



# FoCoSi

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A new clinical finding sheds light on follicular-like conjunctivitis associated with silicone hydrogels

## Abstract

### Aim

The purpose of this article is to describe follicular-like conjunctivitis associated with silicone hydrogels (FoCoSi) in silicone hydrogel contact lens wearers as a novel subtype of the well-described contact lens induced papillary conjunctivitis (CLPC).

### Methods

A total of 1,211 patients who wore silicone hydrogels were included in this prospective, non-randomised, single centre study. Subjective symptoms and clinical signs were evaluated for daily wear (DW) and continuous wear (CW) populations for several (lotrafilcon A, lotrafilcon B, senofilcon A, galyfilcon A) silicone hydrogel lens types. The CCLRU and other specifically developed grading scales were used for evaluation. Grading of 2 and above was rated as clinically significant.

### Results

The clinical presentation of FoCoSi could be confirmed and showed an incidence of 3.8 per cent. Lotrafilcon A followed by senofilcon A on a CW modality presented, with a risk ratio of 2.49 and 1.53, respectively, the highest affinity for developing FoCoSi. Fluorescein positive spots showed the closest correlation with subjective symptoms reported by patients and divided FoCoSi into an active and dormant form. Besides deposition on the contact lens surface, air pollution like ozone or fine and ultrafine particles seems to be an important factor in developing FoCoSi.

### Conclusion

FoCoSi is a novel and relevant subtype of CLPC. Further studies should be performed to validate these findings and answer

several questions about the aetiology of FoCoSi and CLPC.

### Key words

Contact lens-induced papillary conjunctivitis (CLPC), follicular-like conjunctivitis associated with silicone hydrogels (FoCoSi), giant papillary conjunctivitis (GPC)

### Introduction

Contact lens-induced papillary conjunctivitis (CLPC),<sup>1</sup> also known as giant papillary conjunctivitis (GPC), is a well-described condition and a major cause of discontinuation of contact lens wear.<sup>2</sup> It is an inflammatory and usually reversible condition that is characterised by enlarged papillae, hyperaemia of the palpebral conjunctiva and excessive mucous discharge. Symptoms include discomfort, pruritus or itching, foreign body sensation, excessive movement, decentration and deposits on the contact lens, resulting in blurred vision and decreased visual acuity.<sup>37</sup> CLPC can occur bilaterally or in 10 per cent of cases truly unilaterally.<sup>17</sup> Epidemiological studies demonstrated that the presentation of CLPC in hydrogel contact lens wearers has a mean onset time between 4.3 and 31 months after commencing contact lens wear.<sup>11,16,38</sup> Gender was not found to be a relevant associated factor for CLPC.<sup>11</sup> Patients with a history of allergy have been reported to be more susceptible to CLPC.<sup>8,9</sup> Of further significance is the distribution in time of diagnosis of CLPC, with peaks in spring and late summer to early autumn, which was assumed to correlate with ragweed pollen season.<sup>9</sup>

The condition was first reported in 1970 in a patient wearing rigid contact lenses<sup>6</sup> and later by Spring<sup>10</sup> in 1974 in patients wearing hydrophilic contact lenses, and has since been frequently reported in wearers of both rigid and soft contact lenses.<sup>11-15</sup> The

incidence of CLPC varies but is greatest with soft contact lens wear (from 1.9 per cent to 45 per cent),<sup>16,21</sup> especially while wearing conventional extended wear (EW) soft contact lenses.<sup>22</sup> Disposable soft contact lenses, especially if wearing time is less than three weeks, showed a significantly lower incidence of CLPC than conventional soft lenses.<sup>13,14,19</sup> No CLPC at all was found in patients wearing their contact lenses on a one-week or one-day replacement cycle.<sup>23</sup> Preliminary studies and case reports by Stern and Skotnitsky<sup>21</sup> suggest that there is a greater occurrence of CLPC with silicone hydrogel (SiHy) lenses. When comparing six nights of extended wear to 30 nights of extended wear with SiHy, there was no difference in the occurrence of CLPC.<sup>18</sup>

### Aetiology

Papillae are small protuberances with nerve endings that respond to stimulation. A vascular supply is observed radiating from a vessel occupying the central fibrotic core of each papillae.<sup>25-27</sup> The conjunctival epithelium overlying the giant papillae is thickened and irregular, with many invaginations into the stroma. Excised papillae consist of conjunctival epithelial cells, goblet cells, mucous granules in non-goblet epithelial cells, inflammatory leucocytes including mast cells, plasma cells, lymphocytes, eosinophils, basophils and neutrophils in the epithelium, basophils in the substantia propria and newly-formed vessels among excessive fibrosis.<sup>28-35</sup> Recent immuno-histochemical studies have demonstrated an increase in the number of CD4+ T cells, memory T cells, eotaxine and cytokine production in GPC specimens compared with normal tissue.<sup>36-39</sup>

Sulfidopeptide leukotriens produce increased microvascular permeability in a variety of tissues, which results in oedema formation due to the extravascular ac-

cumulation of plasma. Leukotriens (LT) are found in a higher concentration in patients with CLPC and in patients with allergies, and LT acts independently of histamine.<sup>64</sup> Immunoglobulin (IgE and IgG) antibodies in the tears and degranulated mast cells in ocular tissue were increased in patients with CLPC.<sup>40,41</sup> All those results indicate that it is an immunoglobulin mediated type 1 hypersensitivity reaction.

There have been reports of prescribing differences in the distribution of papillae across the tarsal conjunctiva with different contact lens types.<sup>42,43</sup> EW Studies with SiHy have indicated that there are two distinct categories of CLPC: general and local.<sup>17,19</sup> CLPC involving enlarged papillae across the entire palpebral conjunctiva is classified as general, and papillae confined to one or two areas, generally in the central region nearest the lid margin, are termed local. Patients with general CLPC typically experience more serious clinical symptoms and have more lens deposits than do patients with local CLPC.<sup>19</sup>

Additionally, CLPC is thought to be an immunologic response to deposits (lipid, protein and mucin<sup>44,45</sup>) on the contact lens surface.<sup>38,46</sup> Studies have provided valuable information about deposit composition and formation mechanisms. Tear protein identified includes lysozym, lactoferrin, protein-G, pre-albumin, albumin and immunoglobulines.<sup>47-53</sup> Protein deposition varies in amount and activity and is driven primarily by contact lens polymer composition, water content, pore size and mainly ionic nature. Lysozyme is mainly deposited

on negatively charged substrates, whereas albumin is deposited on neutral and/or positively-charged materials.

Higher water content contact lenses graded from the US Food and Drug Administration (FDA) group II and group IV have a tendency to have more deposits than lower water content lenses. Ionically charged contact lens polymers (FDA group III and group IV) tend to attract proteins, such as lysozyme. Contact lenses of FDA group IV tend to have the greatest deposition of protein.

Whereas protein is taken into the aqueous phase, lipid becomes associated with the polymer matrix itself, independent of material ionicity. Interestingly, the protein deposition is largely unrelated to subjective differences, whereas lipid deposition is related to both material composition and inter-subject differences in tear film components, blink factors and environmental factors.<sup>50,53</sup> SiHy materials have deposition profiles different from those seen with conventional hydrogel lenses. The surfaces of SiHy materials are characteristically hydrophobic, with typically significantly lower quantities of protein and higher levels of lipid deposition being measured.<sup>54,58</sup>

*In vitro* study<sup>59</sup> and *in vivo* study found the highest amount of lipid adsorption (non-polar cholesterol and polar phosphatidylethanolamine) in SiHy with senofilcon A, followed by galyfilcon A, (FDA group I), and balafilcon A (FDA group III), whereas the lowest adsorption was with lotrafilcon A and B (FDA group I). However, lipids alone do not appear to be antigenic.<sup>60</sup> On the other

hand, interaction among depositing materials may play a role because it has been shown that lipid deposits on FDA group IV lenses may inhibit deposition of lysozyme.<sup>61</sup>

There were no differences in lysozym accumulation between five different SiHy materials until five days of wearing time, but increases consistently after a longer period of wearing time, without reaching a plateau like the FDA group IV materials.<sup>62</sup> Jones and co-workers<sup>50,51</sup> found approximately 50 per cent denatured lysozyme on balafilcon A *ex vivo* lenses and 80 per cent on lotrafilcon A *ex vivo* lenses. Galyfilcon A lenses denatured only about 25 per cent of the lysozyme *in vitro* but approximately 50 per cent *in vivo*.

This difference in denaturation suggests *in vivo* factors such as the presence of other tear components (for example, lipid), lens surface drying during the interblink period, and shear forces during blinking may all contribute to denaturation of surface proteins during in-eye wear. Another study has demonstrated that protein denaturation may play an important role in the development of CLPC.<sup>43</sup> This study is of significant interest, because of CLPC being reported at higher levels with silicone-based lenses than with conventional lens materials.<sup>21</sup>

Pollen and other allergenic substances adhere to the surface of the contact lens, too, especially in patients with a poor tear film and poor contact lens wetting.<sup>23</sup> Additionally, the coated contact lens induces physical trauma to the conjunctival epithelium, resulting in the release of chemotactic factors, such as neutrophilic chemotactic factor (NCF), causing the influx of various inflammatory cells.<sup>63</sup>

In CLPC patients, NCF was increased 15 times the level of asymptomatic patients. Biochemical characterisation of the conjunctival factors showed that NCF are proteins of high molecular weights and are capable of producing a GPC-like inflammatory reaction in the upper tarsal of rabbits when they are injected daily for seven days.<sup>68</sup> Furthermore, the eventual activation of lipoxigenase results in the release of LK, too.<sup>64</sup>

So far, there has been no correlation between CLPC with a particular contact lens type or specific deposits. There have been no studies that have shown a biochemical or morphologic difference between the coating on contact lenses from patients with and without CLPC. Ballow and colleagues<sup>65</sup> have shown that when coated contact lenses from patients with CLPC are placed on monkey eyes, a papillary

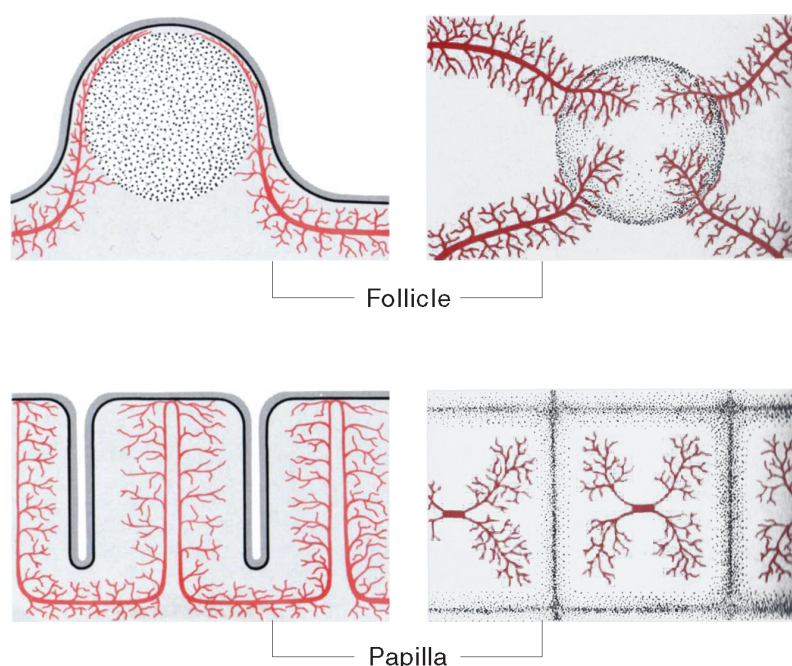


Figure 1. Papilla versus follicle. GOH Naumann. *Pathologie des Auges* 1980; 12: 252

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tarsal reaction develops with more of IgE and IgG. However, if coated contact lenses from asymptomatic patients are placed on the eyes of monkeys, a papillary reaction does not occur; neither is there an increase of tear immunoglobulin.

The second most prevalent sign of CLPC, after the inflammation of the conjunctiva, is excessive mucous. There is no increasing of the number of mucous secreting goblet cells;<sup>66</sup> moreover, the mucus vesicles in non-goblet epithelial cells contribute dramatically to the increase of mucous production.<sup>67-68</sup> Excess mucous in the tear film interferes with vision by coating the contact lens surface and increased contact lens movement. Patients may report accumulation of mucous in the nasal corner of the eye, especially on waking.<sup>48</sup>

In summary, the origin of CLPC appears to be a combination of mechanical irritation and immunological hypersensitivity reaction.<sup>48</sup>

## Purpose of this study

Papillae consist of a vascular supply that is observed radiating from a vessel occupying the central core of each papilla.<sup>22-24,48</sup> In contrast, as a differential diagnosis, follicle has a white centre obscuring underlying vessels<sup>22</sup> (Figure 1).

*In vivo* confocal microscopy showed in follicular conjunctivitis, a hyporeflective core containing hyporeflective round cells surrounded by a hyper-reflective capsule and vessels,<sup>69</sup> so follicles appear as round to oval elevations measuring between 0.5 and 1.5 mm in diameter with a grey-white centre. They can be seen in the inferior and superior tarsal conjunctiva and less often, on bulbar or limbal conjunctiva. Patients may complain of ocular itching, foreign body sensation, tearing, redness and photophobia.

Typical signs of viral conjunctivitis include preauricular adenopathy, epiphora, hyperaemia, chemosis, subconjunctival haemorrhage, follicular conjunctival reaction and occasionally a pseudo-membranous or cicatricial conjunctival reaction.<sup>70-76</sup> The disease typically begins in one eye and progresses to the fellow eye over a few days. The second eye is usually less significantly involved.<sup>77,78</sup> Presumed diagnosis with clinical findings, especially follicles, scanty watery discharge and preauricular adenopathy were consistent with laboratory

findings in 76 per cent of cases.<sup>79</sup>

Viral conjunctivitis is typically characterised by a mononuclear cellular response with preponderance of lymphocytes or monocytes. In early stages neutrophils can be numerous.<sup>80</sup> Interestingly, there is a seasonal variation in the aetiology of acute adenoviral conjunctivitis, reaching the peak in summer, followed by winter and spring, whereas Herpes simplex infections showed no seasonal peaks.<sup>79</sup> The reason for these differences remains unclear in the studies. Three to four days after onset of the symptoms, the cornea shows a diffuse epithelial keratitis, followed at one week by a focal epithelial keratitis that persists for up to two weeks.

Around this time, subepithelial infiltrates may be noticed beneath the focal epithelial lesions. They exhibit a round or nummular shape, may persist for months or years,<sup>80</sup> and represent an immune response to adenoviral antigens deposited in the corneal stroma. Follicles are most seen in viral (adenovirus and herpes simplex virus) or chlamydial infections<sup>77,78,81,82</sup> but were never described as a finding in CLPC.

There are few papers in literature prescribing a follicular-like response of the upper conjunctiva in CLPC<sup>22,37,43,81</sup> besides the response of papillae formation. This reaction was presumed in severe cases with a longer period of time to be a cicatrization of the conjunctiva surface at the apex of the papillae and appear in a cream/white colour.<sup>22,81</sup> Sugar and co-workers<sup>82</sup> presumed a thickening of the overlaying conjunctiva as the reason for a milky appearance in some cases of GPC after keratoplasty. In earlier stages the papillae apex can display infiltrates, which appear in a whitish colour as well.

Fluorescein staining occurs with epithelial cell damage and frequently occurs with papillae with apices that are flattened or crater-like.<sup>21,37,81</sup> The reason for those alterations was presumed to be the initiating

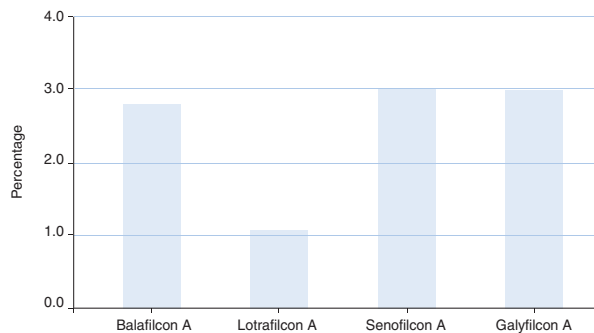


Table 1. Contact lens material

mechanical trauma. Greiner<sup>43</sup> in contrast found no fluorescein staining over those whitish papillae in GPC due to an epithelialised foreign body. Despite the importance of differential diagnosis of contagious viral or chlamydial infection, risk factors and aetiology of this specific condition are not well understood.

After the introduction of silicone hydrogel contact lenses, we thought we saw more of those whitish apices of papillae in patients with CLPC. The purpose of this study was to examine the distinct clinical presentations of follicular-like conjunctivitis associated with silicone hydrogels (FoCoSi) in cases with CLPC in a large number of silicone hydrogel lens wearers.

The study involved prospectively collected data from subjects wearing their contact lenses on a regular modality and replacement schedule. The data were compared with an asymptomatic control group.

## Materials and method

The study was conducted from the kontaktlin-senstudio baertschi in Bern, Switzerland. A prospective, non-randomised, single centre study design was chosen for this research project. A total of 1,211 active silicone hydrogel contact lens wearers were included for the current analysis. Subjects with prior contact lens experience, as well as subjects with no prior contact lens wear experience (neophytes) were included. They had to have actively worn their lenses in their usual wearing mode, extended wear (EW) or daily wear (DW), between 1 January 2007 and 31 December 2007.

## Demographic statistics

All subjects who wore silicone hydrogels in the period of the analysis were considered for the study. No exclusions due to age were made. Subjects ranged in age from 10 to 80 years with a mean of 34.09 and 63 per cent of them were female.

## Materials

The contact lens materials included in the study were four different types of silicone hydrogel contact lenses: lotrafilcon A, balafilcon A, galyfilcon A and senofilcon A. All possible variations, such as toric or multifocal designs were included as well. The distribution of the used contact lens materials are listed in Table 1: 29.9 per cent of all subjects used senofilcon A, galyfilcon A material was used by 29.7 per cent, followed by balafilcon A with 28 per cent, lotrafilcon A was used by 12.3 per cent.

## Method

The cornea, bulbar conjunctiva, upper and lower tarsal conjunctiva were examined. Examination was made under both white light and cobalt blue light with a yellow fluorescein enhancement filter using a wide range of magnification levels.

Fluorescein was used to detect corneal and conjunctival staining and to enhance the contrast in papillary size and definition. The reported symptoms were graded as well as tearing at the moment of FoCoSi. Additionally, preauricular lymph nodes were palpated and graded, and the anterior portion of the eye was observed to rule out any associated viral infections.

Finally, predominance to pollen allergy reaction was noted as well. Clinical diagnosis of CLPC and FoCoSi was based

on biomicroscopic findings of papillary changes of the upper and lower palpebral conjunctiva. All subjects with enlarged papillae presenting a follicular-like appearance were classified as FoCoSi. An example of a FoCoSi event is shown in Figures 2 and 3. Notice the numerous white spots with the absence of the central vascular tuft, whereas the surrounding papillae are present with a central vessel. This conjunctival change can be seen using the slitlamp biomicroscope; however, with Adobe Photoshop 7.0 software modified colour presentation, the FoCoSi differences can be observed much better.

Grading for follicular-like papillae presented in the upper and lower lid was divided into several subdivisions. Quantity of present follicular-like papillae, fluorescein positive spots, hyperaemia and oedema, and the character of tear secretion were graded from zero to 4.

## Contact lens examination

To describe possible correlations of the appearance and frequency of FoCoSi, various contact lens parameters and wearing modalities were noted. Besides the type of the contact lens used, additionally listed were the age of the contact lens, wearing modality, movement and appearance of any material defects, and care solution used were noted with specifically developed grading

scales from zero to 4. As deposits on the surface of a contact lens are an important factor in the comfort of wearing contact lenses and can trigger CLPC, five different types of deposits (lipid, mucin, hydrophobic spots, cosmetics and mixed deposits) were noted and graded, too.

## Statistical analyses

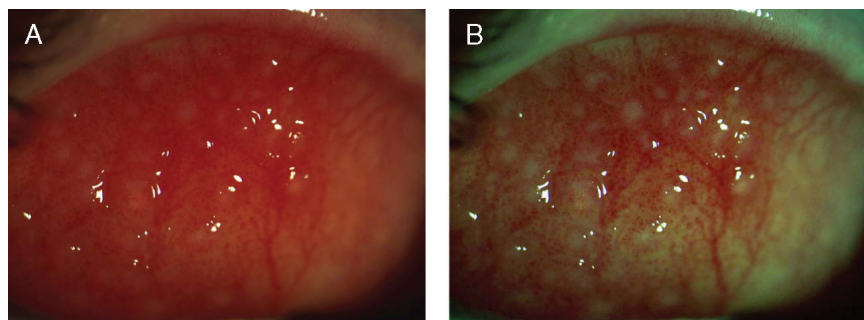
Data were included in this study from subjects who began EW or DW and attended at least one scheduled EW or DW visit. The first adverse response to contact lens wear during EW or DW was used to categorise the subject eyes into groups. Eyes that did not develop any adverse response to contact lens wear during the follow-up period were retrospectively categorised as asymptomatic controls. The adverse response groups included FoCoSi only. Clinical and subjective variables were collected at scheduled and unscheduled visits. Data for all events in the right or left eye or both eyes were recorded for clinical variables. All continuous variables were compared for differences among controls and the FoCoSi group using analysis of variance with mixed and random effects. Multiple comparisons were performed with Tukey HSD post hoc analysis. Categorical variables such as percentage of reported symptoms were compared between the groups using the chi-squared test and followed by Fisher exact test for multiple comparisons. Statistical significance was set at  $p \leq 0.05$  for clinical variables.

## Results

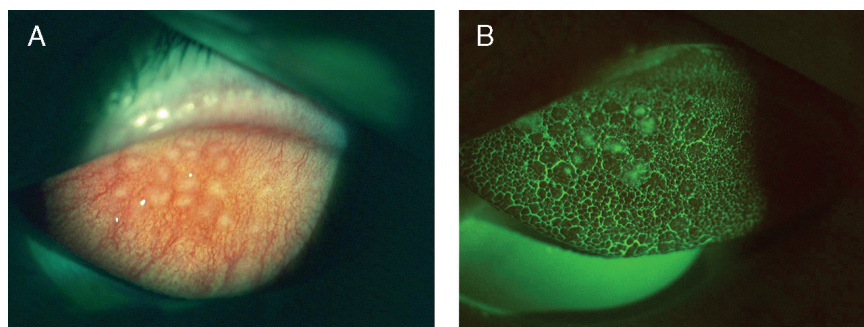
### General results

A total of 46 FoCoSi subjects were seen, which was an incidence of 3.8 per cent. Subjects ranged in age from 19 to 63 years with a mean of 31.98 years of age and 56.5 per cent of them were female. Gender ( $p = 0.058$ ) and age ( $p = 0.633$ ) are not significant factors for the development of FoCoSi. For gender there was a tendency for males to be more prone to developing FoCoSi than females. Seasonal differences in occurrence of FoCoSi events showed peaks in January, April and essentially during June until August (Table 2).

Allergies against pollen were associated in only 50 per cent of all subjects with FoCoSi. There was no correlation between reported allergy propensity and the seasonal distribution of FoCoSi events ( $p = 0.108$ ).



**Figure 2.** FoCoSi example as original picture (A) and as a software modified version (B)



**Figure 3.** FoCoSi of one eye presented on slitlamp under normal light (A) and with fluorescein staining (B)

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## Results of slitlamp examination of cornea and conjunctiva

None of the subjects with FoCoSi showed either positive preauricular lymphadenopathy finding or any viral reaction or conspicuousness of the cornea or conjunctiva. None of the subjects exceeds grading 2 in the lower palpebral conjunctiva for papillae. In the superior palpebral conjunctiva, only 15.3 per cent showed moderate to severe papillae formation with severe hyperaemia and oedema of the palpebral conjunctiva. The FoCoSi reaction was exclusively found in the superior palpebral conjunctiva. Of the subjects, 22.8 per cent showed monocular FoCoSi response. Observing the superior palpebral conjunctiva for each eye separately, 33.7 per cent showed from one to five, 26.1 per cent showed from six to 10, 13.0 per cent had from 11 to 20 and 4.3 per cent showed more than 20 FoCoSi spots.

Classification into local and general form of appearance was performed. All subjects presenting fewer than 11 follicular-like papillae formations were labelled as local, whereas the others were labelled as general form of distribution; 83.6 per cent were classified as local and 16.4 per cent of the subjects showed the general form of distribution. FoCoSi subjects with the general form reported significantly ( $p = 0.003$ ) more symptoms.

Fluorescein staining was performed for two reasons: first, papillae are more visible and easier to grade; and second, to reveal persisting FPS on the apex of FoCoSi. Not all of the FoCoSi subjects showed FPS; 36.6 per cent presented the whole superior conjunctiva as fluorescein negative, 23.9 per cent had one FPS, 22.5 per cent had from one to three fluorescein positive spots, 11.3 per cent had from four to six FPS and 5.6 per cent had more than six FPS. Observing the correlation between the numbers of FoCoSi spots found and the amount of FPS showed that for the group with more than 20 FoCoSi spots, the highest amount of FPS was noted as well. This finding was statistically significant ( $p = 0.020$ ).

A similar result was found for oedema,

so that the oedema was more severe in the group with more than 20 FoCoSi spots. Again, this is a statistically significant finding ( $p = 0.015$ ) (Table 3). Additionally, the correlation between the reported subjective symptoms and objective findings of FoCoSi in the meaning of the amount of FoCoSi spots, the oedema and the amount FPS in the superior palpebral conjunctiva was calculated. Interestingly, all three parameters presented similar results.

If the objective findings of FoCoSi were worse, the reported symptoms were worse, as well. In detail, if the oedema were graded worse, the symptoms were graded worse as well. That finding was strongly significant ( $p = 0.002$ ). For the amount of FoCoSi spots in general, the same statistically significant correlation was found as it was for oedema findings ( $p = 0.003$ ) (Table 4).

Finally, the more FPS observed in superior palpebral conjunctiva, the more severe subjective symptoms were described. Statistically, this correlation showed the weakest significance ( $p = 0.032$ ) from the observed three findings. In comparing subjects without FPS reaction and those with more than six spots, there was a strong statistical correlation ( $p = 0.001$ ) indicating that a higher FPS

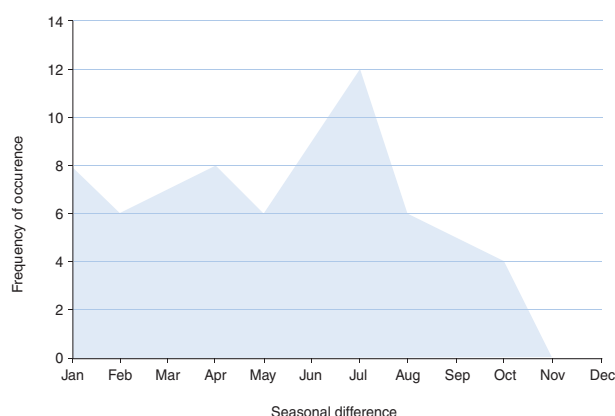


Table 2. Seasonal difference in occurrence of FoCoSi events

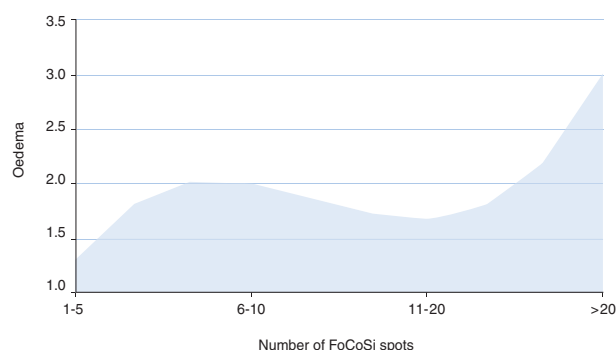


Table 3. Correlation between the amount of FoCoSi and oedema

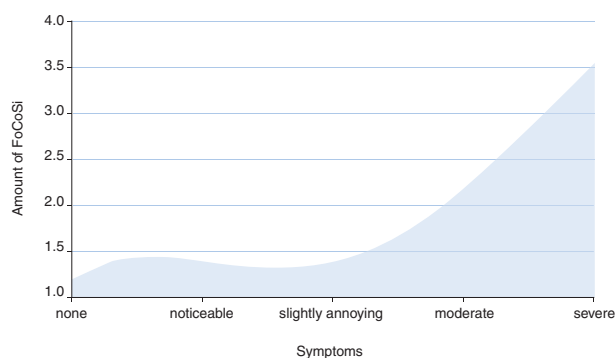


Table 4. Correlation between symptoms and amount of FoCoSi in the superior palpebral conjunctiva

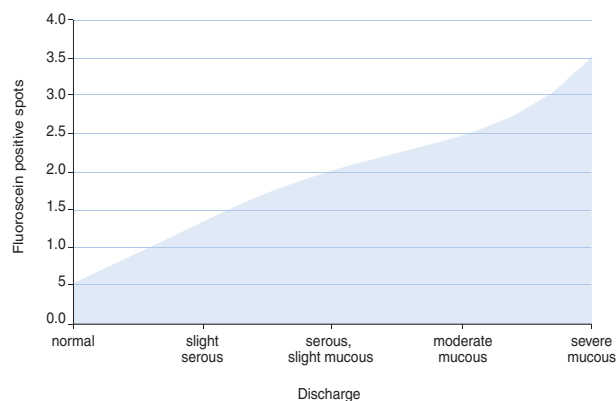


Table 5. Correlation between discharge and FPS

grading results in more severe symptoms.

There was a statistically significant correlation between the character of the noted tear secretion and the conjunctival oedema and FPS, respectively ( $p < 0.050$ ). If the subjects had severe oedema or a higher amount of FPS, the discharge was more severe and more mucous-like (Table 5).

### Results of the contact lens section

The contact lens types most often involved in FoCoSi were senofilcon A (45.7%), lotrafilcon A (26.1%), balafilcon A (19.6%) and galyfilcon A (8.7%); and none of the subjects presenting FoCoSi used lotrafilcon B. Due to the small number in the cohort, lotrafilcon B was not considered for statistical evaluation. These results were statistically significant ( $p = 0.005$ ) compared with the asymptomatic control group. To be clearly evident, the risk ratio for developing FoCoSi for each contact lens material used was calculated and can be seen in Table 6. Lotrafilcon A (2.12) and senofilcon A (1.53) showed the highest risk ratio, followed by balafilcon A (0.70) and galyfilcon A (0.29).

The contact lenses were worn in different modalities; 56.5 per cent used their contact lenses on CW basis, up to one month as a

maximum, with the exception of one week for senofilcon A material. Wearing modality and contact lens material did not differ significantly ( $p = 0.338$ ). Life span of each contact lens worn, at the time of FoCoSi happened, was reported; 61.9 per cent of the contact lenses were over the half-time of their life span.

### Solution and deposits analysis

None of the findings in the solution category was statistically significant for a correlation with FoCoSi. The degree of deposits and type of material deposited on the surface were reported for each subject. Lipids are a common deposition for SiHy. In this study 22.8 per cent did not have any visible lipid deposits, 44.6 per cent had slight lipid deposition, 20.7 per cent had mild deposition and 12.0 per cent had moderate deposition. Interestingly, no subject had severe lipid deposition. While mucin is heavily produced in CLPC, deposition of mucin material would be logical, but 76.7 per cent of subjects showed no mucin deposits at all, 13.3 per cent showed slight deposition, 7.8 per cent had mild and 2.2 per cent moderate mucin deposition. Again, none of the subjects showed severe deposition.

There was no statistically significant correlation between the severity of conjunctival oedema, or FPS in the superior palpebral conjunctiva, and the amount of the previously discussed specific depositions on the contact lens surface ( $p > 0.050$ ). Finally, the amount of mixed depositions was noted; 57.6 per cent showed no deposition at all, 19.6 per cent slight, 12.0 per cent mild, 5.4 per cent moderate and 5.4 per cent severe mixed depositions. Subjects with more severe follicle-like papillae formations (oedema  $p = 0.021$ , staining  $p = 0.008$  and FPS  $p = 0.032$ ) where observed with significantly more mixed deposition (Table 7).

Comparing the different contact lens materials and the type of deposition noted, there were no significant differences found for the different depositions, except for lipid. Balafilcon A material does attract statistically significantly more lipids ( $p = 0.012$ ) than the other materials.

## Conclusion and discussion

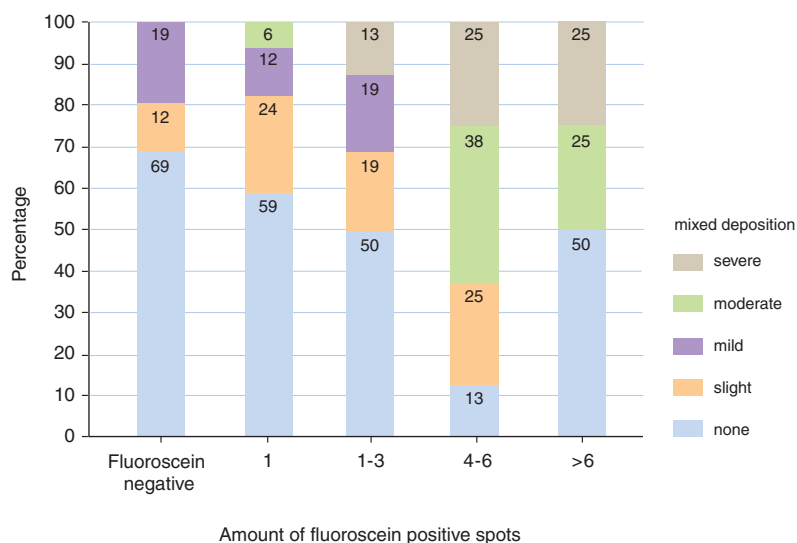
This study confirms the clinical presentation of follicular-like conjunctivitis associated with silicone hydrogels in cases with CLPC.

### Aetiology

The incidence was 3.8 per cent lower than reported in events with CLPC.<sup>16,21</sup> Gender and age were not a significant factor in developing FoCoSi which correlates to CLPC.<sup>11</sup> Whitish appearance in severe CLPC or GPC cases with a longer period of time was presumed to be a cicatrization of the conjunctiva surface at the apex of the papillae and appear in a cream/white colour.<sup>22,81</sup> The onset time for FoCoSi after the first introduction to SiHy contact lenses was between four months and eight years. This indicates that for FoCoSi to occur it is not a matter of time or a chronic pathway. On the contrary, it seems to be an acute reaction. Sugar and colleagues<sup>82</sup> presumed a thickening of the overlying conjunctiva as the reason for a milky appearance in some cases of GPC after keratoplasty. In earlier stages the papillae apex can display infiltrates, which appear in a whitish colour as well. These observations better match the appearance of FoCoSi than a cicatrization of the conjunctiva. If the immunohistochemical studies for CLPC<sup>36-39</sup> represent the same findings in subjects with FoCoSi, infiltration of inflammatory leucocytes could give an explanation for the whitish appearance of FoCoSi. Sulfido peptide LK increases microvascular permeability,<sup>67</sup> which has the potential for creating oedema in the

Material	Cohort (%)	Events (%)	Risk ratio
Balafilcon A	28.0	19.6	0.70
Lotrafilcon A	10.5	26.1	2.12
Senofilcon A	29.9	45.7	1.53
Galyfilcon A	29.8	8.7	0.29

**Table 6. Risk ratio for developing FoCoSi for different contact lens materials**



**Table 7. Correlation between mixed deposition and FPS**

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surrounding conjunctiva, leading to the characteristic shape of FoCoSi.

## Environmental influence

An interesting finding was the seasonal distribution of FoCoSi events with peaks in January, April and during summer until August. Even if studies have shown that patients with a history of allergy seem to be more susceptible to CLPC,<sup>8,9</sup> our findings did not correlate properly with allergies to pollen reported by the subjects. Fifty per cent of all FoCoSi subjects did not report any known allergy at all, and the January reports during winter in particular cannot be explained with pollen counting. Other factors like high pollution of the air could provide an answer to that question.

During the winter season, long periods of atmospheric inversion are common in Switzerland.<sup>83</sup> While the lower parts of Switzerland are predominantly covered by fog, the higher areas enjoy longer periods of sunny days. During atmospheric inversion, temperatures in the lower areas are cooler than in the higher alpine regions, resulting in minimal air exchange between both layers, and the pollution of the air rises dramatically. Other meteorological factors such as ozone (O<sub>3</sub>) and temperature could have an impact on FoCoSi development. From April until August 2007, ozone frequently exceeded the limit value (120 µg/m<sup>3</sup>) published by Swiss federal emission control.<sup>84</sup>

Pollution characterised by elevation of oxides of nitrogen (NO<sub>x</sub>), ozone, tobacco smoke, fine and ultra-fine particulate and diesel exhaust particles seems to enhance allergic disease.<sup>85</sup> Additionally, the bioavailability of grass pollen allergens may be modulated by air pollutants. Interestingly, cleaning pollen from air pollutants reduces the allergic reaction significantly.<sup>86</sup> We have further studies arranged to resolve these questions.

## Unilateral versus bilateral presentation

CLPC was reported only in 10 per cent of the cases as a truly monocular event,<sup>17</sup> whereas a study with data from Australia and India<sup>19</sup> showed with 78.4 per cent the highest amount of unilateral CLPC events reported so far in a study. In our cohort 22.8

per cent of FoCoSi events were unilateral. This phenomenon cannot be explained with unilateral different mechanical irritation as it clearly is in cases with foreign bodies on the ocular surface. All of the FoCoSi subjects have worn the same contact lens material on both eyes and only two lenses had minor material defects that could have introduced unilateral mechanical irritation to the tarsal conjunctiva.

On the other hand, immunological responses were discussed as a reason for CLPC; the fact that there were a great number of unilateral FoCoSi events may indicate that factors other than general immunologic responses may contribute to the pathogenesis of FoCoSi condition. Additionally, ocular viral infections are often unilateral in the beginning but with all the negative corneal and conjunctival findings related to viral infections and negative preauricular lymphadenopathy as well, viral involvement can be ruled out. We have not found a rational explanation for those unilateral findings, so far. Further studies should be conducted on that topic.

## Local versus general form

As described in Australia there are local (81.8 per cent) and general (18.2 per cent) presentations of CLPC.<sup>19</sup> FoCoSi showed a similar distribution (83.6 per cent local versus 16.4 per cent general). In very close agreement with CLPC, FoCoSi subjects with the general form reported significantly ( $p = 0.003$ ) more symptoms; however, the mechanisms of action and aetiology of local versus general CLPC are poorly understood and clinical variables such as physiologic parameters of limbal and bulbar redness, lens surface and lens-fitting parameters could not differentiate between the subjects who developed either local or general CLPC.<sup>19</sup> For FoCoSi, no correlation between local or general form and contact lens material, wearing modality, lifespan of contact lens, movement of contact lens, corneal reaction, or limbal and bulbar redness could be found as well. In summary, none of the included parameters of our study design showed an explanation for the different distribution of local and general FoCoSi form.

## Fluorescein positive spots

In the FoCoSi study, fluorescein positive spots (FPS) appeared as the most relevant objective clinical parameter. Subjects presenting with FPS had more severe symptoms and mucous discharge and as a consequence, heavier coated contact lenses. These spots were always observed

on the apices of follicular-like papillae. In contrast, there was no FPS in normal papillae formation. Due to FPS, the FoCoSi syndrome can be divided into an active and a dormant stage of presentation. The active form only, with FPS, was responsible for the subjective symptoms patients noted, whereas the dormant form, without FPS, was detected only through previously described objective findings. Interestingly, the dormant form was observed only in patients who had previously presented an active form once in their lifetime.

FPS or whitish areas in CLPC or GPC have been discussed in only a few studies so far.<sup>22,37,43,81</sup> Fluorescein staining occurs with epithelial cell damage and frequently occurs with papillae with apices that are flattened or crater-like. The reason for those alterations was presumed to be the initiating mechanical trauma.<sup>22,37</sup> In contrast, Greiner<sup>43</sup> found no FPS over those whitish papillae in GPC due to an epithelialised foreign body.

Lotraficon A, with the highest modulus (1.4) of the studied materials, supports that presumption, but mechanical trauma alone as reason for FoCoSi and FPS seems to be unlikely, because senofilcon A material with a very low modulus (0.6) had the second highest incidence of FoCoSi events. Additionally, senofilcon A contact lenses showed the lowest amount of movement on the bulbar conjunctiva, which should have a positive effect from the mechanical point of view. Finally, in the majority of cases no defects in contact lens edge design—which could have induced FoCoSi or FPS—were found.

Another approach is to recognise FPS as a consequence of an inflammation or immunological process rather than the cause for FoCoSi. The immunohistochemical studies for CLPC<sup>31-37</sup> not only give an explanation of the whitish appearance of FoCoSi caused by inflammatory leucocytes infiltration, it also gives an explanation for FPS as well. Those processes promoting better infiltration of leucocytes can enhance the permeability of the overlying epithelium as well, resulting in possible staining with fluorescein.

## Contact lens influence

Subjects wearing lotraficon A (2.12) and senofilcon A (1.53) contact lenses, respectively, had the highest risk ratio for developing FoCoSi, especially if the contact lenses were worn on a CW modality.

## Deposition on contact lens surface

FoCoSi events may indicate an immunologic response to deposits that accumulate on

the contact lens surface as it was reported for CLPC in several studies. It is believed that these deposits or the exposure of the upper lid to allergens, especially denatured protein,<sup>51</sup> on the contact lens surface is the initiating factor and subsequent immunologic reaction occurs in CLPC. If oedema, the number of FoCoSi spots and especially FPS got worse, mixed deposition on the contact lens surface was increased, which was more likely to be the consequence of the increased mucous discharge rather than the cause.

A shorter replacement schedule of contact lenses, discussed in former studies, was found to be preferable to avoid CLPC,<sup>13-14,19</sup> and especially a one-week replacement cycle showed no CLPC formation at all.<sup>19</sup> These findings make sense to prevent the ocular environment from coming in contact with a high amount of denatured protein depositions; however, 20.1 per cent of FoCoSi events were found in patients wearing their contact lenses one week CW (53.9 per cent of subjects in the CW group: 46.2 per cent senofilcon A and 7.7 per cent galyfilcon A). This finding suggests that another deposition or mechanism hypothesised for CLPC so far may play a role in the aetiology of FoCoSi, if any. On the other hand, the older the life span of the contact lenses, the more prone the subjects were to FoCoSi. This indicates that before FoCoSi can occur, a certain period of interaction between the eye and the contact lens is needed.

SiHy materials have different deposition profiles from those seen in conventional hydrogel lenses and can be summarised as less accumulative to protein but with a higher percentage of denatured protein<sup>50,51</sup> and a significantly higher affinity to lipids.<sup>54,58</sup> Lipid depositions are progressive, cumulative and do not plateau like protein. Because of great intersubject variability in lipid deposition, it was suggested that protein deposition is driven primarily by contact lens material, whereas lipid deposition is related to both material composition and intersubject differences in tear film components, blink factors and environmental factors.<sup>58</sup>

In the present study, the deposition profiles were equal between the different contact lens materials. Only the amount of lipids was greater in balafilcon A than for the other materials, but in contrast this material showed only a low incidence of FoCoSi. It must be said that the amount of deposition was judged only by using slitlamp impression. Subjects with more severe follicle-like papillae formations (oedema  $p = 0.021$ , staining  $p = 0.008$  and FPS  $p = 0.032$ ) were observed with significantly more mixed

deposition, but this indicates more the result rather than the cause of FoCoSi.

Especially in subjects with FPS a severe mucous discharge was frequently observed. Concentrating on lotrafilcon A and senofilcon A with the highest incidence of FoCoSi, in former studies lotrafilcon A showed the highest amount for denatured protein and senofilcon A the lowest. For lipids, senofilcon A showed the highest and lotrafilcon A the lowest amount. Additionally, the two materials are extremely different over a great variety of parameters, for example modulus or coating.

These findings indicate that there is not an easy explanation of how FoCoSi occurs. One may suggest that denatured protein depositions alone are not responsible for FoCoSi; lipid depositions must be considered as well. Even though lipids alone do not appear to be antigenic,<sup>60</sup> they can be transformed or influenced, for example with ozone. These are new ideas to clear up the questions of aetiology of FoCoSi and perhaps give a new approach to solving the questions around CLPC as well. Further studies should be done on that topic.

### Care solution

The contact lens care solution most related to FoCoSi was Opti-Free express (Alcon); however, in comparison with the control group, this finding was not statistically significant ( $p > 0.05$ ) as it is the predominantly used solution in that group. Furthermore, while looking at the high amount of CW subjects who did not use any care solution at all, it seems that the care solution plays a minor role in FoCoSi development and the follicular-like changes are not a reaction to certain solution components.

### Treatment of FoCoSi

The study design was not specifically made for evaluating the treatment of FoCoSi; however, two major treatments, changing wearing modality to DW or wearing daily disposable contact lenses for a two-week to four-week period, seem to be successful in solving the subjective symptoms during FoCoSi. If the subject was in CW, reducing wearing modality to DW was mostly effective enough. If the subject already was in DW, discontinuation of contact lens wear or changing to a daily disposable contact lens was successful. All FoCoSi subjects were able to resolve the syndrome and could continue with contact lens wear after treatment. FPS and oedema were completely resolved but the FoCoSi spots remain with a follicular-like whitish appearance. This was described as the dormant form of

FoCoSi and remains without any subjective complaints. Due to the juridical situation in Switzerland, we were not allowed to use medications for treatment. Further studies on that topic should be done to determine which, if any, medication could bring the dormant FoCoSi back to normal palpebral conjunctival appearance.

## Summary

FoCoSi is a novel and relevant subtype of CLPC. The aetiology seems to be unclear to date and raises new questions about the aetiology of CLPC as well. The theory of a combination of mechanical irritation and immunological hypersensitivity reaction is questionable, because the mechanical irritation of senofilcon A can be classified as very low. On the other hand, lipid deposition on contact lenses rather than protein deposition and air pollution like ozone and fine and ultra-fine particles are a new approach in finding the cause of FoCoSi or CLPC. Fluorescein staining of the apices has shown the highest correlation with subjective symptoms. This is new and clinically interesting knowledge as well.

Finally, the different presentation of FoCoSi, such as local versus general, or bilateral versus unilateral, correlates very well to the reported findings in CLPC but our study design could not give an explanation for the aetiology of those findings. Further studies should be performed to answer all those new questions.

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