidation and degradation rather than denaturation, he said.

Different materials again interacted very differently with lipids. Etafilcon A deposited very low levels of lipids (cholesterol, oleic acid and oleic acid methyl ester) compared to some silicone hydrogel (SiH) materials and also certain Group II hydrogel materials (mid/higher water and non-ionic).

Influencing factors

Dr Lakshman Subbaraman (University of Waterloo, Canada) reviewed factors influencing deposition on contact lenses. Material properties played a 'huge role', he said (Figure 3). Higher water content materials took up greater amounts of protein, as did ionic materials, and those with larger pore sizes allowed greater penetration into the bulk of the lens.

Surface modification of SiHs reduced deposition of both lipid and protein compared with uncoated materials, although the differences appeared to have no significant impact on clinical performance. The size and charge of the deposits themselves were a further relevant factor; smaller proteins were more easily deposited on lenses and penetrated the lens bulk more readily.

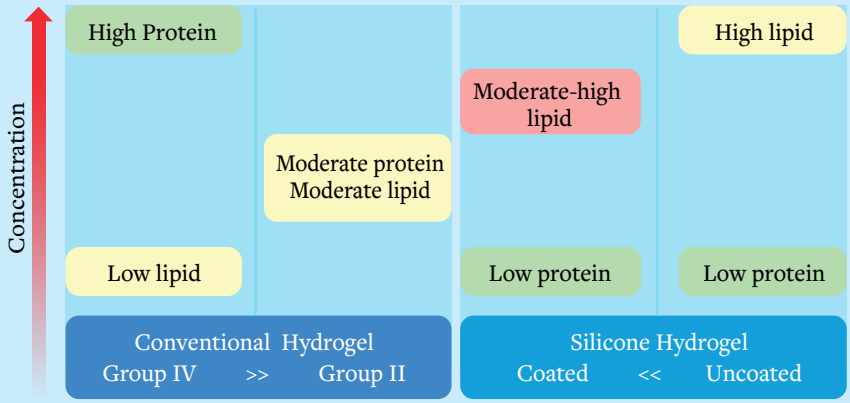

Figure 3. Schematic illustration of trends in lipid and protein deposits on different contact lens materials (After Mann A and Tighe B. Contact lens interactions with the tear film. *Experimental Eye Research* 2013;117:88-98).

Lysozyme is the major protein deposited on contact lenses and makes up 40 per cent of total tear proteins. It has a small molecular size, and is positively charged, so readily deposits on negatively charged substrates with a high water content.

It has been shown that lysozyme quality (denatured versus native), rather than total quantity, correlates with contact lens comfort. A decrease in active lysozyme was correlated to reduced comfort.

A variety of factors can impact protein denaturation. Lens age, environmental factors, lens care solutions or exposure to certain contact lens materials could all result in lysozyme losing its active sites and ultimately reducing comfort. Denatured protein might also act as an antigen and trigger an immunological response in the papillary conjunctiva, resulting in contact lens papillary conjunctivitis (CLPC).

Most studies to date have looked at the quantity of proteins deposited on contact lenses. Methods developed and refined at the University of Waterloo have helped elevate our understanding of deposition to go beyond just quantity to four other important factors: selectivity, speed, location and quality (Figure 4).

Importantly, the influence these factors have on corneal homeostasis, and in particular inflammation, has recently been investigated. To that end, the latest state of the art techniques using electrochemiluminescence (Meso Scale Discovery) were used to demonstrate, for the first time, a direct correlation *in vitro* between denatured lysozyme and inflammatory response using a corneal epithelium model.

They found that Group IV hydrogels *in vitro* deposited very high levels of lysozyme (>200mg/lens after 16h incubation) compared to other materials (<20mg/lens). Etafilcon A deposited >500mg/lens. These materials selectively attracted lysozyme rather than other tear components (>90 per cent of total proteins) relative to other materials (40-60 per cent).

Changing views

Attempts have been made to classify and describe the clinical presentation of contact lens deposition, including the Rudko Scale devised in the 1970s.

But can we trust what we see on the slit lamp, since observed levels of protein may not correlate to measured levels? Clinically, there was some evidence that high levels of visible deposits reduced low contrast visual acuity, but little to support an association between increasing deposition and reduced comfort.

Morgan's group had recently looked at the antimicrobial efficacy of tear film taken from contact lenses and the ability of solutions to prevent denaturation of proteins. They found that proteins extracted from the tear film had 'an incredibly potent biocidal effect' on *Pseudomonas aeruginosa*, with kill rates of up to 6-7 log units.

Contact lens disinfecting solutions were required to have a 3 log unit overnight reduction. 'With naturally derived proteins held in the contact lens, we're getting that level of antimicrobial activity and more for many of our patients. This is really important,' said Morgan, 'and suggests that maybe having high levels of functional tear film proteins attracted to materials might be beneficial.'

A study using a differential scanning calorimetry method demonstrated that one multipurpose solution (a dual disinfection system containing polyaminopropyl biguanide and polyquaternium) was able to maintain or even return denatured tear film proteins to their natural form, with a positive antimicrobial effect.

Maybe it was time to think differently about lens deposition, he concluded.

Influencing factors continued

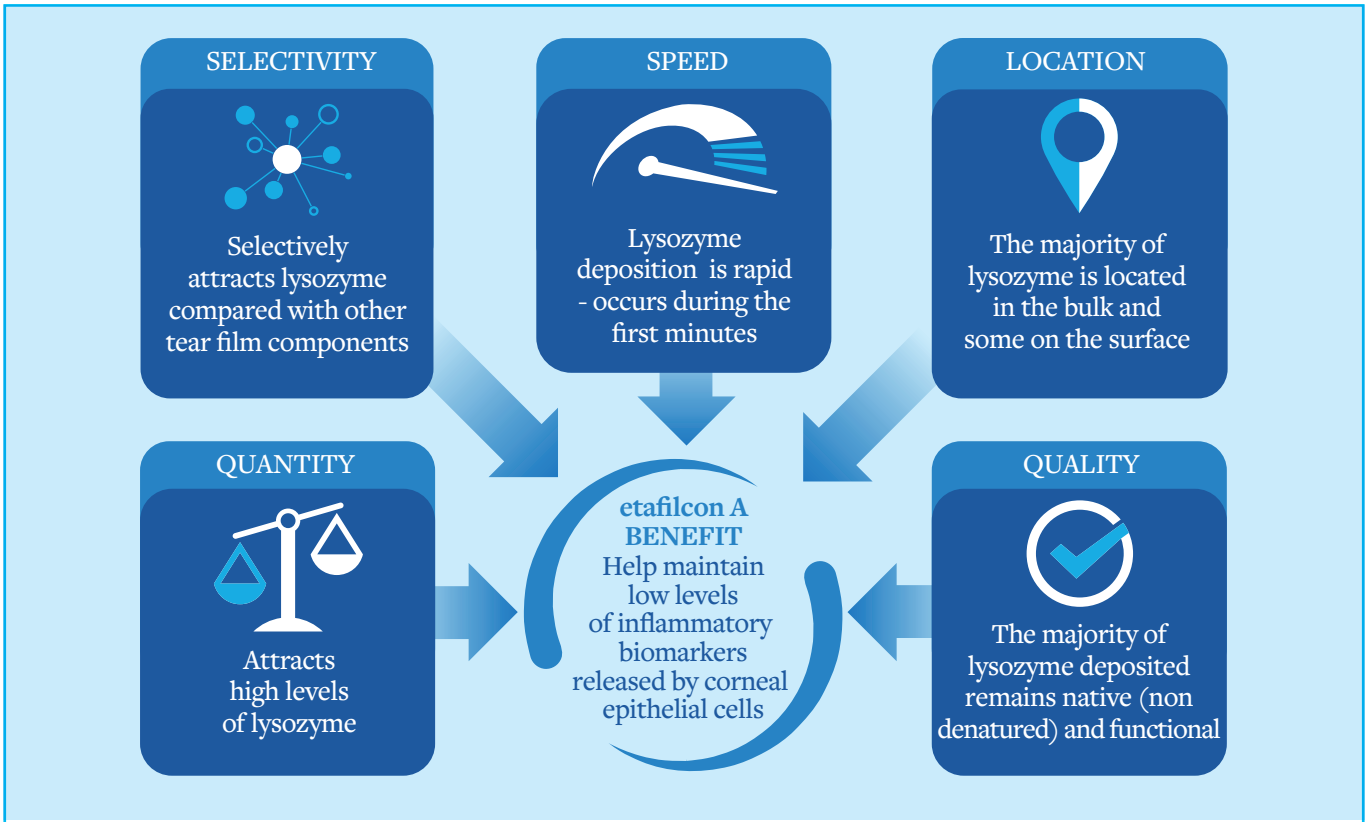

Figure 4. Lysozyme deposition and etafilcon A material

Deposition was rapid, with measurable amounts of lysozyme uptake within the first minute of incubation. Practically all of the lysozyme on etafilcon A was in an active state and it was uniformly distributed in the bulk of the material and on the surface, rather than on the surface alone. Where lysozyme was found on the surface of etafilcon A, it was more likely to remain active than on other materials.

To explore the clinical benefits of these properties in an *in vitro* model, the group conducted the first-ever study to determine the impact of denatured lysozyme on human corneal epithelial cells. They found that, unlike active lysozyme, the denatured form reduced the metabolic activity of epithelial cells and could also alter cell function, although it was not toxic and did not cause cell death. Denatured lysozyme seemed to trigger the release of inflammatory biomarkers known as cytokines from these cells.

Although the importance of the state of protein deposits has long been recognised, this was the first time the impact of denatured lysozyme on corneal cells had been demonstrated, he said.

Beneficial effects

Turning to lipids, Dr Subbaraman explained that, traditionally, lipid deposits were believed to be detrimental in contact lens wear since they increased the risk of bacterial attachment, initiated a potential immunological response and also altered the surface properties of lenses, resulting in decreased comfort.

However, the Tear Film and Ocular Surface Society (TFOS) International Workshop on Contact Lens Discomfort found only three studies to date linking comfort and lipid deposits, and then only a very weak correlation between cholesterol deposition and comfort was demonstrated.

The University of Waterloo group looked at lipid deposition after 14 days' wear of ACUVUE OASYS® in symptomatic and asymptomatic wearers and found significantly higher levels of lipid deposits – cholesterol, cholesterol esters and triolein – in the asymptomatic group.

Although further work was needed, these data suggest that selective adsorption of certain lipids at certain levels could actually improve comfort in contact lens wearers.

New findings on the antibacterial effects of lens deposition were also emerging. Historically, all deposits were considered to increase bacterial binding to contact lenses. But lactoferrin deposited on contact lenses had been shown to be effective at reducing the viability of *Pseudomonas aeruginosa* bound to lenses.

A study in collaboration with researchers at the University of New South Wales, Australia found that when lactoferrin deposits were present, although they increased the total bacterial count, the viability of bacteria was reduced. Cholesterol was shown to have an antibacterial effect in solution but it was not yet known whether the cholesterol found on contact lenses could have a similar effect.

Subbaraman concluded that 'not all deposits were bad' and deposition of certain tear components could actually be beneficial.

Clinical pointers

So what does this all mean for clinicians? **Professor Lyndon Jones** (University of Waterloo) reviewed clinical implications and management strategies for lens deposits to find some answers.

In terms of visual acuity (VA), with older, non-frequently replaced lenses VA was reduced by deposits, but not so with modern frequent replacement lenses since deposits never reached that stage.

Poor wettability (Figure 5) could impact vision quality in some patients, particularly towards the end of the replacement cycle and later in the day, but for most patients this was not an issue.

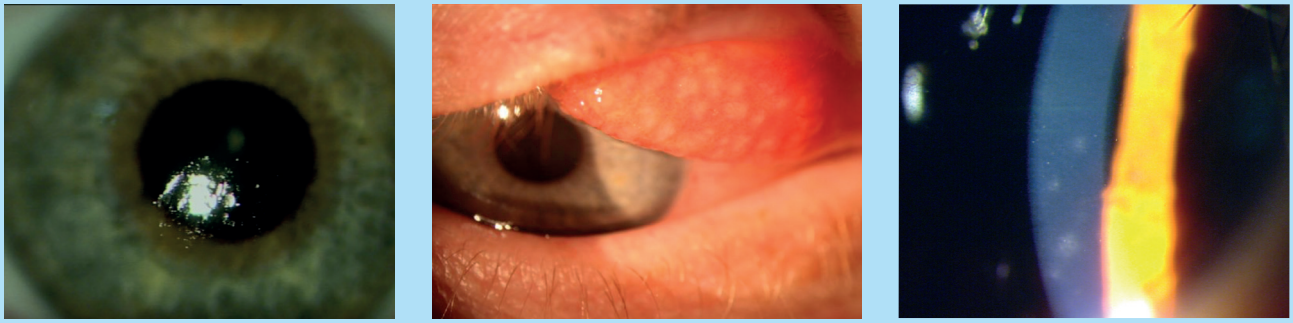

Figure 5. Potential clinical implications of lens deposits include reduced visual acuity due to poor wettability (left), CLPC (centre) and corneal infiltrates (right)

As long as proteins remained active, contact lens papillary conjunctivitis (CLPC, Figure 5) was unlikely. But if proteins denatured, there was potential for lid changes and a possible inflammatory response within cells and within the tear film. And there was a strong correlation between denatured lysozyme and discomfort.

Recent clinical studies have pointed towards a potential role for deposition in the development of corneal infiltrates (Figure 5). Reusable SiH lenses show a consistent two times higher rate of infiltrates than hydrogels, and daily disposables exhibit a protective effect relative to reusable lenses in several studies. Replacing lenses daily was associated with a very low rate of adverse events, especially with Group IV materials. This raised the question of whether the increased risk of infiltrates with SiH materials could in some way be linked with tear film deposition of certain deposits or factors within the tear film in certain wearers? This issue required further consideration, he said.

Think quality not quantity

Jones discussed three options for the clinical management of deposits: choice of material, lens replacement frequency and care regime.

The deposition profile with hydrogels was completely different from that of SiHs. Hydrogels deposited more protein but it was primarily active. Group IV hydrogels showed the most protein deposition but the lowest proportion of denatured protein and very low levels of lipid.

SiHs deposited more lipid than hydrogels and much less protein but most was denatured, particularly 3-4 weeks into the replacement cycle.

Materials that selectively deposited 'good' lipids might be the answer for some patients. *In vitro* studies showed very low cholesterol uptake with etafilcon A lenses. But much higher levels were rapidly deposited on SiH lenses, especially in patients prone to high levels of cholesterol in their tears such as those with meibomian gland dysfunction.

Incorporating a rub and rinse step in the care regime could dramatically reduce visible protein deposits, but rubbing alone had a limited effect on lipid removal.

In summary

Management options available to clinicians were to change material from SiH to hydrogel, or from a neutral hydrogel to a Group IV material that deposited potentially beneficial proteins. Reducing the period of wear – ultimately switching to daily disposables, including a rub and rinse for reusable lenses, and using solutions that incorporated surfactants were also recommended.

'Maybe we were wrong about deposits,' said Jones. 'Tear film components are there for a reason. We should be looking for materials, and solutions, that selectively deposit the components we want and resist those we don't.'

Acknowledgement

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Key Points and Further Reading have been added by Johnson & Johnson Vision Care Institute with authors permission.

Further reading

Omali NB, Subbaraman LN, Coles-Brennan C et al. Biological and clinical implications of lysozyme deposition on soft contact lenses. Optom Vis Sci 2015;92:7 750-7.

Morgan P. Tear film proteins: examining production, role and interaction with contact lenses. Contact Lens Spectrum, April 2010.

Zhao Z, Wei X, Yulina A et al. Proteomic analysis of protein deposits on worn daily wear silicone hydrogel contact lenses. Mol Vis 2008;14:2016-24.

Suwala M, Glasier MA, Subbaraman L et al. Quantity and conformation of lysozyme deposited on conventional and silicone hydrogel contact lens materials using an in vitro model. Eye Contact Lens 2007;33:138-143.

Ng A, Heynen N, Luensmann D et al. Impact of tear film components on conformational state of lysozyme deposited on contact lenses. J Biomed Mater Res B Appl Biomater 2013;101:7 1172-81.

Senchyna M, Jones L, Louie D et al. Quantitative and conformational characterization of lysozyme deposited on balafilcon and etafilcon contact lens materials. Curr Eye Res 2004;28:25-36.