FoCoSi

Follicular-like Conjunctivitis associated with Siliconhydrogels

Authored by:

Michael Wyss, FAAO
Hammerweg 7, 3400 Burgdorf, Switzerland
mike.wyss@gmx.ch

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Advised by:
Michael Bärtschi, M.S.Optom et M.M.E., FAAO
Dietmar Kümmel, Prof.

Content

1 Abstract

1.1 ***Purpose***

The purpose of this study is to prescribe follicular-like conjunctivitis associated with Siliconhydrogels (FoCoSi) in silicone hydrogel contact lens wearers as a novel subtype of the well prescribed contact lens induced papillary conjunctivitis (CLPC).

1.2 ***Methods***

1211 patients who wore silicon hydrogels were included in this prospective, non-randomised, single center 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) silicon hydrogel lens types. CCLRU and other specifically developed grading scale were utilized for evaluation. Grading of 2 and above was rated as clinically significant. Statistical evaluation was performed for eyes rather than subjects.

1.3 ***Results***

The clinical presentation of FoCoSi could be confirmed and showed an incidence of 3.8%. 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 Protein, Lipid deposition on the contact lens surface and air pollution like Ozone or fine and ultrafine particles seems to be important factors in developing FoCoSi, whereas mechanical irritation played a minor role.

1.4 ***Conclusion***

FoCoSi is a novel and relevant subtype of CLPC. Further studies should be performed to validate these findings and clear up several questions about the aetiology of FoCoSi and CLPC.

Keywords: Giant papillary conjunctivitis (GPC), contact lens-induced papillary conjunctivitis (CLPC), follicular-like conjunctivitis associated with siliconhydrogels (FoCoSi)

2 Introduction CLPC

Contact lens-induced papillary conjunctivitis (CLPC), also known as giant papillary conjunctivitis (GPC), is a well prescribed condition and a major cause of permanently discontinuation of contact lens wear.[1] It is an inflammatory and usually reversible condition that is characterized by enlarged papillae, hyperaemia of the palpebral conjunctiva and excessive mucus 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.[2,3,4,5,6] The condition was first reported in 1970 in a patient wearing rigid contact lenses[5] and later by Spring[7] in 1974 in patients wearing hydrophilic contact lenses and has since been frequently reported in wearers of both rigid and soft contact lenses.[3,4,5,8,9,10,11,12] The incidence of CLPC varies but is greatest with soft contact lens wear (from 1.9% to 45%)[13,14,15,16,17,18] especially while wearing conventional soft contact lenses extended wear (EW).[2,15,19] Disposable soft contact lenses, especially if wearing time is under 3 weeks, showed significant lower incidence of CLPC than conventional soft lenses.[13,14,19] No CLPC at all was found in patients wearing their contact lenses on a 1 week or 1 day replacement cycle.[20] Preliminary studies and case reports by Stern[18] and Skotnitsky[21] suggest that there is a greater occurrence of CLPC with silicone hydrogel (SH) lenses. When comparing six nights of extended wear to 30 nights of extended wear with SH, there was no difference in the occurrence of CLPC.[18]

*2.1 **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 papilla.[22,23,24,86] 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, mucus 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.[3,25,26,27,28,29,30,31,32,86] Recent immunohistochemical 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.[33,34,35,36] Sulfidopeptide leukotriens produce increased microvascular permeability in a variety of tissues, which results in edema formation due to the extravascular accumula-

tion of plasma. Leukotriens (LT) are found in a higher concentration in patient with CLPC and in patients with allergies and LT acts independently of histamine.[86] Immunoglobulin (IgE and IgG) antibodies in the tears and degranulated mast cells in ocular tissue were increased in patients with CLPC.[37,38,39] All those results indicate that it is an Immunoglobulin mediated type 1 hypersensitivity reaction.

The papillae extend from the upper palpebral conjunctiva and appear as round light reflexes giving an irregular specular reflection. The number of papillae can vary from hundreds covering the entire tarsal conjunctiva to one papilla.[22,39] The term GPC has been used to describe inflammation of the tarsal conjunctiva as has been reported with exposed sutures, ocular prosthesis, extruded scleral buckles, cyanoacrylate adhesive, and epithelization of corneal bodies.[29,40,41,42,43,44,45] The response of the tarsal conjunctiva to a raised foreign object suggests mechanical trauma may play a role in the aetiology of this condition. In these cases, enlarged papillae are found localized to the area of the tarsal conjunctiva that is in contact with the stimuli.

2.1.1 GPC compared with vernal keratoconjunctivitis

The term “giant” was coined for the large papillae crowded together to reach a diameter of 1.0 mm or more and is similar to that produced by vernal keratoconjunctivitis (VKC).[37] VKC and GPC develop similar symptoms and clinical signs and are thought to belong to the same clinical spectrum. Pathologic findings of giant papillary proliferation in VKC are characterized by infiltration of inflammatory cells and proliferation of connective tissues in subconjunctival tissue. In the conjunctival epithelium of VKC patients, infiltration of inflammatory cells such as mast cells and basophils is observed. Infiltration of eosinophils,[46,47] helper T cells type 2 (Th2),[48,49] and CD45RO-positive lymphocytes[50] are also observed in the subconjunctival tissue. These findings are compatible with a tissue reaction caused by allergic inflammation. It has been reported that various substances, such as chymase produced by mast cells,[51] Th2 cytokines produced by Th2 lymphocytes, interleukin (IL)-4 and IL-5,[52] eotaxin, which promotes the infiltration of eosinophils,[53] and eosinophil cationic protein, which is one of the eosinophil specific granule proteins, increase in the tears of patients with VKC.[54] Although the histological abnormalities of mast cells, eosinophlis and basophils are present in both conditions, they are present to a much higher degree in VKC than in GPC. Especially the numbers of Eosinophils and percentage of degranulated Mastcells are significantly elevated in VKC, compare to GPC.[26,27]

2.1.2 Contact lens induced papillary conjunctivitis

A more appropriate term that covers the condition of enlarged papillae with contact lens wear is contact lens induced papillary conjunctivitis (CLPC).[55] It can occur bilaterally or in 10% of cases truly unilaterally.[17] 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.[11,16,38] Gender was not found to be a relevant associated factor for CLPC.[11] Patients with a history of allergy have been reported to be more susceptible to CLPC.[20,56,57] Of further significants is the distribution in time of diagnosis of CLPC, with peaks in spring and in late summer to early fall, which was assumed to correlate with ragweed pollen season.[58] There have been reports prescribing differences in the distribution of papillae across the tarsal conjunctiva with different contact lens types.[39,59,60] In Korb's et al [39,56] studies, papillae in soft lens wearers developed first in zone 1 (area closest to the tarsal plate) and the remaining zones (the central tarsal conjunctiva and the region near the lid margin) became involved only after papillae developed in zone 1. In contrast, papillae in hard lens wearers were never observed alone in zone 1 but did occur alone in zones 2 or 3. EW Studies with SH have indicated that there are two distinct categories of CLPC: general and local.[16,21] 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 patients with local CLPC do. The location and limit of the affected area in local CLPC may indicate that local mechanical stimulation is the major cause of this condition, whereas general CLPC, in which the part of the palpebral conjunctiva not directly contacted by contact lenses is also affected, may indicate a general immunological hypersensitivity reaction.[21]

The second most prevalent sign of CLPC, after the inflammation of the conjunctiva, is excessive mucus. There is no increasing of the number of mucus secreting goblet cells,[61] moreover the mucus vesicles in non-goblet epithelial cells contribute dramatically to the increase of mucus production.[62,63] Excess mucus in the tear film interfere with vision by coating contact lens surface and increased contact lens movement. Patients may report accumulation of mucus in nasal corner of the eye, especially upon awakening.[58]

CLPC is thought to be an immunologic response to deposits (lipid, protein and mucin[64,65]) on the contact lens surface.[55,66] Studies have provided valuable information about deposit composition and formation mechanisms. Tear protein identified include

lysozym, lactoferrin, protein-G, pre-albumin, albumin and immunoglobulines.[67,68,69] Protein deposition varies in amount and activity and is driven primarly 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 U.S. Food and Drug Administration (FDA) group II and IV have a tendency to have more deposits than lower water content lenses. Ionically charged contact lens polymers (FDA group III and 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 on material ionicity. Interestingly the protein deposition is largely unrelated to subjective differences, whereas lipid deposition is related to both material composition and intersubject differences in tear film components, blink factors and environmental factors.[64,70,71,72,73] SH materials have different deposition profiles to that seen with conventional hydrogel lenses. The surfaces of SH materials are characteristically hydrophobic, typically significantly lower quantities of protein and higher levels of lipid deposition being measured.[74,75,76,77,78] In Vitro Study[79] and in Vivo study[72] found the highest amount of Lipid adsorption (non-polar Cholesterol and polar phosphatidylethanolamine) in SH 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.[80] 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.[81] The kinetics of protein showed no differences in Lysozym accumulation between 5 different SH materials until 5 days of wearing time. But increases consistently after a longer period of wearing time, without reaching a plateau like the FDA group IV materials.[82,]Jones and co-workers [68,69] found approximately 50% denatured lysozyme on balafilcon A ex vivo lenses and 80% on lotrafilcon A ex vivo lenses. Galyfilcon A lenses denatured only about 25% of the lysozyme in vitro but approximately 50% 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. An other study has demonstrated that protein denaturation may play an important role in the development of CLPC.[53] This fact is of significant interest at this time, because CLPC being reported at higher levels with silicon-based lenses than with conventional lens materials.[21]

Other factors such as meibomian gland dysfunction (MGD)[17,83] have also been suggested to be involved in the cause of CLPC. In contrast, the second study on that topic from Molinary et al [84] couldn't find any correlations between MGD and CLPC anymore.

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.[24] 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.[17,61,85] In CLPC patients NCF was increased 15 times the level of asymptomatic patients. Biochemical characterization 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 7 days.[82] Further more, the eventual activation of Lipoxygenase results in the release of LK too.[86]

After all, there has been no correlation between CLPC with a particular contact lens type or specific deposits so far. 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 et al.[63] have shown that when contact lenses from patients with CLPC are placed on monkey eyes, a papillary tarsal reaction develops with more of IgE and IgG. However, if contact lenses from asymptomatic patients (but have coated contact lenses) are placed on the eyes of monkeys, a papillary reaction does not occur, nor is there an increase of tear immunoglobulins.

In summary, the origin of CLPC appears to be a combination of mechanical irritation and immunological hypersensitivity reaction.[58]

*2.2 **Purpose of this study***

Papillae consist of a vascular supply which is observed radiating from a vessel occupying the central core of each papilla.[22,23,24,58] In contrast, as a differential diagnosis, follicle has a white center obscuring underlying vessels.[22] (Figure 1) In vivo confocal microscopy showed in follicular conjunctivitis, a hyporeflective core containing hyporeflective round cells surrounded by a hyperreflective capsule and vessels.[87] So follicles appear as round to oval elevations which measuring between 0.5 to 1.5 mm in diameter with a grey-white center. 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, hyperemia, chemosis, subconjunctival haemorrhage, follicular conjunctival reaction and occasionally a pseudo membranous or cicatricial conjunctival reaction. [88,89,90,91,92,93,94] 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.[95,96] Presumed diagnosis with clinical findings, especially follicles, scanty watery discharge and preauricular adenopathy were consistent with laboratory findings in 76%.[91]

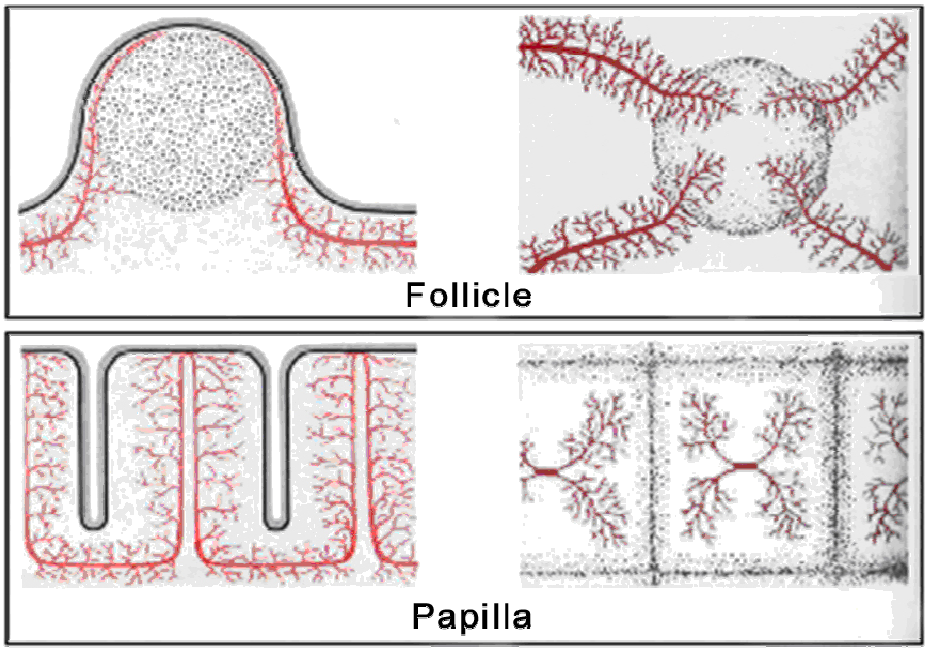


Figure 1: Papilla versus Follicle (GOH Naumann Pathologie des Auges 1980;12:252)

Viral conjunctivitis is typically characterized by a mononuclear cellular response with preponderance of lymphocytes or monocytes. In early stages neutrophils can be numerous.[92] 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.[89,97] The reason for these differences remain unclear in the studies. The cornea shows 3 to 4 days after onset of the symptoms a diffuse epithelial keratitis, followed, at 1 week, by a focal epithelial keratitis that persists for up to 2 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,[98] 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 [89,90,93,94] but were never prescribed so far as a finding in CLPC. Despite there is few literature which prescribing a follicular-like response of the upper conjunctiva in CLPC [24,39,44,99] besides the response of papillae formation. This reaction was presumed in

severe cases with a longer period of time to be a cicatrisation of the conjunctiva surface at the apex of the papillae and appear in a cream/white colour.[24,96] Sugar et al[41] 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.[24,36,94] The reason for those alterations was presumed to be the initiating mechanical trauma. Greiner[38] in contrast found no fluorescein staining over those whitish papillae in GPC due to an epithelialized 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 introduction of Siliconhydrogel contact lenses we had a strong feeling of seeing more 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 Siliconhydrogels (FoCoSi) in cases with CLPC in a large number of Siliconhydrogel lens wearers. The study involved prospectively collected data from subjects wearing their contact lenses on a regular modality and replacement schedule. The data was compared with an asymptomatic control group.

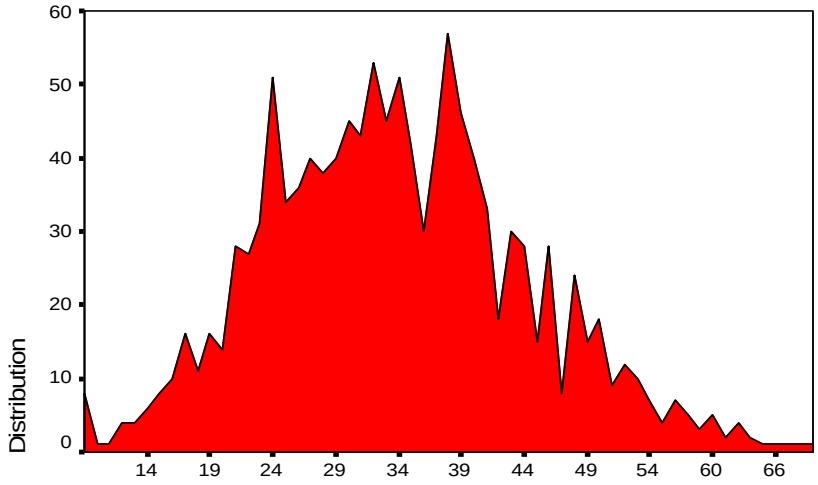
3 Material and Methods

The study was conducted from the kontaktlinsenstudio baertschi in Bern, Switzerland. A prospective, non randomised, single center study design was chosen for this research project. 1211 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), in between the period of January 1st 2007 and December 31st 2007. All included subjects had no history of ocular or systemic problems and no history of use of any medications that may affect contact lens wear.

All four clinicians involved in clinical trials at the kontaktlinsenstudio baertschi underwent concordance training in ocular responses to ensure measurements were in close agreement. All experimental protocols are complied with the Declaration of Helsinki for Experimentation on Humans, 1975 and revised in 1983.

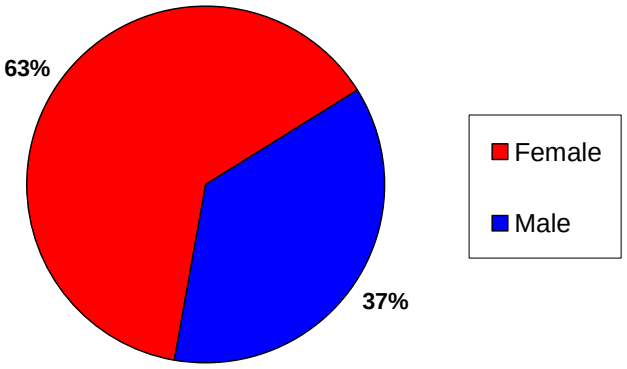
*3.1 **Demographic Statistics***

All subjects who wore silicon 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% of them were female (Table 1 + 2).



N	1211
Mean Score	34.09
Median	33
SD +/-	10.242
Minimum	10
Maximum	80

Age **Table 1**



Gender **Table 2**

*3.2 **Follow-up Schedule***

Every Patient was controlled at least two times, in a six month interval, during the study period. Neophytes for EW underwent a period of DW before beginning EW. During EW subjects were examined at 24hours, at one week and one month to assess the ocular response to EW. Thereafter subjects were seen at six month intervals for the duration of the study. If an additional adverse event happened, the patient was forced to come in for an unscheduled visit in the first three days after awareness of the event. As an adverse event were the following subjective symptoms defined:

- Itchiness or scratchiness of one or both eyes (like feelings of an allergic reaction against Pollen) especially during evenings. These symptoms will be getting worth while rubbing or touching the eyes.
- Increased production of mucus during wearing time of contact lenses.

- Decreased visual acuity and dislocation of contact lenses, due to enormous depositions on the surface of the contact lenses.

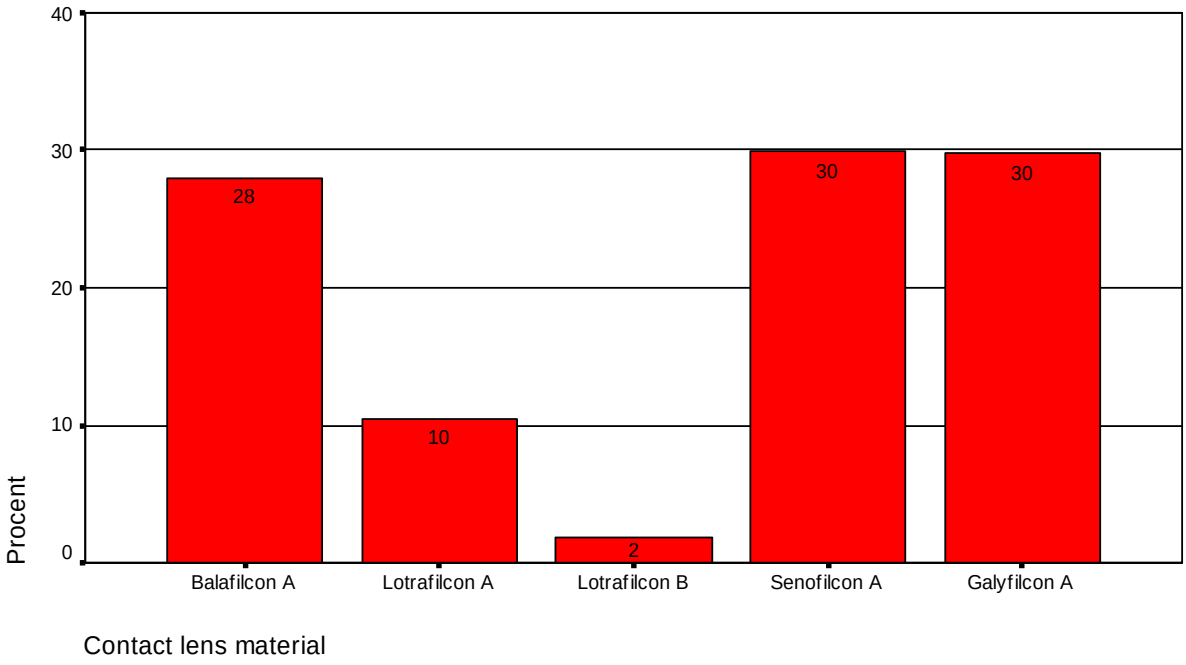
3.3 Materials

The contact lens materials included in the study were five different types of silicone hydrogel contact lenses: Lotrafilcon A, Lotrafilcon B, Balafilcon A, Galyfilcon A and Senofilcon A. The material properties can be viewed in Material[100] Table 3. All possible variation, such as Toric or Multifocal Designs were included as well.

Brand Name	**PureVision**	**Night & Day**	**Acuvue Advance**	**Acuvue Oasys**	**AirOptix**
Manufacturer	Bausch & Lomb	Ciba Vision	Vistakon	Vistakon	Ciba Vision
Material	Balafilcon A	Lotrafilcon A	Galyfilcon A	Senofilcon A	Lotrafilcon B
Dk	99	140	60	103	110
Dk/t	110	175	86	147	138
Center thickness (mm @ -3.00D)	0.09	0.08	0.07	0.08	0.08
Water content (%)	36	24	47	38	33
BC (mm)	8.6	8.4 / 8.6	8.3 / 8.7	8.4 / 8.8	8.6
Refractive Index	1.426	1.43	1.41	1.42	1.42
Surface Treatment	Plasma Oxidation	Plasma Coating	Hydraclear	Hydracelar plus	Plasma Coating
UV filter	No	No	Yes	Yes	No
FDA Group	III	I	I	I	I
Initial Modulus (MPa)	1.1	1.4	0.4	0.6	1.2
Tensile Modulus (psl)	148	238	65	68	190
Relative Initial Dehydration Rate	1.9	1	2.4	1.8	1.5

Material **Table 3**

The distribution of the used contact lens materials can be seen in Table 4 and distribution is listed as follows: 29.9% of all subjects used Senoflicon A, Galyfilcon A Material was used by 29.7%, followed by Balafilcon A with 28%, Lotrafilcon A used 10.5% and finally Lotrafilcon B was used by 1.9%.



Contact lens Type **Table 4**

3.4 Methods

First of all, visual acuity was noted as Visus (20/20 correlates to 1.0) according DIN / EN ISO normative data. (Table 5)

Visus DIN / EN ISO	Snellen 6m	USA
2.0	6/3	40/20
1.6	6/3.75	32/20
1.25	6/4.8	25/20
1.0	6/6	20/20
0.8	6/7.5	20/25
0.63	6/10	20/32
0.5	6/12	20/40
0.4	6/15	20/50
0.32	6/20	20/63
0.25	6/24	20/80
0.2	6/30	20/100
0.16	6/38	20/125
0.125	6/48	20/160
0.1	6/60	20/200
0.08		20/250
0.063		20/317
0.05		20/400

Visus vs. Snellen **Table 5**

The cornea, bulbar conjunctiva, upper and lower tarsal conjunctiva were examined using the Bon Digipro 2 digital slit lamp biomicroscope with a resolutions of single pictures up to 1392 x 1040 Pixel and Videos up to 800 x 600 Pixel including a 5 step Galilean magnification changer (5x,10x,16x,25x,40x). 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 subject reported symptoms was graded as none (0), noticeable symptoms but without any limitations in contact lens wear (1), slight annoying symptoms with slightly limitations in contact lens wear (2), moderate symptoms and limitations in contact lens wear (3) and finally severe symptoms with severe limitations in contact lens wear (4). Subjects tearing at the moment of FoCoSi was graded as normal (0), pronounced tear meniscus (1), rarely overflowing tears (2), common overflowing tears (3) and excessive tearing or epiphora (4). Additionally, subjects preauricular lymph nodes were palpated and graded as no finding (0) or positive reaction (1) and furthermore the anterior portion of the eye was observed to rule out any probably associated virus infections. Finally subjects predominance to pollen allergy reaction was noted as no allergy history (0), reaction typically occurs in Spring (1), Summer (2), Spring and Summer (3) or 12 month atopic (4).

3.4.1 Cornea

The cornea was inspected and graded for 6 (Stromal edema, Microcysts/vacuols, Vascularisation, fluorescein Staining, corneal Infiltrates and scarring of cornea) different hallmarks. Gradings above 2 were considered as clinical relevant. Stromal edema was graded as no striae (0), 1-5 striae (1), 6-20 striae with less than 5 folds and mild haze (2), more than 20 striae with more than 5 folds and moderate haze (3) and opacity from limbus to limbus (4). Microcysts/Vacuols were graded as none present (0), 1-10 present (1), 11-30 present (2), 31 – 70 present (3) and more than 70 microcysts/Vacuols (4). Vascularisation was graded as not visible (0), less than 1mm (1), between 1.0 to 1.5mm (2), between 1.6mm to 2.0mm (3) and more than 2.0mm (4). Additionally localisation of vascularistation was graded as superior (0), inferior (1), temporal (2), nasal (3) and circular (4). For fluorescein staining were 3 different gradings developed, distinguish the area, localisation and depth. In detail the gradings for area was no staining (0), 1-20 punctate staining (1), 21-40 punctate staining (2), more than 41 punctate, diffuse region of staining (3) and dense areas with fluent areas. Staining localisation was graded as superior (0), inferior (1), temporal/nasal (2), central (3) and staining over the whole cor-

nea (4). Finally depth was graded as no stroma diffusion (0), delayed diffusion of about 30-60sec (1), delayed diffusion of about 5-29sec (2), immediate, slight diffusion (3) and immediate diffusion into a wide area of the stroma (4). Infiltrates were graded for 4 different category groups (appearance of Infiltrates, localisation, depth, fluorescein staining). The appearance of infiltrates was graded as no infiltrates visible (0), faint infiltrates (1), mild distinguished infiltrates (2), moderate, round distinguished infiltrates (3), severe, not round distinguished infiltrates (4). Localisation of present infiltrates was graded as superior (0), in periphery (1), in midperiphery (2), central (3) and whole cornea affected (4). Depth in which the infiltrates were present was graded as epithelial (1), subepithelial (2), anterior stroma (3) and associated substance loss of the cornea in effected area (4). Fluorecein staining over the present infiltrate was graded as no staining (0) negative (dark spots) staining (1), epithelial staining (2), delayed diffusion into stroma (3) and immediate diffusion into stroma (4). Finally present scars in corneal stroma was graded as none (0), diffuse scars smaller than 2mm (1), focal scars 2-4mm big (2), focal scars bigger than 4mm (3) and loss of cornea integrity (4).

3.4.2 Conjunctiva

The bulbar conjunctiva was divided into a limbal zone (1) and a bulbar zone (2) respectively (Figure 2).

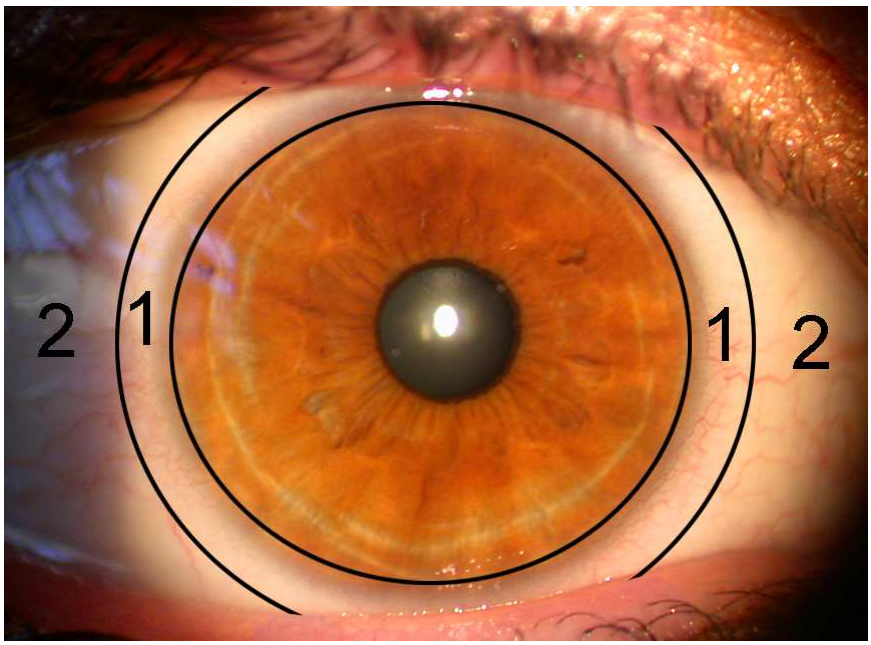


Figure 2: Conjunctiva devided into limbal zone (1) vs. bulbar zone (2)

Both zones were inspected for Hyperemia and Edema. For Hyperemia the grading was defined as no redness (0), slight focal Hyperemia (1), slight diffuse Hyperemia (2), moderate local or diffuse Hyperemia (3) and severe circular Hyperemia (4) for the limbal

zone and severe episcleral or scleral Hyperemia (4) for the bulbar zone. Grading for Edema for both zones was defined as no Edema (0) and slight Edema without conjunctiva folds (1). Grading (2) for the limbal zone was defined as severe local Edema, for the bulbar zone as several local Edema spots. Grading (3) was defined for limbal zone as slight circular Edema and for the bulbar zone as moderate general Edema. The highest Score (4) was given by severe circular Edema (Chemosis) for the limbal zone and for the bulbar zone for severe general Edema (Chemosis).

The palpebral conjunctiva can be divided into five zones (Figure 3). Zone 1 nearest the palpebral border, zone 2 the central area, and zone 3 the area along the lid margin of the palpebral plate. Zone 4 the area near the nasal region and zone 5 the area near the temporal region. CLPC is classified as local if papillae are present in only one or two zones of the conjunctiva and general if papillae are scattered across more than two zones or over the entire conjunctiva.[35] All of the five zones were assessed in the analysis.

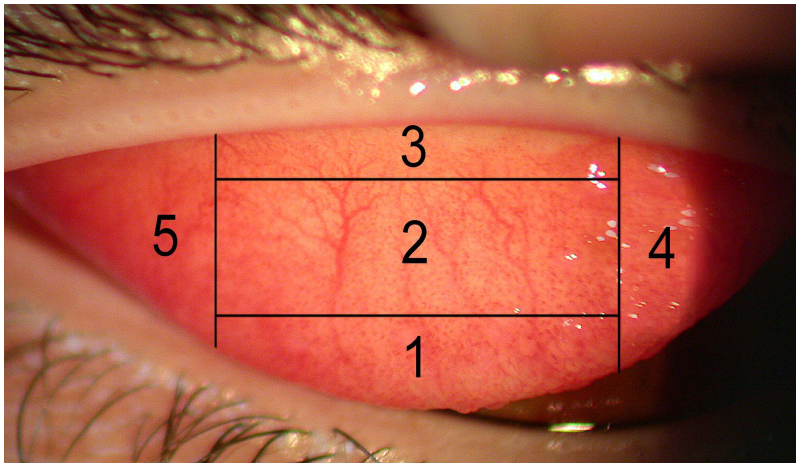


Figure 3 Five zones of the upper palpebral conjunctiva (right eye shown)

In examining the upper and lower palpebral conjunctiva, the size and location of the papillae, staining of the papillae and conjunctival hyperemia were noted and graded after the clinical grading scale developed by the CCLRU grading scales from zero to 4 in which 0.0 corresponds to no response, 1.0 corresponds to slight, 2.0 corresponds to mild, 3.0 corresponds to moderate, and 4.0 corresponds to severe response.[101,102,103] (Figure 4)

Hyperemia and papillae of the upper and lower palpebral conjunctiva were graded using the CCLRU grading scales as well. Any grading exceeding grade 2 was considered clinical relevant. If papillae were 0.3 mm or greater in diameter, with increased hyperaemia, the condition was classified as CLPC.[34,44]

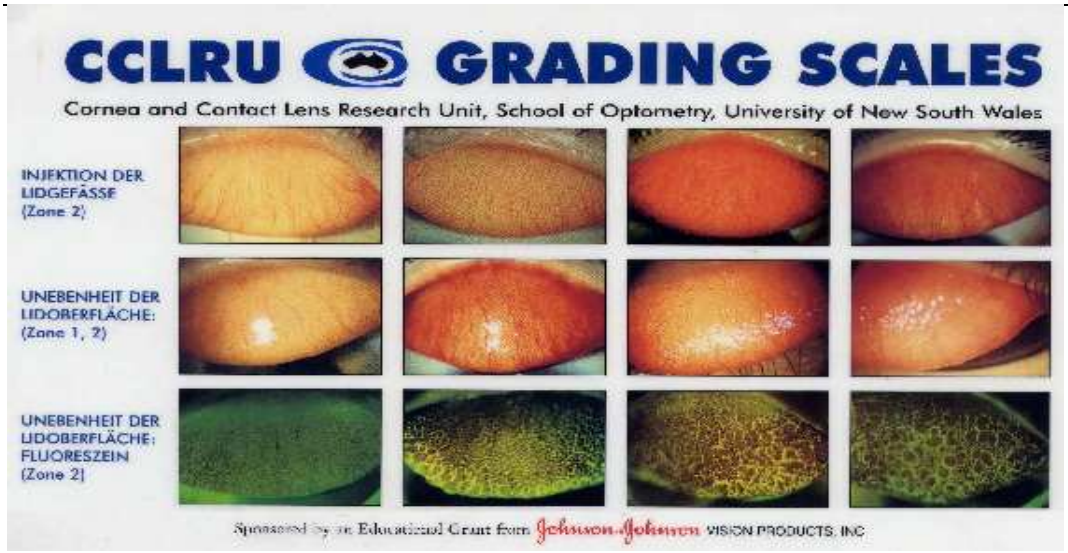


Figure 4: CCLRU Grading Scale 0 – 4 for the upper Lid Conjunctiva

Clinical diagnosis of CLPC and FoCoSi was based on biomicroscopic findings of papillary changes of the upper and lower palpebral conjunctiva. As FoCoSi classified were all subjects, which shown enlarged papillae that assumes a follicular-like appearance with the absence of the usual central vessel characteristic of papillae. An example of a FoCoSi event is shown in Figure 5. 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 changing's can be seen using the slit lamp biomicroscope, however with Adobe Photoshop 7.0 software modified colour presentation, the FoCoSi differences can be observed much better. In Figure 5 the modified picture contains less red but more blue light. In detail the photoshop colour balance was changed as follows:

- colour code value for medial tone and lights: cyan -100
- colour code value for deep tone: red +14

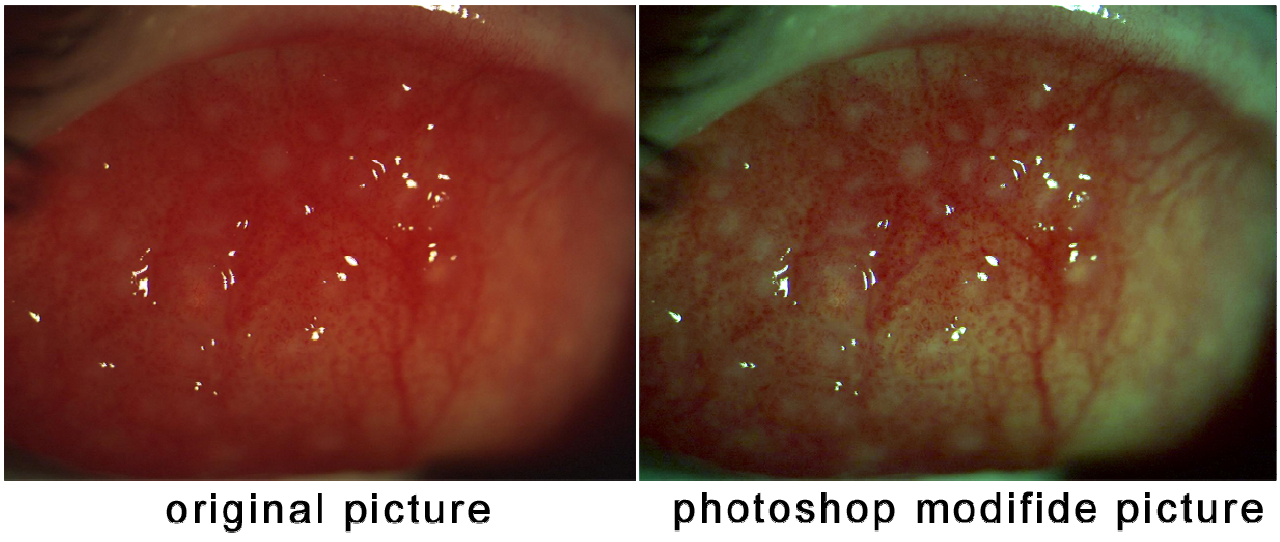


Figure 5: FoCoSi example as the original picture and as a software modified version

Grading for follicular-like papillae presented in the upper and lower lid was devided into several subdivisions. First of all, the quantity of present follicular-like papillae was graded as none (0), 1 to 5 spots (1), 6 to 10 spots (2), 11 to 20 spots (3) and more than 20 spots (4). If at least 1 FoCoSi spot was present, fluorescein staining was evaluated and graded as no staining (0), 1 fluorescein positive spot (FPS) (1), 2 to 3 FPS (2), 4 to 6 FPS (3) and more than 6 FPS (4). Additionally if at least 1 FoCoSi spot was present, the Hyperemia and Edema was graded for that area as none (0), slight Hyperemia and rough surface (1), slight Hyperemia with Edema (2), moderate Hyperemia with Edema and slight mucous discharge (3) and severe Hyperemia with Edema and heavy mucous discharge (4). Additionally the character of tear secretion was graded as normal (0), slight serous (1), serous discharge with slight mucous (2), moderate mucous discharge with some lid lashes sticking together (3) and severe mucous discharge with lid lashes sticking together (4).

3.4.3 Contact lens examination

In order to prescribe possible correlations on the appearance and frequency of FoCoSi, a variety of different contact lens parameters and wearing modalities were noted. Besides the type of the used contact lens, additionally listed was the age of the contact lens, wearing modality, movement and appearance of any material defects were noted with specifically developed grading scales from zero to 4. The age of the contact lens was noted as discontinued lens wear in the last days (0), very first day (1), one third of planned replacement time (2), two third of planned replacement time (3) and right before replacement (4). Wearing modality was noted as discontinued lens wear in the last days (0), DW (1), flexible wear (FW) (2), maximum one week of EW (3) and continuous wear (CW) up to a maximium of one month, 1 week for Senoflicon A respectively (4). Vertical movement of the contact lens during normal blinking in main gaze was noted as more than 1.5mm (0), between 1.0mm and 1.5mm (1), between 0.5mm and 1.0mm (2), lover than 0.5mm (3) and no movement at all (4). Finally material defects were noted as no defects (0), slightly uneven edges (1), small tears at the edge (2), peaces of material lack on the edge (3) and central defects (4).

The type and frequency of the used contact lens solutions was assessed with grading scales from zero to 4 as well, in which (0) corresponds to daily use, (1) corresponds to once in a week, (2) corresponds to once in 2 weeks, (3) corresponds to less than once in 2 weeks, and (4) corresponds to no use at all. Solutions were divided into no solution used (0), multipurpose biguanid (1), multipurpose polyquad (2), Peroxide Systems (3)

and manual cleaner or protein removing agent (4). As deposits on the surface of a contact lens are an important factor in comfort of wearing contact lenses and can be a trigger for CLPC, five different types of deposits (Lipid, Mucin, hydrophobic spots, cosmetics and mixed deposits) were noted and graded. The Grading scale was again from 0 to 4 in which (0) corresponds no deposits, (1) corresponds to slightly (1-2mm area), (2) corresponds to mild (3-4mm area), (3) corresponds to moderate (bigger than 5mm area) and (4) corresponds to severe (Vacc effected).

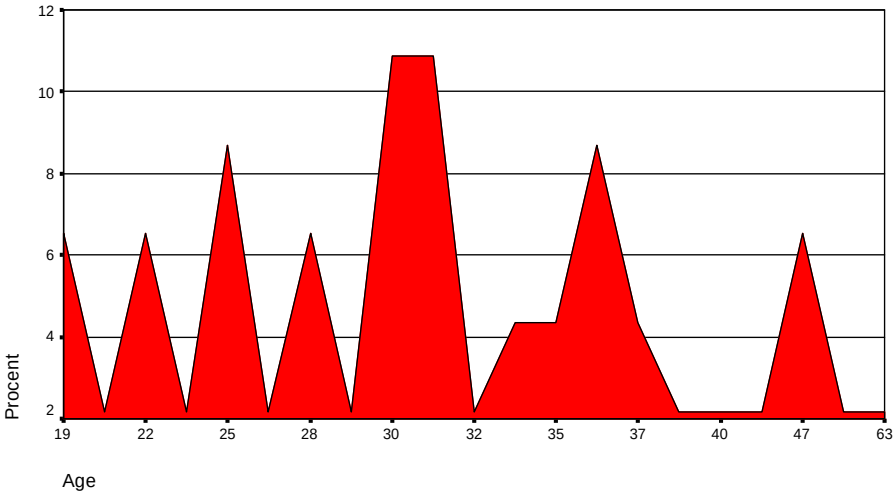
3.5 ***Statistical Analyses***

Data from subjects that began EW or DW attended at least one scheduled EW or DW visit were included in this study. The first adverse response to contact lens wear during EW or DW was used to categorize the subject eyes into groups. Eyes that did not develop any adverse response to contact lens wear during the follow-up period were retrospectively categorized 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 subjects reporting 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. SPSS (Version 12) was used for all data analyses.

4 Results

4.1 ***General Results***

A total of 46 FoCoSi subjects were seen, which was an incidence of 3.8%. Subjects ranged in age from 19 to 63 years with a mean of 31.98 years of age and 56.5% of them were female (Table 6 + 7). 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 for developing FoCoSi than female subjects.



N	46
Mean Score	31.98
Median	31.0
SD +/-	8.953
Minimum	19
Maximum	63

Table 6 Age distribution

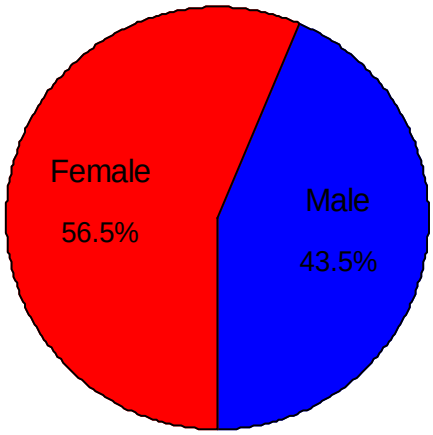


Table 7 Gender distribution

Seasonal differences in occurrence of FoCoSi events showed peaks in January, April and essentially during June until August (Table 8).

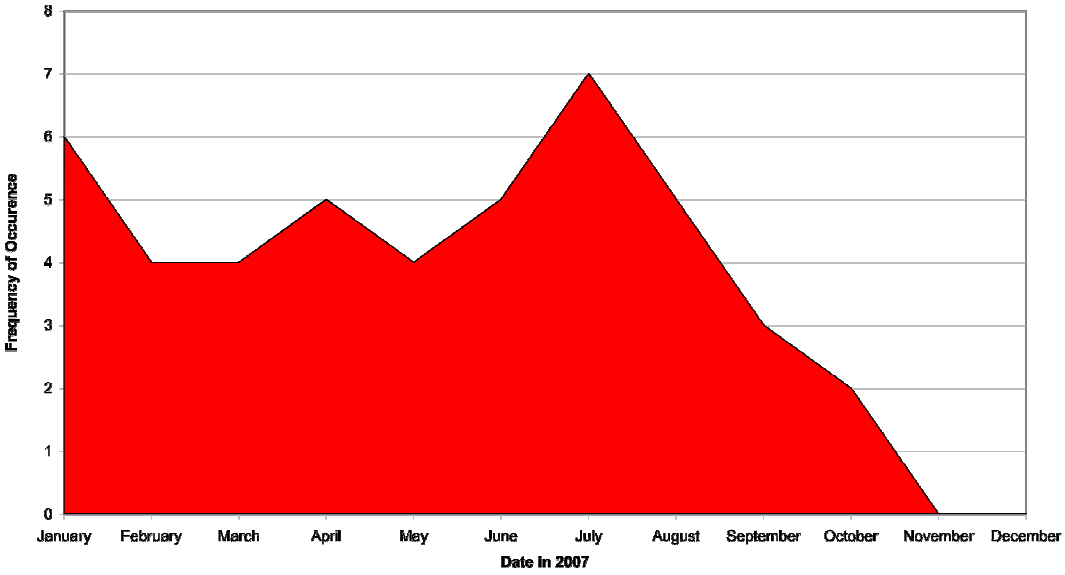


Table 8 Seasonal Difference in occurrence of FoCoSi Events

Allergies against Pollen were only associated in 50% of all subjects with FoCoSi. Of those subjects with Pollen allergies the season of allergy reaction was noted as during

Spring in 28.3%, during Summer in 10.9% and during the whole Pollen season from Spring to Summer 8.7%. Atopic reactions during the whole year had 2.2% of the subjects prescribed. (Table 9) There was no correlation between reported allergy propensity and the seasonal distribution of FoCoSi events. (p=0.108)

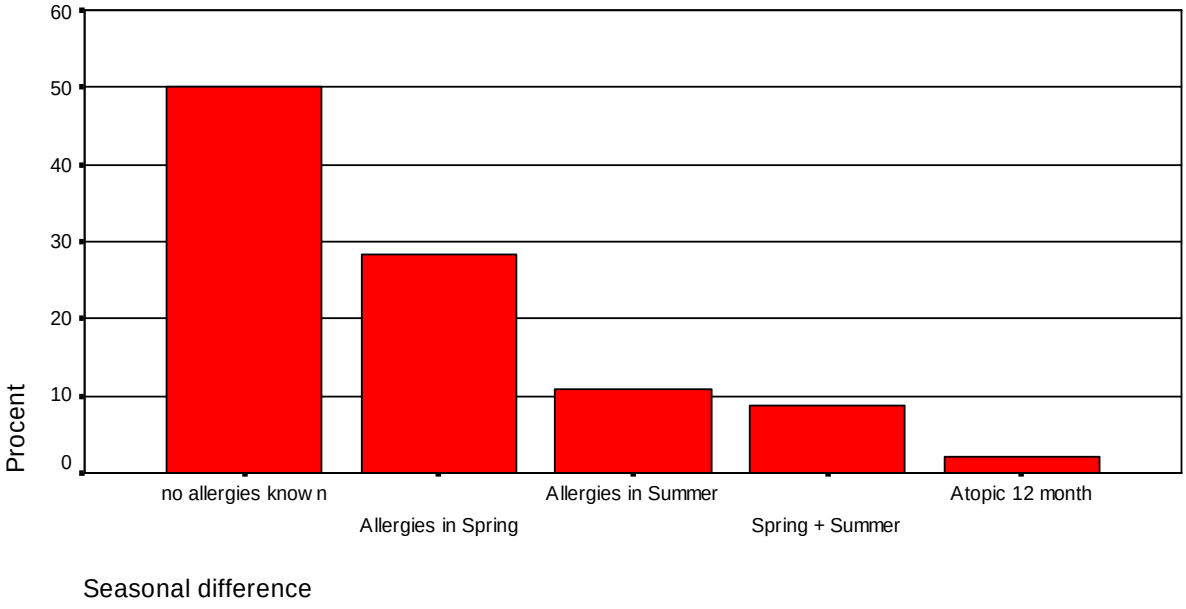


Table 9 Allergy against Pollen

Tearing was in great majority of the subjects with FoCoSi (80.4%) normal, pronounced tear meniscus was observed in 17.4% and rarely overflowing tears were noted in 2.2%. None of the subjects showed excessive tearing or epiphora. (Table 10)

None of the subjects presented with FoCoSi showed pre-auricular lymphadenopathy.

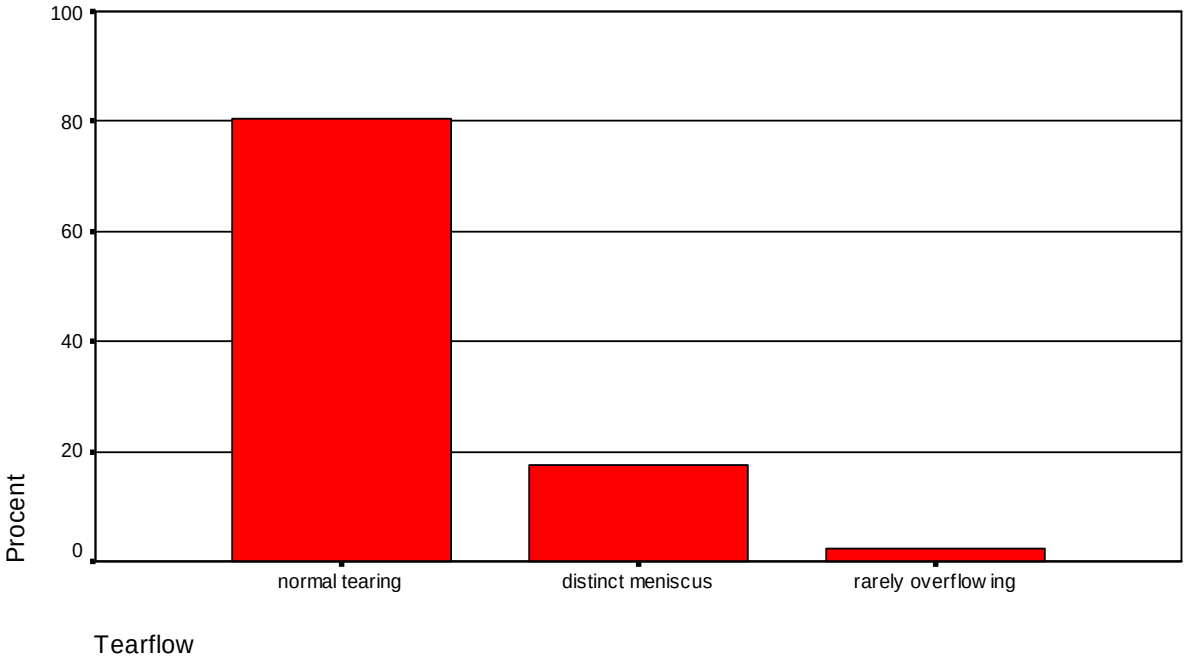


Table 10: Tearflow in subjects with FoCoSi

53.3% reported no symptoms at all during the event of FoCoSi. Noticeable symptoms but without any limitations in contact lens wear was found in 15.2%, slight annoying symptoms with slightly limitations in contact lens wear in 13.0%, moderate symptoms and limitations in contact lens wear in 16.3% and finally severe symptoms with severe limitations in contact lens wear was reported in 2.2% of the subjects. (Table 11)

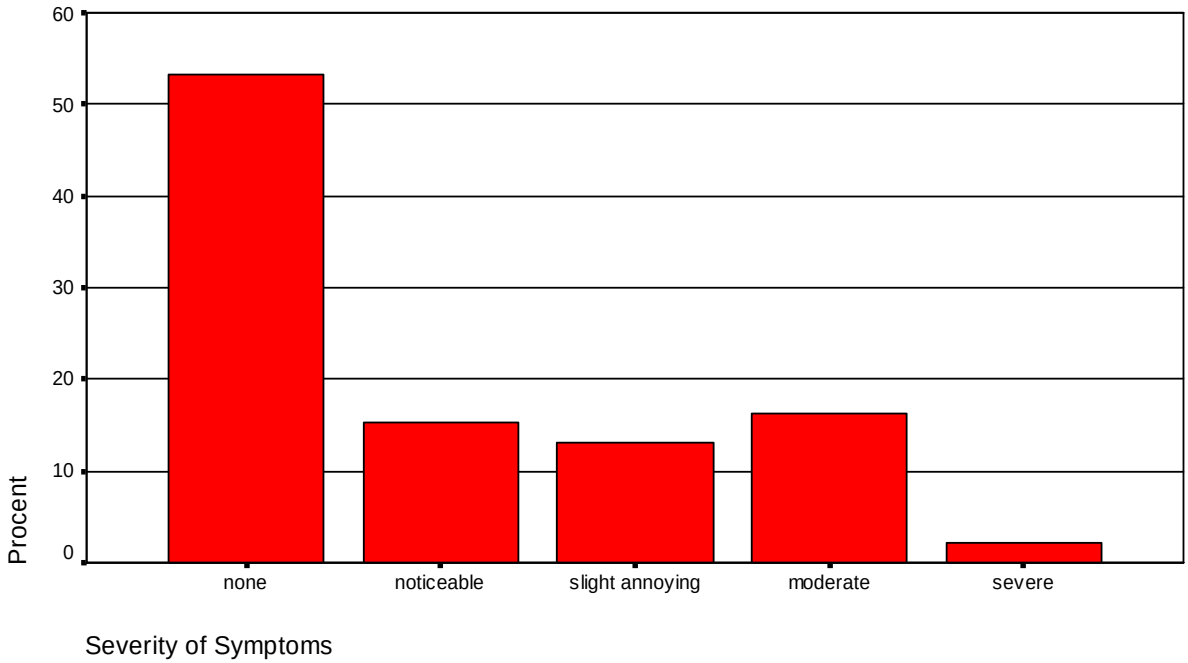


Table 11 Severity of Symptoms

*4.2 **Results of slitlamp examination of Cornea and Conjunctiva***

4.2.1 Cornea

No subject with FoCoSi showed stromal Edema, Microcysts or Vacuols. Only 1 subject presented staining, 2 subjects (2.2%) presented infiltrates respectively. The 2 subjects with Infiltration had subepithelial Infiltrates in the superior periphery and showed no positive fluorescein staining. The single staining subject presented 1-20 epithelial punctates in the inferior part of the cornea. Vascularisation was noted as no vascular penetration into the cornea in 72.8% of subjects with FoCoSi, 18.5% had vascularisation smaller than 1mm in 94.1% in a circular presentation, 5.9% showed that amount of vascularisation in the temporal part of the cornea. 8.7% had vascularisation between 1mm and 2mm, 50% of them presented that amount of vascularisation circular and 25% superior, respectively inferior. Finally no scarring was present in 90.2% of subjects with FoCoSi. 6.5% showed just small diffuse scarring, where 3.3% had focal scars between 2mm and 4mm in size. The study wasn't designed to distinguish if the results of the cornea section were persistent before FoCoSi occur, or if those findings were newly developed during a

FoCoSi event. The main reason in that study for the cornea section was to rule out any viral infection.

4.2.2 Conjunctiva

No subject with FoCoSi showed limbal hyperemia or limbal edema above the clinical relevant grading of 2. The bulbar conjunctiva showed no hyperemia over grade 2 as well. Only 1.1% showed a bulbar edema with grade 3 but none of the subjects had a grading above 3. None of the subjects over exceed grading 2 in the lower palpebral conjunctiva for papillae. In the superior palpebral conjunctiva only 6.5% of the subjects showed no increased numbers and sizes of papillae. 43.5% had slight papillae with slight hyperemia, 34.8% showed mild hyperemia with papillae below 1mm size, 12.0% showed moderate papillae formation with a size between 1-3mm and moderate hyperemia and edema, whereas 3.3% showed severe papillae formation bigger than 3mm in size with severe hyperemia and edema of the palpebral conjunctiva. (Table 12)

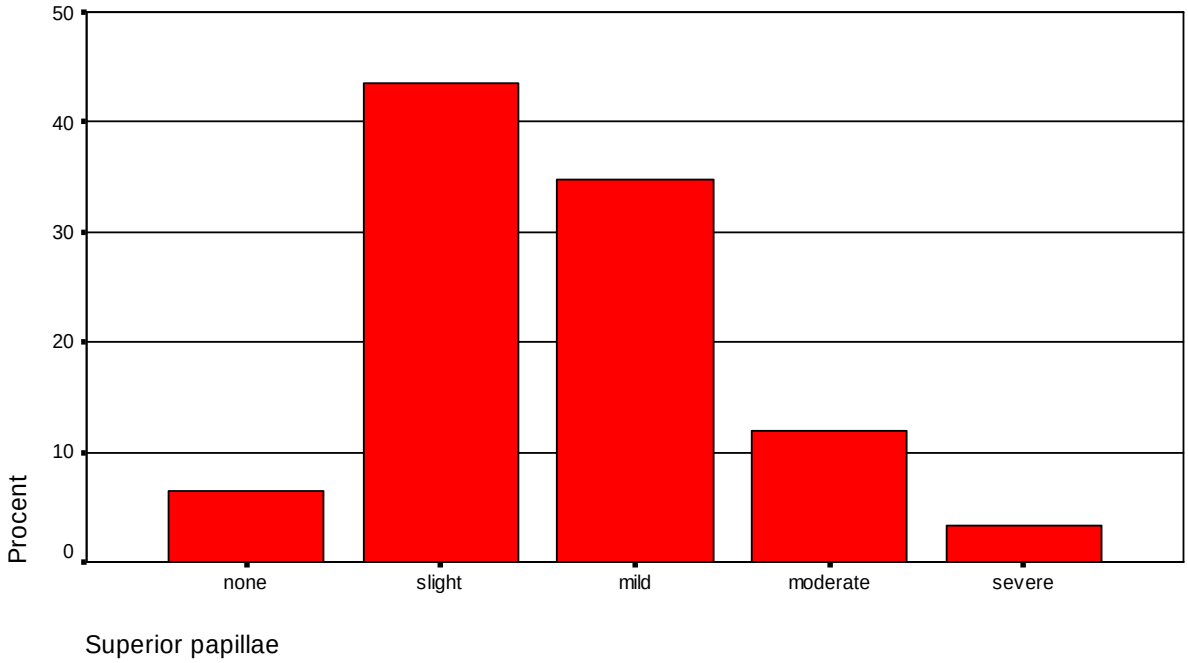


Table 12: Papillae in the superior palpebral conjunctiva

Follicular-like papillae were not found in the lower palpebral conjunctiva of any FoCoSi subject. The FoCoSi reaction was only found in the superior palpebral conjunctiva. Every appearance of FoCoSi was graded as a clinical significant finding, in contrast to the other findings which were graded as clinically significant above the grading 2. 22.8% of the subjects showed only monocular FoCoSi response. Observing the superior palpebral conjunctiva for each eye separately, 33.7% showed 1-5, 26.1% showed 6-10, 13.0% had 11-20 and 4.3% showed more than 20 FoCoSi spots. (Table 13)

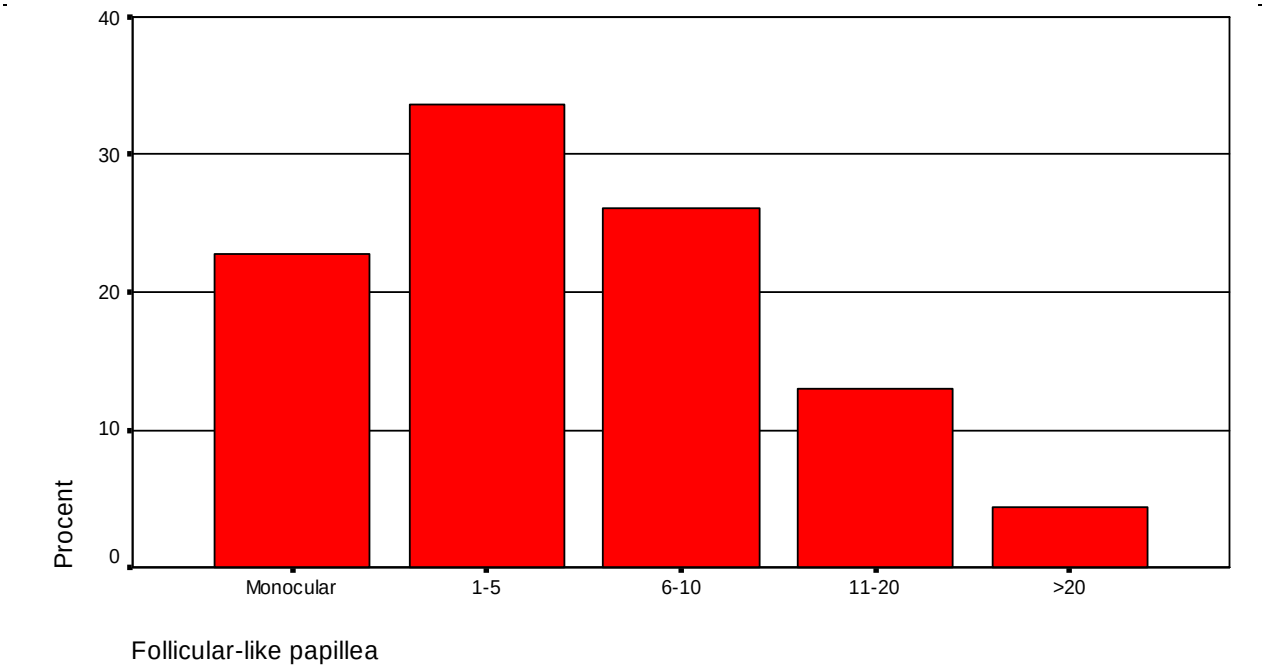


Table 13: Numbers of follicular-like papillae formation in superior palpebral conjunctiva

Classification into local and general form of appearance was performed as well. All subjects presenting less than 11 follicular-like papillae formation were labelled as local, whereas the others labelled as general form of distribution. 83.6% were classified as local and only 16.4% 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. With fluorescein staining the papillae itself are better visible and easier to grade and to reveal persisting FPS on the apex of some papillae, or better FoCoSi respectively. (Figure 6) Not all of the FoCoSi subjects showed FPS, 36.6% presented the whole superior conjunctiva as fluorescein negative. 23.9% had 1 FPS, 22.5% had 1-3 fluorescein positive spots, 11.3% had 4-6 FPS and 5.6% had more than 6 FPS.

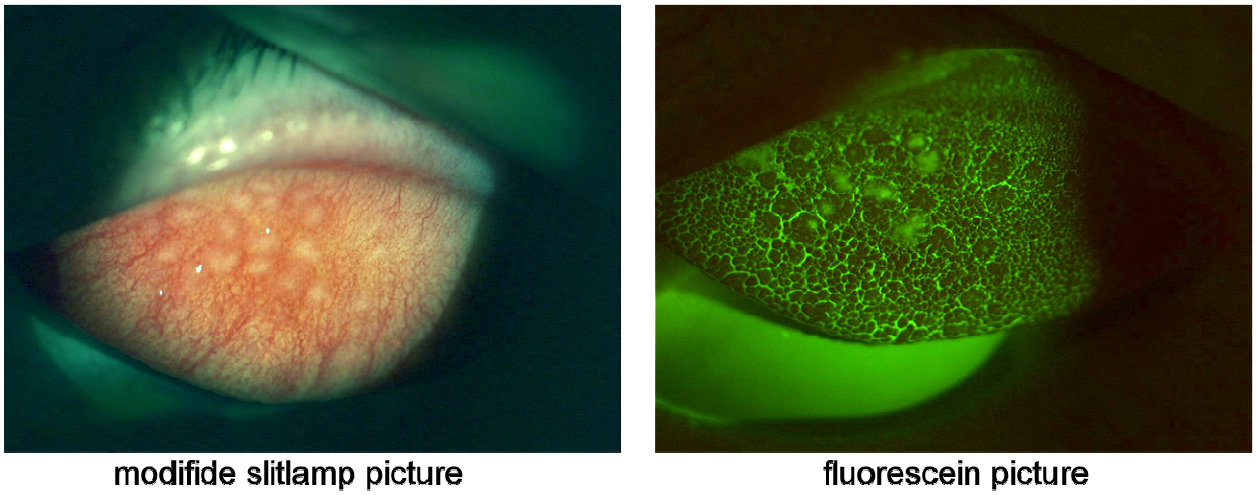


Figure 6: FoCoSi of one eye presented on a slitlamp under normal light and with fluorescein staining

14.1% of subjects with FoCoSi were graded with no Hyperemia and Edema of the superior conjunctiva, 35.2% showed slight Hyperemia and a rough surface, 22.5% showed slight Hyperemia with Edema, 23.9% moderate Hyperemia with Edema and slight mucous discharge and 4.2% showed severe Hyperemia with Edema and heavy mucous discharge. Observing the correlation between the amount of FoCoSi spots found and the amount of FPS showed that for the group with more than 20 FoCoSi spots noted, the highest amount of FPS was noted as well. This finding was statistically significant (p=0.020). (Table 14) The similar result was found for Edema, in order that the Edema was more severe in the group with more than 20 FoCoSi spots. This finding was statistically significant as well (p=0.015). (Table 15) Additionally the correlation between the reported subjective symptoms and objective findings of FoCoSi in the meaning of the amount of FoCoSi spots, the edema and the amount FPS in the superior palpebral conjunctiva was calculated. Interestingly all three parameters presented similar results.

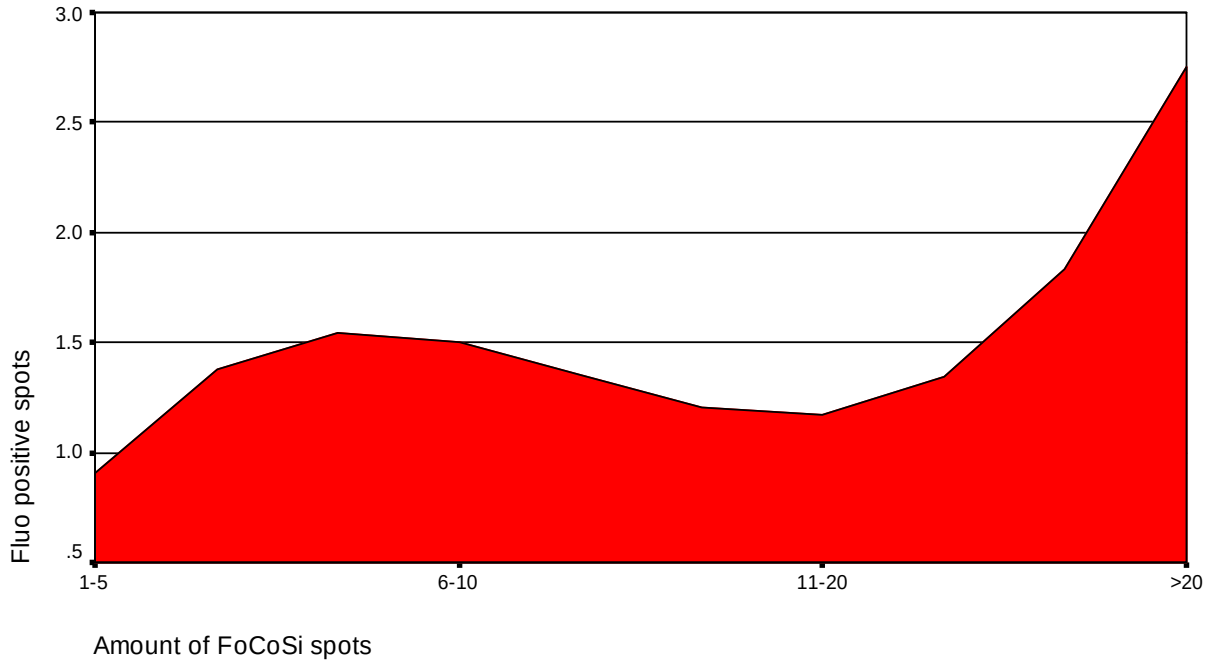


Table 14: Correlation between the amount of FoCoSi and FPS

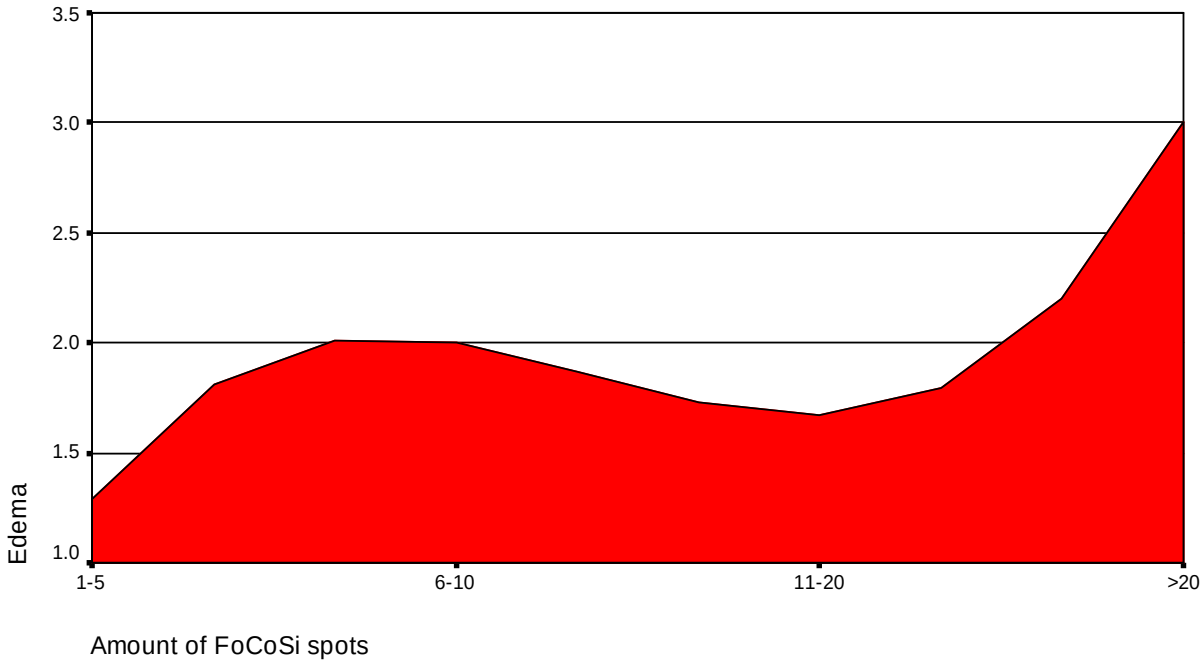


Table 15: Correlation between the amount of FoCoSi and Edema

If the objective findings of FoCoSi were worth, the reported symptoms were worth as well. In detail, if the edema was graded worth, the symptoms were graded worth as well. That finding was strongly significant (p=0.002). (Table 16) For the amount of FoCoSi spots in general the same statistically significant correlation was found as it was for edema findings (p=0.003). (Table 17) Finally the more FPS were observed in superior palpebral conjunctiva, the more severe subjective symptoms were prescribed. Statistically showed that correlation the weakest significance (p=0.032) from the observed three findings. In comparing subjects without FPS reaction and those with more than 6 spots, there was a strong statistically correlation (p=0.001) indicating that a higher FPS grading results in more severe symptoms. (Table 18)

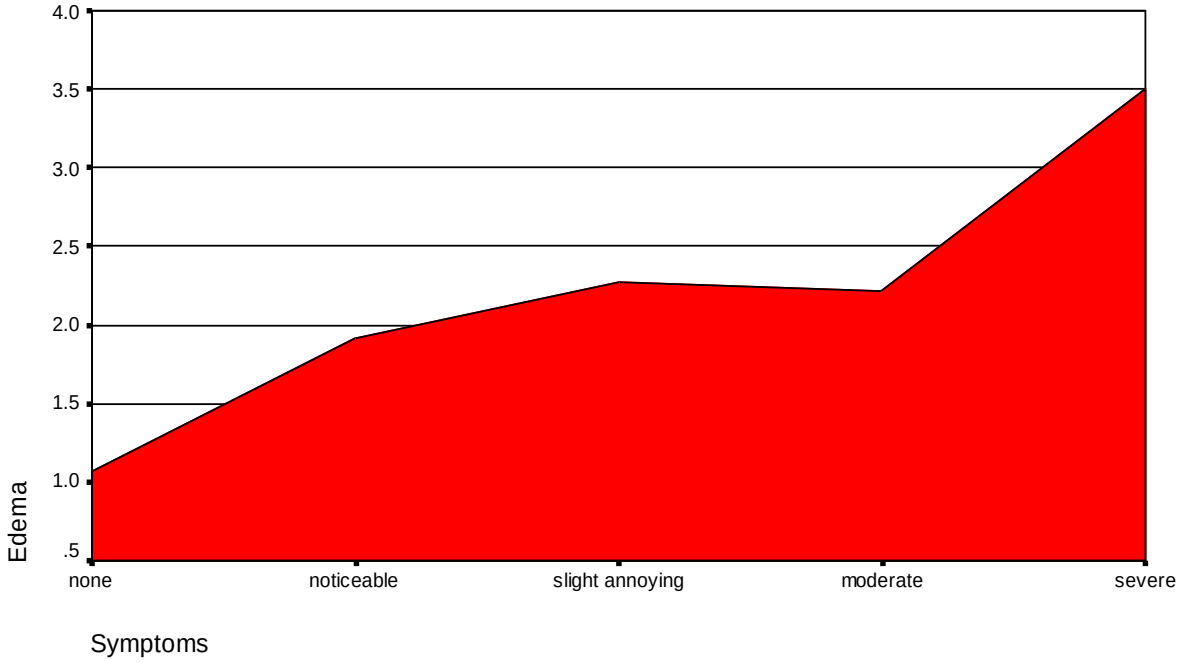


Table 16: Correlation between Symptoms and Edema in the superior palpebral conjunctiva

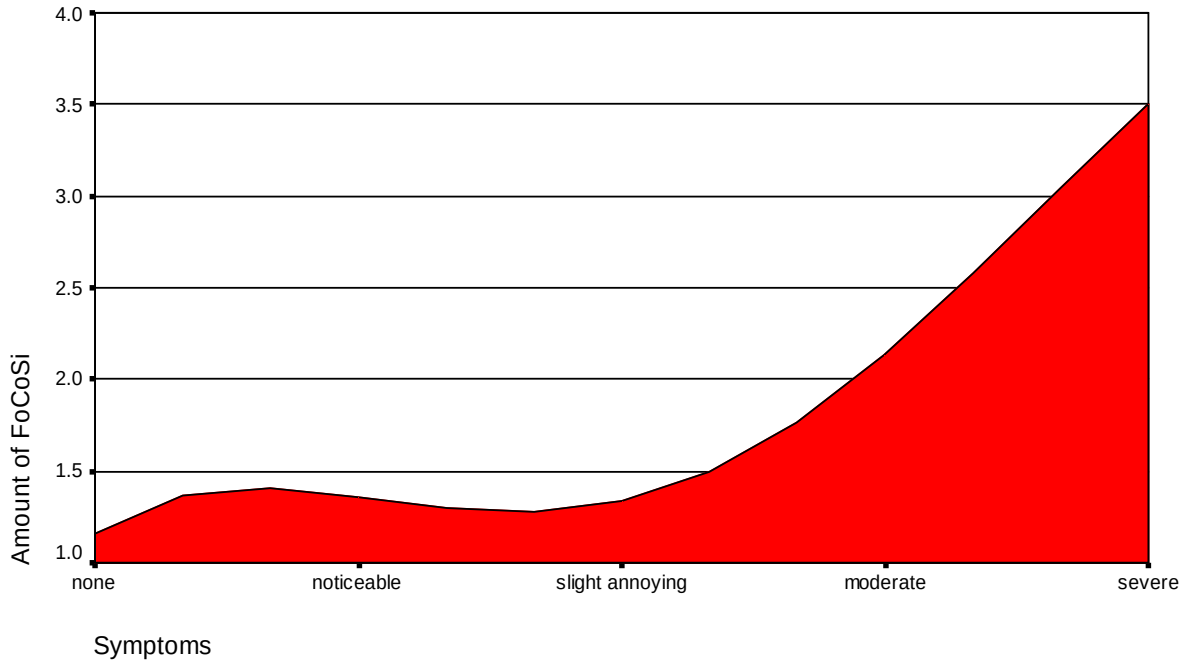


Table 17: Correlation between symptoms and the amount of FoCoSi in the superior palpebral conjunctiva

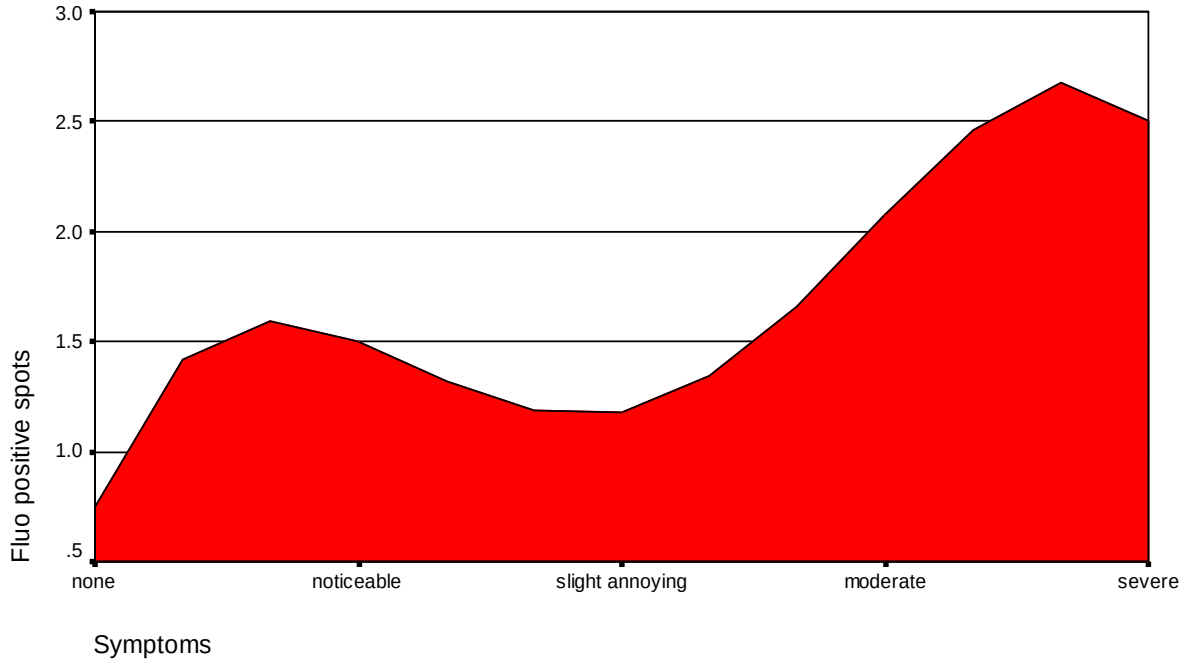


Table 18: Correlation between symptoms and FPS in superior palpebral conjunctiva

Finally 57.6% of subjects had normal tear secretion, 17.4% had slight serous tears, 13.0% had serous discharge with slight mucous, 9.8% had moderate mucous discharge with some lid lashes sticking together and 2.2% had severe mucous discharge with lid lashes sticking together. There was a statistically significant correlation between the character of the noted discharge and the conjunctival edema and FPS respectively ($p<0.050$). If the subjects had severe edema or a higher amount of FPS, the discharge was more severe and more mucous like. (Table 19 and Table 20)

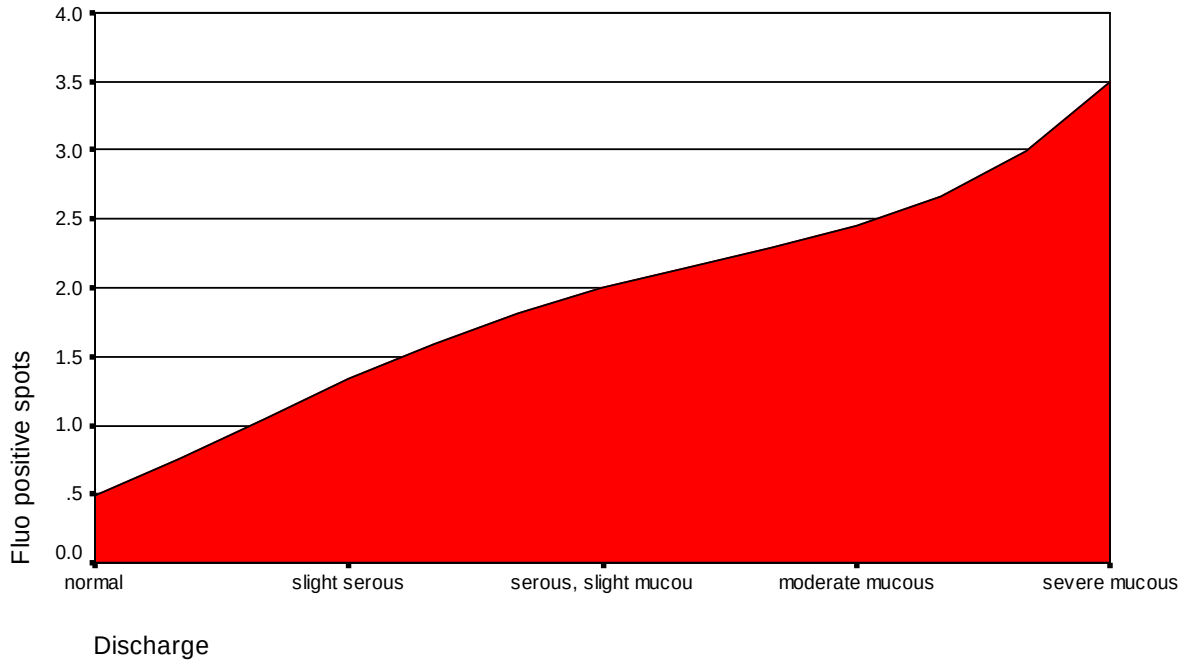


Table 19: Correlation between discharge and **FPS**

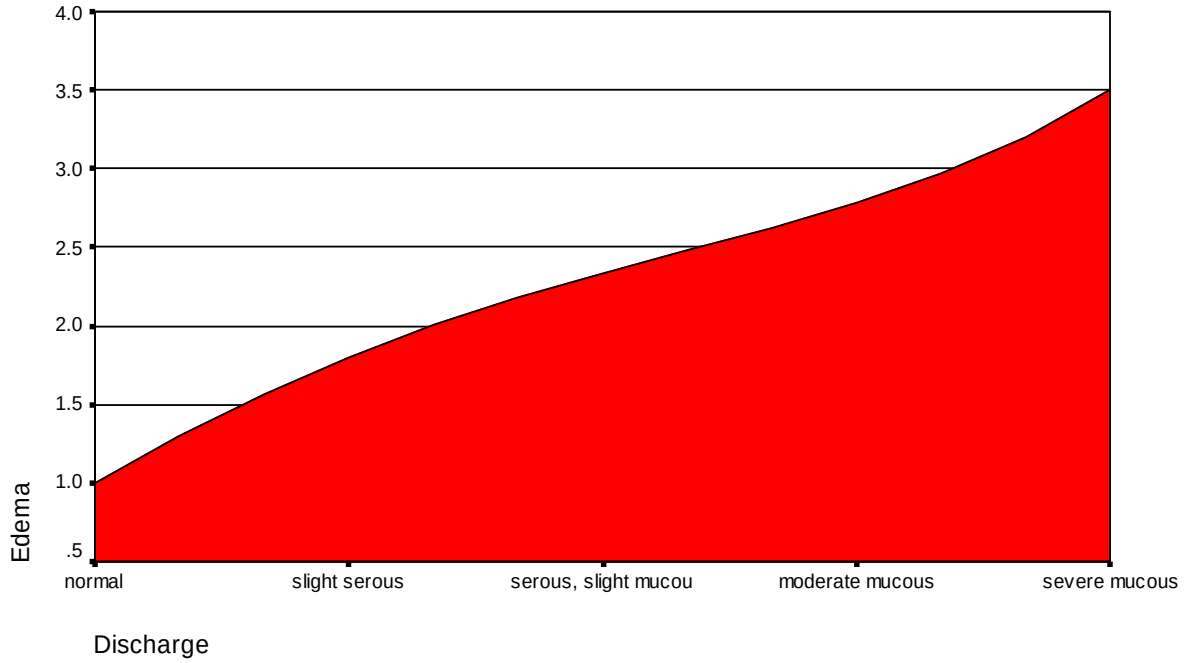


Table 20: Correlation between discharge and conjunctival edema

*4.3 **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%), 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. (Table 21) These results were statistically significant (p=0.005) in compare 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 22.

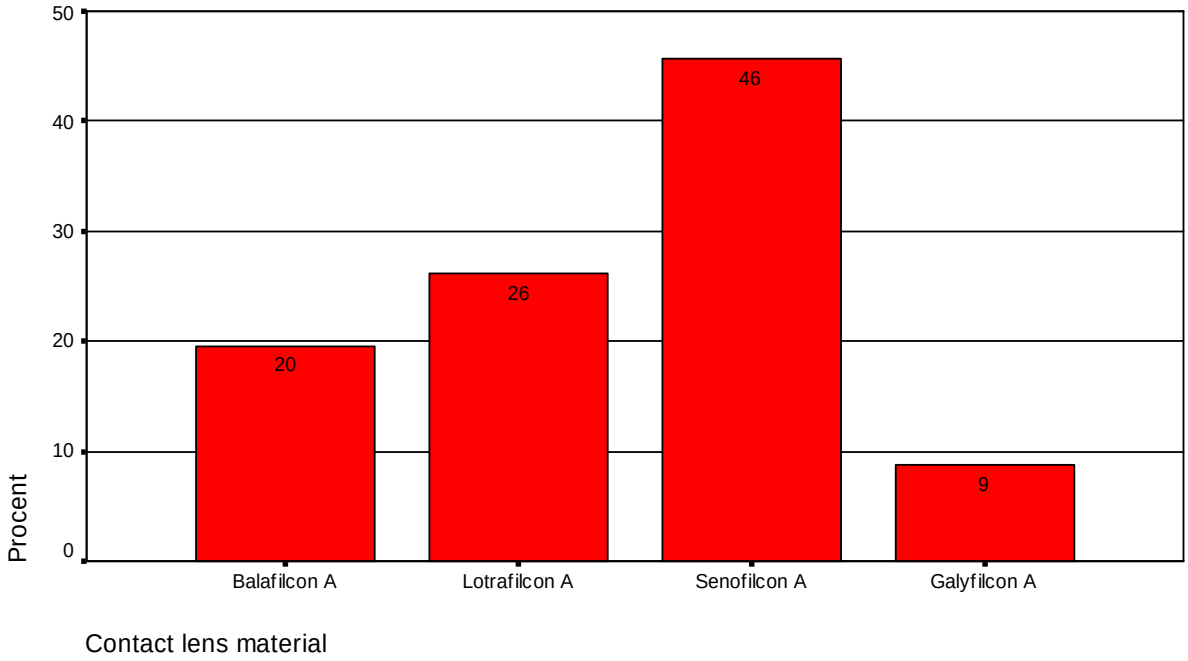


Table 21: Contact lens type showed FoCoSi

Lotrafilcon A (2.49) and Senofilcon A (1.53) showed the highest risk ratio, followed by Balafilcon A (0.70) and Galyfilcon A (0.29).

Material	Cohort	Events	Risk-Ratio
Balafilcon A	28.0%	19.6%	0.70
Lotrafilcon A	10.5%	26.1%	2.49
Senofilcon A	29.9%	45.7%	1.53
Galyfilcon A	29.8%	8.7%	0.29

Table 22: Risk-Ratio for developing FoCoSi, for the different contact lens materials

The contact lenses were worn in different modalities. 56.5% used their contact lenses on CW basis, up to 1 month as a maximum, except 1 week for Senofilcon A material respectively. 26.1% used their contact lenses DW only, whereas 15.2% slept in their contact lenses 1 time in a week on a regular basis (EW). Finally 2.2% of subjects slept with their contact lenses sometimes, (FW) but usually not. (Table 23)

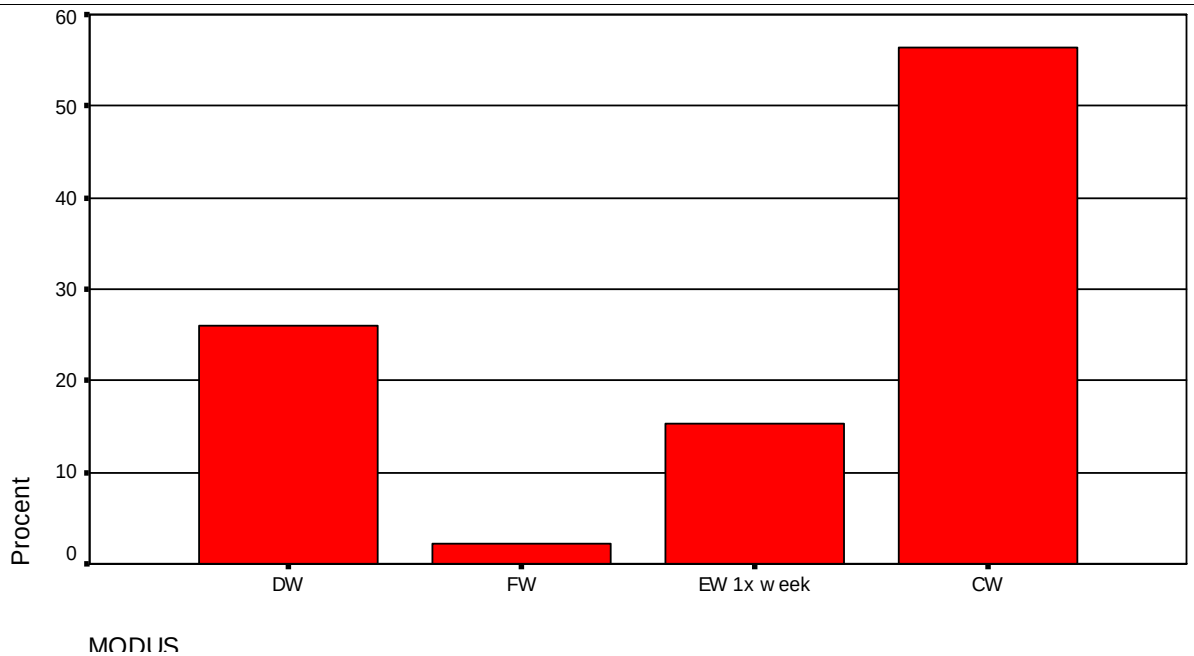


Table 23: Wearing modality

Wearing modality and contact lens material did not differ significantly (p=0.338). In the DW group 41.7% used Senofilcon A, 25.0% used Balafilcon A and finally Lotrafilcon A and Galyfilcon A contact lens material was used in each 16.7%. 50% of FW and EW subjects used Senofilcon A, whereas each 4.3% used Balafilcon A and Lotrafilcon A respectively. Finally in the CW group 46.2% used Senofilcon A, 30.8% used Lotrafilcon A, 15.4% used Balafilcon A and 7.7% used Galyfilcon A (Table 24).

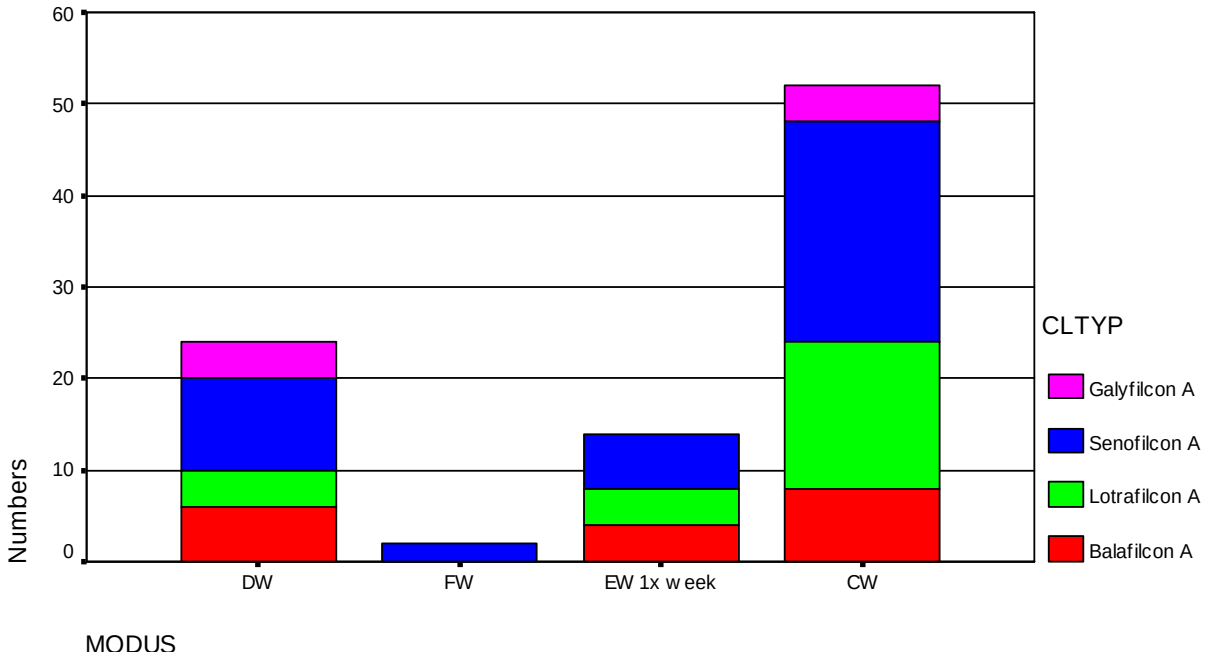


Table 24: Wearing modality and used contact lens material

The life span of each contact lens worn, at the time of FoCoSi happened, was reported. 40.2% of the contact lenses were on their end of life span, whereas 33.7% were in first third of their life span. 21.7% were in second third of life span and each 2.2% of subjects

had the contact lens the first day on the eye or discontinued wearing their contact lenses. (Table 25)

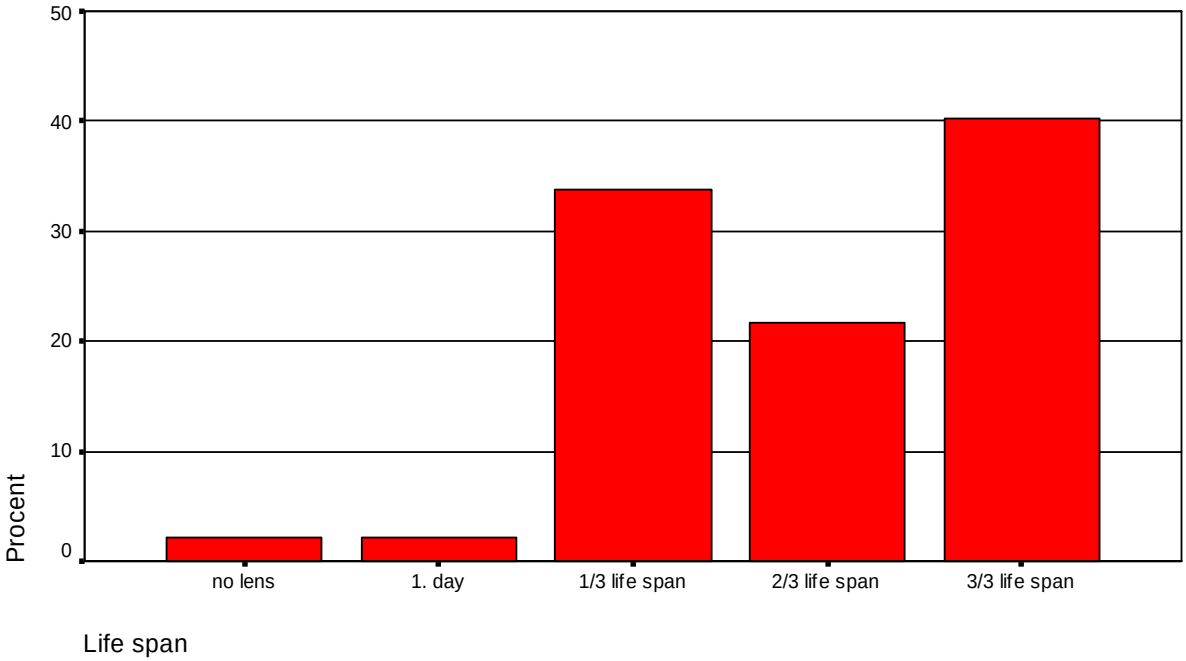


Table 25: Life span of worn contact lenses

Only 2 contact lenses had small tears on the edge (2.2%), all the other contact lenses showed no material defects at all. The great majority (91.3%) of contact lenses showed movement of 0.5mm to 1.0mm (80.4%) or lower than 0.5mm (10.9%). 5.4% showed movement up to 1.5mm and 3.3% showed movement above 1.5mm.

4.3.1 Solution Analysis

79.3% of all FoCoSi subjects used a Polyquad preserved multipurpose solution (MPS), 10.9% used no lens care solution at all, all of those subjects wearing modality was CW. 6.5% used Peroxide and 1.1% used an additional manually cleaning system (Table 25). Polyquad was used by 75% of subjects which used their contact lenses DW, whereas 16.7% of them used Peroxide and 8.3% used a Biguanid preserved MPS. Subjects wearing FW or EW modality, 87.5% used Polyquad MPS and 12.5% respectively used Peroxide as their lens care solution. Of the CW subjects again the great majority used Polyquad MPS (78.9%) but was only used for special disinfecting purpose, for example after swimming or long flights, 19.2% had no lens care solution at all, whereas one subject (1.9%) used an additional manual cleaner during the period of FoCoSi. None of those CW subjects used Biguanid MPS. None of the correlations found above were statistically significant (p=0.494) (Table 27).

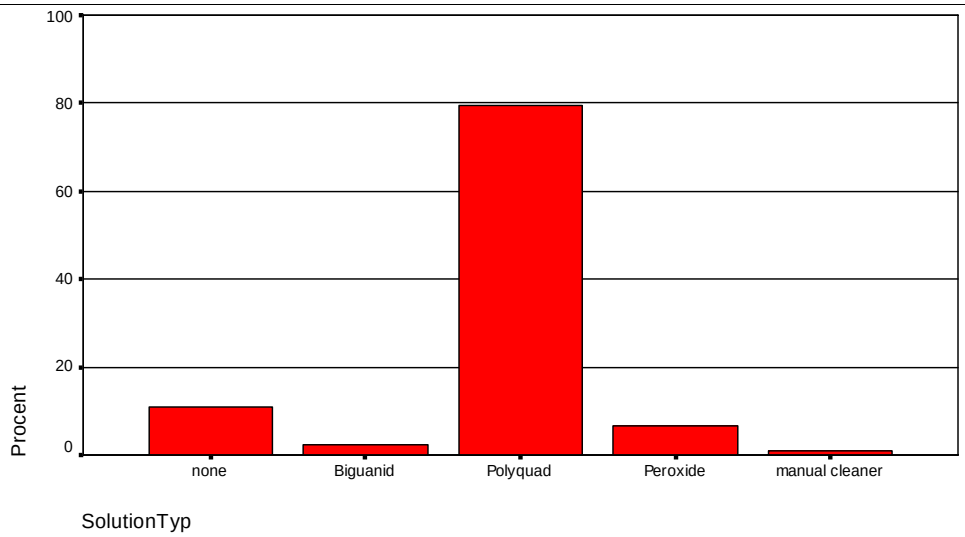


Table 26: Solution Type, independent of wearing modus

Additionally the frequency of solution application during the FoCoSi event was reported as well. 41.3% of FoCoSi subjects never used lens care solution, 28.3% used their solution everyday, 21.7% once in a week, 6.5% less than once in 2 weeks and 2.2% used their solution once in 2 weeks. (Table 28) Comparing this data with the contact lens material showed that for the Balafilcon A group each third used the solution daily, once in a week and less than once in 2 weeks or never. For the Lotrafilcon A group; 50% never used a solution, 33.3% used the solution once in a week and 16.7% everyday. In the Galyfilcon A group 50% used the solution everyday and the other 50% never. Finally in the Senofilcon A group 52.4% never used a solution or less than once in 2 weeks, 28.6% used it everyday, 14.3% once in a week and 2.2% used it just once in 2 weeks. (Table 29) There was no correlation between used contact lens material and application frequency of the solution. (p=0.592)

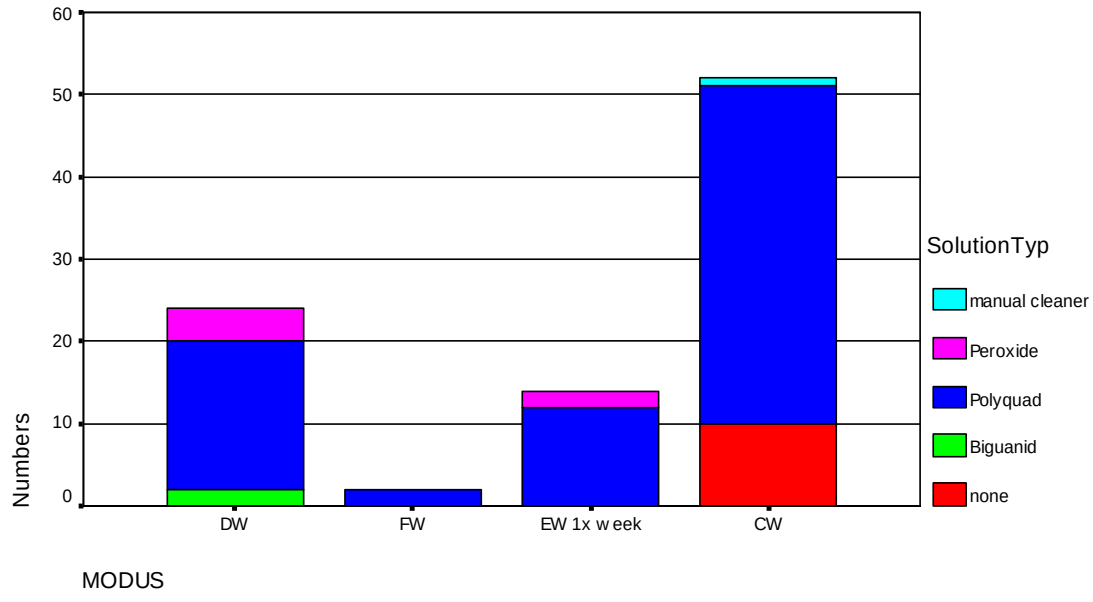


Table 27: Solution Type, dependent of wearing modus

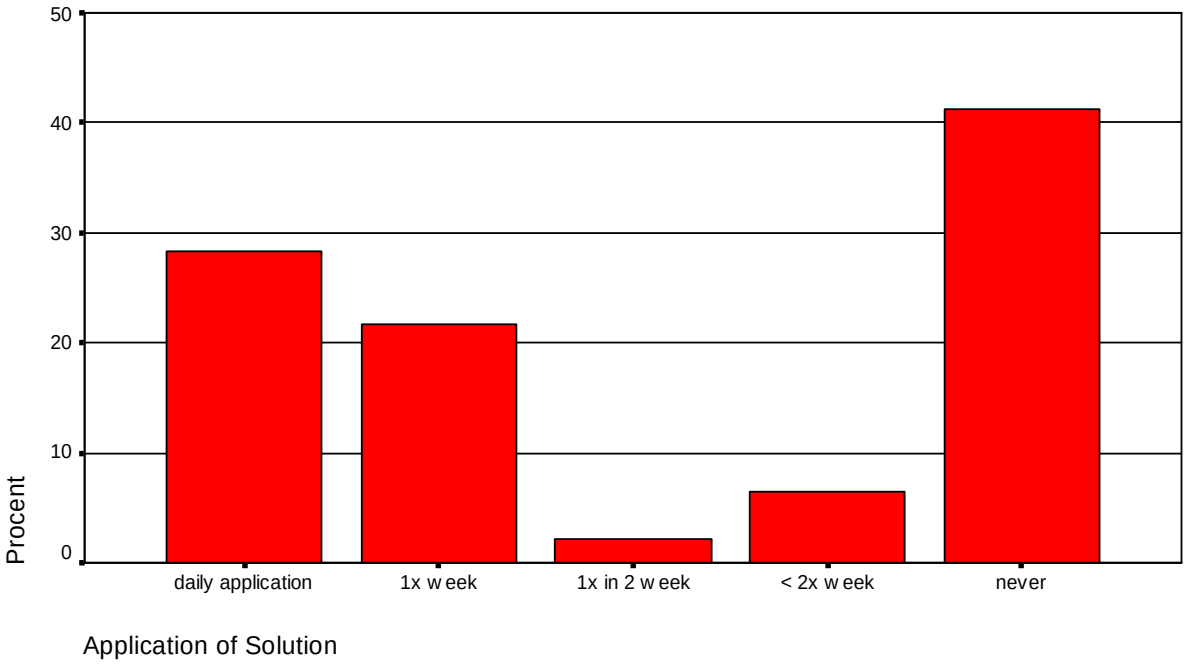


Table 28: Application frequency of solution

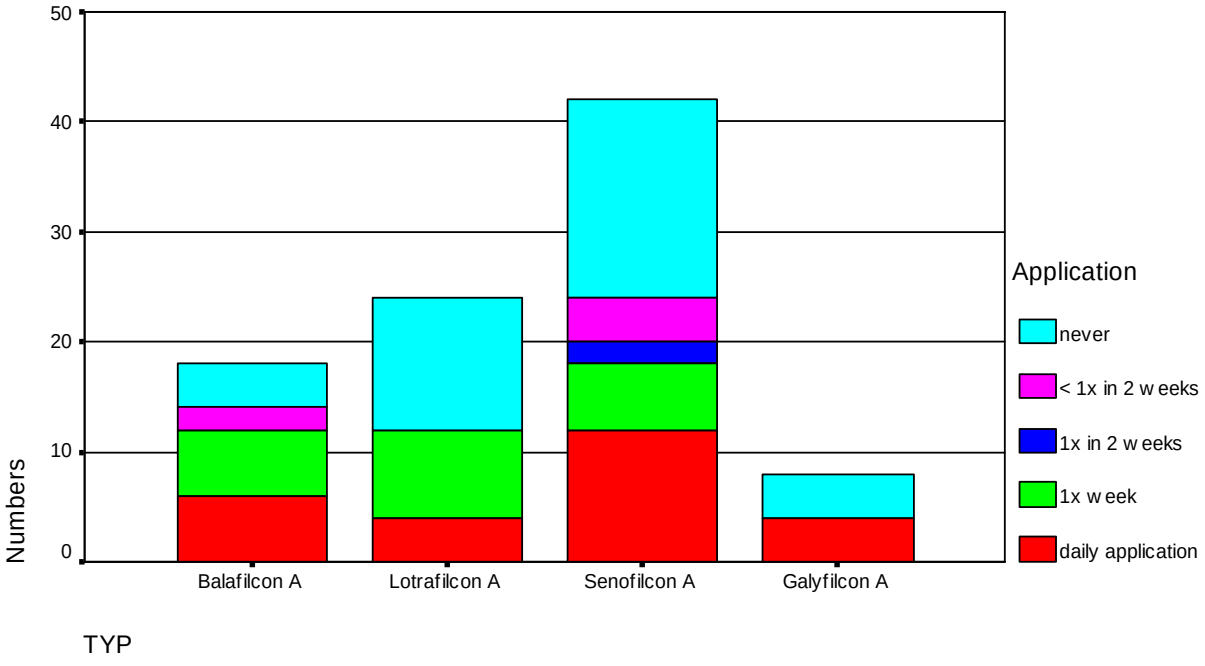


Table 29: Contact lens material and solution application frequency

4.3.2 Deposits

The degree of deposits and type of material deposited on the surface was reported for each subject. Lipids are a common deposition for SH. In this study 22.8% did not have any visible Lipid deposits, 44.6% had slight lipid deposition, 20.7% had mild deposition and 12.0% 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% of subjects showed no mucin deposits at all, 13.3% showed slight deposition, 7.8% had mild and 2.2% moderate mucin deposition. Again none of the subjects showed severe deposition. Hydrophobic spots where rarely observed. 90.2% had no spots at all, 3.3% slight dry spots and 6.5% had mild hydrophobic spots. None of the subjects had moderate or severe hydrophobic areas. A surprisingly high amount (89.1%) of the subjects had no deposits of cosmetic products. 6.5% had slight, 3.3% mild and 1.1% severe cosmetic depositions. None of the subjects had moderate cosmetic deposition. There was no statistically significant correlation between the severity of conjunctival edema, nor FPS in the superior palpebral conjunctiva and the amount of the previous discussed specific depositions on the contact lens surface (p>0.050).
Finally the amount of mixed depositions was noted. 57.6% showed no deposition at all, 19.6% slight, 12.0% mild, 5.4% moderate and 5.4% severe mixed depositions. Subjects with more severe follicle-like papillae formations (Edema p=0.021, Staining p=0.008 and FPS p=0.032) where observed with significantly more mixed deposition. (Table 30 and Table 31)

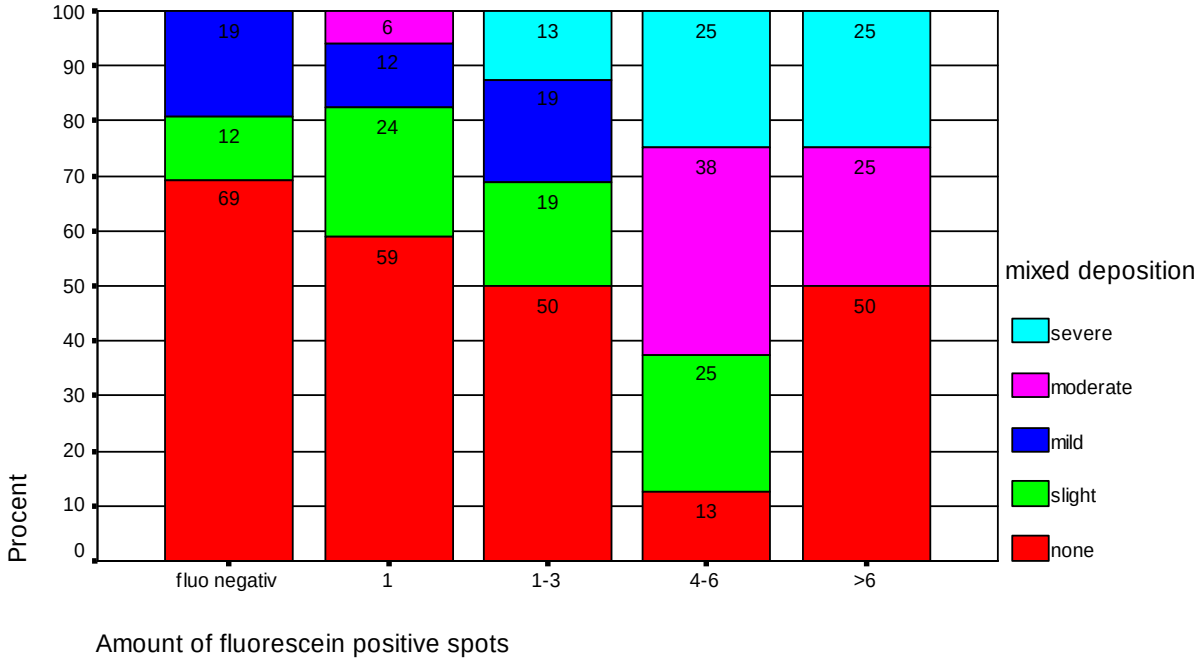


Table 30: Correlation between mixed deposition and **FPS**

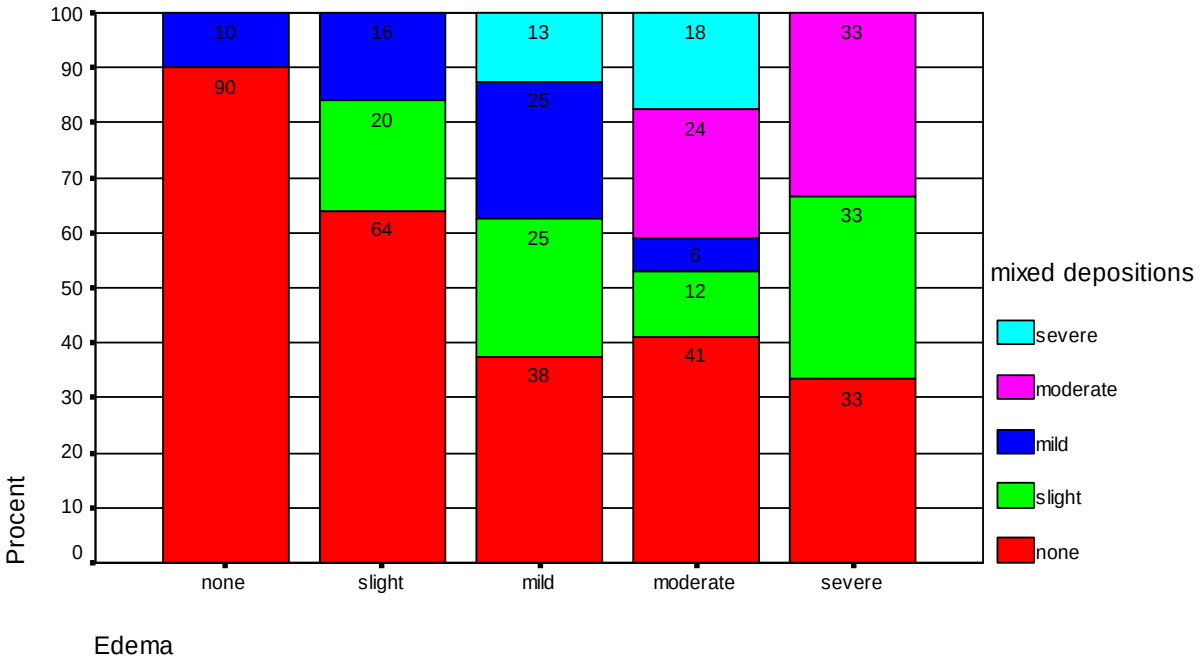


Table 31: Correlation between mixed deposition and conjunctival edema

Comparing the different contact lens materials and the type of deposition noted, there were no significantly 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. (Table 32)

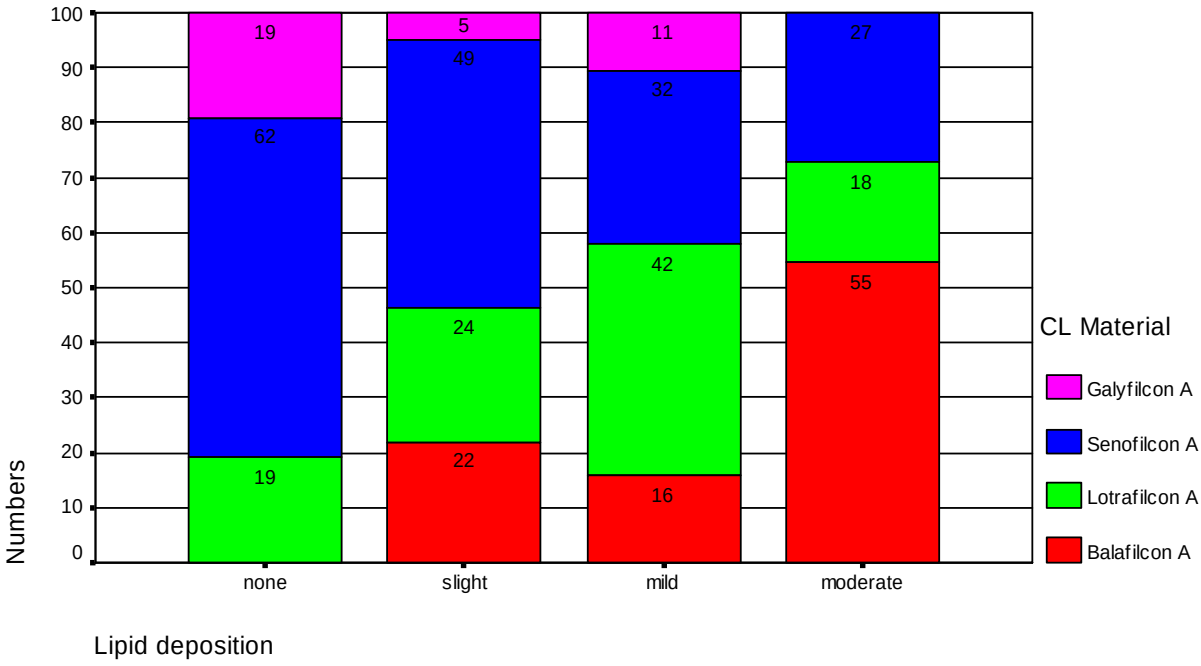


Table 32: Comparing lipid deposition and contact lens materials

5 Conclusion and Discussion

This study confirms the clinical presentation of follicular-like conjunctivitis associated with Siliconhydrogels (FoCoSi) in cases with CLPC.

5.1 ***Aetiology***

The incidence was with 3.8% quite lower than reported in events with CLPC[13-21]. Gender and age were not a significant factor in developing FoCoSi which correlates to CLPC.[11] Whitish appearance in severe CLPC or GPC cases with a longer period of time was presumed to be a cicatrisation of the conjunctiva surface at the apex of the papillae and appear in a cream/white colour.[24,96] The onset time for FoCoSi after the first introduction to SH contact lenses, was between 4 month and 8 years. This indicates that it is not a matter of time or a chronical pathway that FoCoSi occur. To the contrary it seems to be an acute reaction. Sugar et al[44] 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. These observings matches better to the appearance of FoCoSi than a cicatrisation of the conjunctiva. If the immunohistochemical studies for CLPC[33-39] represent the same findings in subjects with FoCoSi, infiltration of inflammatory leucocytes could give an explanation of the whitish appearance of FoCoSi. Sulfidopeptide LK increasing microvascular permeability,[86] which has the potential for creating an edema in the surrounding conjunctiva leading in the characteristic shape of FoCoSi.

5.1.1 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,[20,53-54] our findings did not proper correlate with allergies to pollen reported by the subjects. 50% of all FoCoSi subjects did not report any known allergy at all. Especially the January reports, during winter, can't be explained with pollen counting. Other factors like high pollution of the air could give an answer to that question. During the winter season, long period of atmospheric inversion condition are common in Switzerland.[104] While the lower parts of Switzerland are predominantly covered by fog, the higher areas enjoy longer period of sunny days. During that condition temperature in the lower parts 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 (O3) and Temperature could have an impact on FoCoSi development as well. During April until August

2007 O3 frequently over exceed the limit value (120 µg/m3) published by swiss federal emission control.[105] Pollution characterized by elevation of oxides of nitrogen (NOx), O3, tobacco smoke, fine and ultra fine particulate and diesel exhaust particles seems to enhance allergic disease.[106] Additionally the bioavailability of grass pollen allergens may be modulated by air pollutants. Interestingly, cleaning those pollen from air pollutants, reduces the allergic reaction significantly.[107] We have further studies arranged to clear up these questions.

5.1.2 Unilateral vs. bilateral presentation

CLPC was reported only in 10% of the cases as a truly monocular event,[17] whereas a study with data's from Australia and India[21] showed with 78.4% the highest amount of unilateral CLPC events reported so far in a study. In our cohort 22.8% of FoCoSi events were unilateral. This phenomenon can't be explained with unilateral different mechanical irritation as it clearly is in the prescribed GPC cases with foreign bodies on the ocular surface.[37-42] All of the FoCoSi subjects have worn the same contact lens material on both eyes and only two lenses had minor material defects, which could have introduced unilateral mechanical irritation to the tarsal conjunctiva.

On the other hand immunological responses were discussed as a reason for CLPC,[33-35,38,55,84-85] 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 pre-auricular lymphadenopathy as well, viral involvement can be ruled out. We did not find a rational explanation for those unilateral findings so far. Further studies should be done on that topic.

5.1.3 Local vs. general form

As prescribed in Australia there are local (81.8%) and general (18.2%) presentations of CLPC.[21] FoCoSi showed a similar distribution (83.6% local vs. 16.4% general). In very close agreement with CLPC,[21] FoCoSi subjects with the general form reported significantly (p=0.003) more symptoms. However, the mechanisms of action and aetiology of local vs. 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.[21] 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 nor 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.

5.1.4 Fluorescein positive spots (FPS)

In the FoCoSi study, FPS appeared as the most relevant objective clinical parameter. Those subjects presenting FPS had more severe symptoms, mucus discharge and so for 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 only detected through previously prescribed objective findings. Interestingly, the dormant form was only observed in patients previously presented an active form once in their lifetime.

FPS or whitish areas in CLPC or GPC have been discussed in only few studies so far.[24,39,44,108] 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.[24,39,94] Greiner[41] in contrast found no FPS over those whitish papillae in GPC due to an epithelialized foreign body. Lotrafilcon A with the highest modulus (1.4) of the studied materials give support to that presumption. But mechanical trauma alone, as reason for FoCoSi and FPS seems to be unlikely, since Senofilcon A material with a very low modulus (0.6) had the second highest incidence of FoCoSi events. Additionally Senoflicon 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 there were in the majority no defects on contact lens edge designs found, which could have induced FoCoSi or staining.

Another approach is to recognize FPS as a consequence of an inflammation or immunological process rather than the cause for FoCoSi. The immunohistochemical studies for CLPC[33-39] not only gives an explanation of the whitish appearance of FoCoSi caused by inflammatory leucocytes infiltration, further more it 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.

*5.2 **Contact lens influence***

Subjects wearing Lotrafilcon A (2.49) and Senofilcon A (1.53) contact lenses reyspectively had the highest risk-ratio for developing FoCoSi. Especially if the contact lenses were worn on a CW basis.

5.2.1 Deposition on contact lens surface

FoCoSi events may be indicative of an immunologic response to deposits that accumulate on the contact lens surface as it was reported for CLPC in several studies.[17,53-54,59,61-63,83] It is believed that these deposits or the exposure of the upper lid to allergens, especially denatured protein,[53] on the contact lens surface is the initiating factor and subsequent immunologic reaction that occurs in CLPC. In the present study, if FoCoSi gets worth, edema and the numbers of FoCoSi and especially the amount of FPS, the amount of mixed deposition on the contact lens surface was increased as well. But that presents more the consequence of the increased mucus discharge rather than the cause. A shorter replacement schedule of contact lenses was discussed in former studies to be preferable to avoid CLPC,[13-14,19] especially 1 week replacement cycle showed no CLPC formation at all.[20] These findings make sense in order to prevent the ocular environment from getting in contact with high amount of denatured protein depositions. However, 20.1% of FoCoSi events were found in patients wearing their contact lens 1 week CW (53.9% of subjects in the CW group: 46.2% Senoflicon A and 7.7% Galyfilcon A). This finding suggests that, other deposition or mechanism hypotised 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 for FoCoSi. This indicates that there is a certain time of interaction between the eye and the contact lens needed, before FoCoSi occur.

SH materials have different deposition profiles to that seen with conventional hydrogel lenses and can be summarized as less accumulative to protein but with a higher percentage of denatured protein[61-62] and with a significant higher affinity to lipids.[72-77] Lipid depositions are progressive, cumulative and does 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.[70] 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 for FoCoSi. There must be said, that the amount of deposition was only judged by using slit

lamp impression. Subjects with more severe follicle-like papillae formations (Edema p=0.021, Staining p=0.008 and FPS p=0.032) where 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 mucus discharge was frequently observed. Concentrating on Lotrafilcon A and Senofilcon A with the highest incidence of FoCoSi, in former studies Lotraficon A showed the highest amount for denaturated Protein and Senofilcon A the lowest.[76] For lipids Senofilcon A showed the highest and Lotrafilcon A the lowest amount.[70,77] 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 occur. 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[77] they can be transformed or influenced for example with O3. These are new ideas to clear up the questions of aetiology of FoCoSi and perhaps giving a new approach for solving the questions around CLPC as well. Further studies should be done on that topic.

5.2.2 Care Solution

The most related contact lens care solution with FoCoSi was Optifree express® (Alcon). In compare with the control group, this finding was not statistically significant (p>0.05), it is the predominant solution used in that group as well. Furthermore, while looking at the high amount of CW subjects, which 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 changing's are not a reaction to certain solution components.

5.3 Treatment of FoCoSi

The study design wasn't specificly made for evaluating the treatment of FoCoSi. However, two major treatments, changing wearing modality to DW or wearing daily disposable contact lenses for a 2 week to 4 week period of time, seems 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. On the other hand, with that treatment only FPS and edema was completely solved. The FoCoSi spots itself remain with a follicular-like whitish appearance as prescribed as the dormant form of FoCoSi without any subjective complains.

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 figure out which, if any, medication could bring the dormant FoCoSi back to normal palpebral conjunctival appearance.

5.4 ***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, since 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 O3 and fine and ultrafine particles are a new approach in finding the cause for FoCoSi or CLPC. Fluorescein staining of the apices has shown the highest correlation with subjective symptoms. This is a new and clinically interesting knowledge as well. Finally the different presentation of FoCoSi like focal vs. general or bilateral vs 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. For clearing up all those new questions further studies should be performed.

6 Acknowledgments

I would like to thank my advisors Michael Bärtschi and Dietmar Kuemmel for their advice, expert guidance, interest and continual support.

7 Appendix

7.1 Information letter for Patients

Frau
Patient
Adress
ZIP City

Studie über Beschwerden beim Tragen von Kontaktlinsen

Sehr geehrte Frau Patient

Wir freuen uns, Sie zu unseren KundInnen zählen zu dürfen und hoffen Sie haben viel Spass beim Tragen Ihrer Kontaktlinsen.
Wir sind seit vielen Jahren aktiv in der Forschung tätig. Während dem ganzen Jahr 2007 führen wir eine Studie zur genauen Analyse von spezifischen Beschwerden beim Tragen von Kontaktlinsen durch. Wir möchten Sie, sowie über 1000 weitere KundInnen, mit diesem Schreiben über diese Studie informieren. Diese wird im Rahmen der Diplomarbeit zum Master of Science von Herrn Wyss durchgeführt. Wir bitten Sie, beim Vorkommen einer oder mehrerer der unten aufgeführten Symptome, innerhalb von 3 Tagen unsere Praxis zu kontaktieren und für eine kurze Dokumentation (10-15min) zu uns zu kommen. Selbstverständlich ist diese im Rahmen der Studie kostenlos. Bitte beachten Sie, dass es sich bei dieser Dokumentation nicht um eine reguläre Kontaktlinsenkontrolle handelt und diese auch nicht ersetzen kann!

Symptome:

- Juckende oder beissende Augen (ähnlich einer Pollenallergie) insbesondere am Abend. Meist werden die Symptome durch Reiben in den Augen noch verstärkt.
- Erhöhte Schleimproduktion der Augen und Absonderung während dem Tragen Ihrer Kontaktlinsen.
- Verminderte Sicht und schlechter Sitz der Kontaktlinse, bedingt durch enorme Ablagerungen auf der Kontaktlinse.

Es handelt sich um eine seltene, meist zeitlich sehr beschränkte Herabsetzung des Tragekomforts beim Tragen von Kontaktlinsen, deswegen versuchen wir mit diesem Schreiben möglichst alle Betroffene zu erfassen. Herzlichen Dank für Ihre Mitarbeit.

Mit freundlichen Grüssen

Michael Wyss, dipl. Augenoptiker FAAO

7.2 ***Grading Sheet***

Graduierung "FoCoSi" Studie 2007

Sektion A: Anamnese

1	Medikamente										
2	Beschwerden	GRAD	0	keine	1	leicht spürbar, keine Einschränkungen	2	schwach störend, leichte Einschränkungen	3	mässige Probleme, Einschränkungen	4	Starke Probleme, starke Einschränkungen
3	Pollenallergie bekannt	GRAD	0	keine	1	Frühling	2	Sommer	3	Frühling + Sommer	4	12 Mte. Atopiker
4	Tränenfluss	GRAD	0	normal	1	ausgeprägter Meniskus	2	selten Überlaufen	3	oft Überlaufen	4	exzessiver Tränenfluss
5	pre-auricular	GRAD	0	nicht geschwollen	1	geschwollen	2					

Sektion B: Spaltlampenbefunde (Biomikroskopie)

Cornea

1	Stromales Ödem	GRAD	0	kein	1	1-5 Striae	2	6-20 Striae, <5 Falten, milde Trübung	3	>20 Striae + >5 Falten, starke Trübung	4	Trübung von Limbus zu Limbus
2	Mikrozysten/Vakuolen	GRAD	0	keine	1	1 bis 10	2	11 bis 30	3	31 bis 70	4	>70
3	Vaskularisation	GRAD	0	keine	1	<1mm	2	1.0 - 1.5mm	3	1.5 - 2.0mm	4	>2.0mm
3a	Lokalisation	GRAD	0	oben	1	unten	2	temporal	3	nasal	4	Zirkulär
4	Cornea Anfärbung	GRAD	0	keine	1	1 bis 20 Punktate	2	21 - 40 Punktate	3	>41Punktate, diffuse Flecken	4	dichte, fliessende Bereiche
4a	Lokalisation	GRAD	0	oben	1	unten	2	temporal/nasal	3	zentral	4	gesamte Cornea
4b	Tiefe	GRAD	0	keine Stromadiffusion	1	verzögerte Diffusion (30-60sec)	2	verzögerte Diffusion (5-29sec)	3	sofortige, mässige Diffusion	4	sofortige, ausgedehnte Diffusion
5	Infiltrate	GRAD	0	keine	1	Spuren	2	milde Form	3	gemässigte Form	4	schwere Form
5a	Lokalisation	GRAD	0	oben	1	Peripherie	2	Midperipherie	3	zentral	4	gesamte Cornea
5b	Tiefe	GRAD	0	Epithelial	1	Subepithelial	2	vorderes Stroma	3	Stroma	4	assoziierter Substanzverlust
5c	Fluorescein	GRAD	0	kein Staining	1	negatives Staining	2	Epithelial Staining	3	verzögerte Diffusion	4	sofortige Diffusion
6	Narben	GRAD	0	keine	1	Spuren, <2mm diffus	2	focal, 2-4mm	3	focal, >4mm	4	Substanz verlust

Conjunctiva

7	limbale Rötung	GRAD	0	keine	1	leicht vermehrte, lokale Füllung	2	schwach vermehrte, diffuse Füllung	3	mässig vermehrte, lokale / diffuse Füllung	4	starke zirkuläre (Ciliary Flush) Füllung
8	limbales Ödem	GRAD	0	keine	1	lokales leichtes Ödem, keine Bindehautfalten	2	lokales starkes Ödem	3	zirkuläres schwaches Ödem	4	zirkuläres starkes Ödem (Chemose)
9	bulbäre Conjunctiva Rötung	GRAD	0	keine	1	leicht vermehrte, lokale Füllung	2	schwach vermehrte, diffuse Füllung	3	mässig vermehrte, lokale / diffuse Füllung	4	Starke diffuse episklerale/skleral Füllung
10	bulbäre Conjunctiva Ödem	GRAD	0	keine	1	lokales leichtes Ödem, keine Bindehautfalten	2	lokale mehrere Ödem Herde	3	mässiges generalisiertes Ödem	4	starkes generalisiertes Ödem (Chemose)
11	Papillen inferior	GRAD	0	Regelmässiger, seidiger Eindruck	1	körnige Oberfläche, leichte Bindehautrötung	2	Papillen <1mm, schwache Bindehautrötung / Ödem	3	Papillen 1-3mm, mässige Rötung / Ödem	4	Papillen >3mm, starke Rötung / Ödem
12	Papillen superior	GRAD	0	Regelmässiger, seidiger Eindruck	1	körnige Oberfläche, leichte Bindehautrötung	2	Papillen <1mm, schwache Bindehautrötung / Ödem	3	Papillen 1-3mm, mässige Rötung / Ödem	4	Papillen >3mm, Schleimproduktion, starke Rötung / Ödem
13	Follikel inferior	GRAD	0	keine	1	1 bis 5	2	6 bis 10	3	11 bis 20	4	>20
13a	Follikel aktiv fluopositiv	GRAD	0	keine	1	1	2	1 bis 3	3	4 bis 6	4	>6
13b	Ödem	GRAD	0	kein	1	körnige Oberfläche, leichte Bindehautrötung	2	schwache Rötung / Ödem	3	mässige Rötung / Ödem / Schleimbildung	4	starke Rötung / Ödem / Schleimbildung
14	Follikel superior	GRAD	0	keine	1	1 bis 5	2	6 bis 10	3	11 bis 20	4	>20
14a	Follikel aktiv fluopositiv	GRAD	0	keine	1	1	2	1 bis 3	3	4 bis 6	4	>6
14b	Ödem	GRAD	0	kein	1	körnige Oberfläche, leichte Bindehautrötung	2	schwache Rötung / Ödem	3	mässige Rötung / Ödem / Schleimbildung	4	starke Rötung / Ödem / Schleimbildung
15	Sekretion	GRAD	0	normale Sekretion	1	leicht serös	2	serös, schwach Mukös	3	mässig Mukös, leicht verklebte Wimpern	4	stark Mukös, verklebte Wimpern

Sektion C: Kontaktlinsenbefunde

Ablagerungen

1	Lipide	GRAD	0	keine	1	leicht = 1-2mm	2	schwach = 3-4mm	3	mässig = grossflächig >5mm	4	stark = Vacc beeinträchtigt
2	Mucin	GRAD	0	keine	1	leicht = 1-2mm	2	schwach = 3-4mm	3	mässig = grossflächig >5mm	4	stark = Vacc beeinträchtigt
3	hydrophobe Stellen	GRAD	0	keine	1	leicht = 1-2mm	2	schwach = 3-4mm	3	mässig = grossflächig >5mm	4	stark = Vacc beeinträchtigt
4	Kosmetikartickstände	GRAD	0	keine	1	leicht = 1-2mm	2	schwach = 3-4mm	3	mässig = grossflächig >5mm	4	stark = Vacc beeinträchtigt
5	Mischablagerungen	GRAD	0	keine	1	leicht = 1-2mm	2	schwach = 3-4mm	3	mässig = grossflächig >5mm	4	stark = Vacc beeinträchtigt

Kontaktlinsen

6	Typ	GRAD	0	Balafilcon A	1	Lotrafilcon A	2	Lotrafilcon B	3	Senofilcon A	4	Galyfilcon A
7	Alter	GRAD	0	Karenz in den letzten Tagen	1	1. Tag	2	1/3 der Lebensdauer	3	2/3 der Lebensdauer	4	3/3 vor Austausch
8	Modus	GRAD	0	Karenz in den letzten Tagen	1	DW	2	FW = maximal 1x pro Woche	3	EW = max 1 Woche	4	CW = bis zu 1 Monat (J&J = 1 Woche)
9	Bewegung	GRAD	0	>1.5mm	1	1.0-1.5mm	2	0.5-1.0mm	3	<0.5mm	4	keine Bewegung
10	Materialdefekte	GRAD	0	keine	1	unsaubere Ränder	2	Risse im Rand	3	Ausreisser am Rand	4	zentrale Risse

Pflegemittel

11	Pflegemittel Typ	GRAD	0	keines	1	Multifunktionslösung Biguanid	2	Multifunktionslösung Polyquad	3	Peroxid System	4	manueller Reiniger, Proteinentfernung
12	Anwendung	GRAD	0	tägliche Anwendung	1	1x Woche	2	1x in 2 Wochen	3	<2x Woche	4	nie
13	Visus											

7.3 ***Observation Sheet***

Beobachtungsbogen "FoCoSi" Studie 2007

Sektion A: Anamnese Patient/Datum: _____

OD			OS
GRAD	1	Medikamente	GRAD
GRAD	2	Beschwerden	GRAD
GRAD	3	Pollenallergie bekannt	GRAD
GRAD	4	Tränenfluss	GRAD
GRAD	5	pre-auricular Lymphknoten	GRAD

Sektion B: Spaltlampenbefunde (Biomikroskopie)

OD			OS
		Cornea	
GRAD	1	Striae/Falten	GRAD
GRAD	2	Mikrozysten/Vakuolen	GRAD
GRAD	3	Vaskularisation	GRAD
GRAD	3a	Lokalisation	GRAD
GRAD	4	Cornea Anfärbung	GRAD
GRAD	4a	Lokalisation	GRAD
GRAD	4b	Tiefe	GRAD
GRAD	5	Infiltrate	GRAD
GRAD	5a	Lokalisation	GRAD
GRAD	5b	Tiefe	GRAD
GRAD	5c	Fluorescein	GRAD
GRAD	6	Narben	GRAD
		Conjunctiva	
GRAD	7	limbale Rötung	GRAD
GRAD	8	limbales Ödem	GRAD
GRAD	9	bulbäre Conjunctiva (Rötung)	GRAD
GRAD	10	bulbäre Conjunctiva (Ödem)	GRAD
GRAD	11	Papillen inferior	GRAD
GRAD	12	Papillen superior	GRAD
GRAD	13	Follikel inferior	GRAD
GRAD	13a	Follikel aktiv fluo+ (Anzahl)	GRAD
GRAD	13b	Ödem	GRAD
GRAD	14	Follikel superior	GRAD
GRAD	14a	Follikel aktiv fluo+ (Anzahl)	GRAD
GRAD	14b	Ödem	GRAD
GRAD	15	Sekretion	GRAD

Sektion C: Kontaktlinsenbefunde

OD			OS
		Ablagerungen	
GRAD	1	Lipide	GRAD
GRAD	2	Mucin	GRAD
GRAD	3	hydrophobe Stellen	GRAD
GRAD	4	Kosmetikarückstände	GRAD
GRAD	5	Mischablagerungen	GRAD
		Kontaktlinsen	
GRAD	6	Typ	GRAD
GRAD	7	Alter	GRAD
GRAD	8	Modus	GRAD
GRAD	9	Bewegung	GRAD
GRAD	10	Materialdefekte	GRAD
		Pflegemittel	
GRAD	11	Pflegemittel Typ	GRAD
GRAD	12	Anwendung	GRAD
OD	13	**Visus**	OS

7.4 *Collected Raw Data*

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