Glistening formation and light scattering in six hydrophobic-acrylic intraocular lenses

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Title: Glistening formation and light scattering in six hydrophobic-acrylic intraocular lenses.

Short title: Light scattering from IOLs with glistenings.

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Introduction

Glistenings are fluid-filled microvacuoles that were first discovered in poly-methyl-methacrylate IOLs in 1984.[1] Recently, however, glistenings have predominantly been reported in association with AcrySof material.[2-11] Clinical studies have shown that this postoperative complication affects from 11% to 100% of implanted IOLs, depending on the type of IOL material and the elapsed postoperative time.[2-12] Glistening effects on the quality of vision of affected patients have proved inconclusive though. In three cases, the presence of glistenings resulted in IOL explantation.[13-15] Although visual acuity[5] (VA) and contrast sensitivity[11,16] (CS) have been reduced in three other studies, a number of researchers did not find decreased visual function in eyes with glistenings.[2,3,6-9,11,16-20] Recent laboratory studies have, however, shown that glistenings are more likely to degrade vision by inducing glare symptoms (straylight) than lowering VA or CS, opening a new line of research.[21,22]

Optical effects of glistenings result from the refractive index difference between that of microvacuoles and IOL polymer.[4] These differences in refractive indices cause redirection of light and light scattering.[23] This phenomenon makes glistenings visible in a slit-lamp examination, as a small portion of light is scattered backward to the observer.[24] However, for visual function, backward scattering is relatively unimportant; the important scattering is forward scattering, the light scattered towards the retina.[24,25] Then scattered and unscattered light is projected onto the retina to form the image with decreased contrast.[24,25] Although forward light scattering may lower CS,[26] it is typically related to glare symptoms, which can be quantified using a clinical device and expressed as straylight.[25]

Light scattering from glistenings has been assessed in vivo using Scheimpflug photography (backward) or a C-Quant straylight meter (Oculus Optikgeräte GmbH) (forward).[10,11,27,28] The former approach has proved controversial.[29] Two studies have reported straylight in patients with glistenings that was assessed using the C-Quant device.[10,11] Those studies, however, showed rather inconclusive results. Glistenings that had developed naturally in the eye, but were measured in a laboratory setting have shown strong scattering effects.[13,30] In a recent study straylight from in vitro induced glistenings was assessed with a modified straylight meter.[22] That study demonstrated a straylight increase that was directly proportional to the number of glistenings. It focused on one IOL material (AcrySof), however, and one may question whether this proportionality rule and scattering effects will differ between IOLs.

Therefore, the purpose of this research was to study glistening development in 30 lenses (six IOL models) from five manufacturers that were subjected to an accelerated aging protocol; and to evaluate glistening effects on straylight in different IOLs.

Materials and Methods

IOLs

In this experimental study, we evaluated five samples of six different IOL models: CT Lucia 601P (Zeiss), PY60AD (Hoya), SN60WF (Alcon), MA60AC (Alcon), Aktis SP NS-60YG (Nidek), and Avansee (Kowa). Main characteristics of the studied IOLs are listed in Table 1. Although these IOLs fall generally into one group that can be called hydrophobic acrylic lenses, the material used to manufacture each IOL is different, using a unique composition of polymers (Table 1). This results in differences in the properties of the IOLs and their susceptibility to develop glistenings.[31] The IOL manufacturers often describe the biomaterial as "proprietary" and the precise composition of hydrophobic acrylic polymers is typically not disclosed by the IOL manufacturer. All lenses were of recent manufacture with at least 3 years expiry, and most were identifiably manufactured in 2017. The lenses were removed from their packaging and submerged in a balanced saline solution (BSS) in glass bottles. The IOLs were kept in a wet state during the entire course of this experiment. It was found that sometimes a superficial layer of BSS compound precipitates formed on the upward lens surface, but it was not associated with any specific IOL model. As this process appeared to be an artifact of the laboratory condition, those deposits were removed by rinsing and gently wiping the lenses with a damp absorbent swab to avoid a potential confounding effect.

Accelerated in vitro glistening induction

The IOLs were incubated for 24 hours in a laboratory oven at a temperature of 45°C. Afterwards, they were placed for 2.5 hours in a water bath at 37°C. This method has been proposed by IOL manufacturers to simulate the aging of the IOL material.[32] The temperature of 37°C was maintained during microscopic and straylight analysis by the use of either a heated stage or keeping them immersed in a pre-heated solution.

Image recording and analysis

Overview photographs were obtained using dark-field microscopy (Meiji Techno, Japan). Those images were not used for the assessment and quantification of glistenings. A BX50 microscope (Olympus, Japan) with a 10x objective lens was used for gross examination and recording of images for digital processing. A minimum of 5 photographs was taken from the central and/or peripheral part of the lens, depending on glistenings distribution in the IOL.

Images were analyzed using a custom-made software (Image Processing Toolbox, Matlab (MathWorks, Inc.), which was described in detail in a recent article,[22] to obtain the number of microvacuoles (MV) per mm² and their mean size.

Straylight measurements

Straylight levels of the IOL were measured using a modified clinical straylight meter, the C-Quant (Oculus Optikgeräte GmbH).[33] This device assesses straylight at an effective angle of 7°. In a clinic, the C-Quant is used to assess in vivo light scattering of the eye, however, the modification allows one to measure in vitro straylight originating from the IOL, independent of the examiner's eye.[33] The principle of this modification and its application have been described in previous papers and the protocol is well established.[22,30,33] In the current study, we followed that same protocol with the exception that a temperature of 37°C (as opposed to room temperature) was maintained during straylight assessment. The output of the C-Quant device is the logarithm of the straylight parameters, log(s), which is expressed in terms of degrees squared per steradian ($\mathrm{deg}^2/\mathrm{sr}$). As some low straylight level may result from the optical set-up, the straylight of the setup without the test IOL was measured separately and later subtracted from straylight measured with the IOL in place. Two straylight measurements were performed for each condition.

Light scattering of the IOLs was measured before (one lens per model) and after (all IOLs) the accelerated aging procedure. Straylight results that had been obtained prior incubation served as a reference. Additionally, straylight from the studied IOLs was compared with that of a 20-, 70- and 80-year-old crystalline lens. These normative data were derived from the International Commission on Illumination standard.[34]

Statistical analysis

Numerical outcomes of the straylight assessment and the glistening analysis were averaged based on the assessed condition and the lens model and expressed as the mean ± standard deviation (SD). Linear regression was performed on the effect of the total glistenings number on straylight. For this analysis, results of a recent study on light scattering from glistenings[22] were also included to increase sample size and accuracy of the linear model. The descriptive statistics and the regression analysis were performed with Excel software (Microsoft Corp.).

Results

Glistenings formation

Glistenings were found in all but one of the studied IOL models. Figure 1 shows representative microscopic photographs of each IOL recorded following the accelerated aging process. The mean number of glistenings and their size are presented in Table 2. The highest density of glistenings was found in the PY-60D IOLs ranging from 3058 to 4061 MV/mm^2, though, the developed microvacuoles were of the smallest size. The MA60AC IOLs demonstrated on average the second highest number of glistenings, but the glistenings severity was not fully consistent across the studied MA60AC samples showing a wide range of 136 to 1312 MV/mm^2. This model also demonstrated the largest size of glistenings found in our study. In the Avansee lenses, there were virtually no glistenings present. The number of glistenings found in each IOL sample is presented in Figure 2.

The glistening distribution pattern differed between the IOL models. In MA60AC, SN60WF, PY60AD and CT Lucia lenses, the density of microvacuoles decreased from the center to the periphery. The reverse was the case in the Aktis lenses, which showed glistenings only in the periphery, but none in the center. However, increased diffuse light scattering was observed in the Aktis lenses, which resulted in a whitish appearance of the IOL (Figure 3).

Straylight measurements

The mean straylight parameter (±SD) of the IOLs prior incubation ranged from 0.1 to 1.3 deg^2/sr (Figure 4, blue bars). In most of the lenses, the measured straylight levels increased following the accelerated aging procedure (Figure 4, gray bars). Straylight of the CT Lucia was 1.09±0.99 deg^2/sr, for the PY-60AD it was 19.30±2.07 deg^2/sr, for the SN60WF and MA60AC IOLs it was 1.15±0.15 deg^2/sr and 5.95±3.67 deg^2/sr, respectively, for the Aktis it was 1.71±0.84 deg^2/sr, and for the Avansee it was 0.95±0.24 deg^2/sr.

Given the absence of glistenings in the Avansee and an unorthodox distribution of glistenings in the Aktis, these IOLs were excluded from a comparison between the straylight parameters and the total number of glistenings. This analysis confirmed a strong and proportional relationship ($R^2 = 0.95$) between these two parameters (Figure 5). The corresponding regression function was best fitted as:

$$straylight\ parameter\ s = 0.0048\ \times number\ of\ glistenings\ per\ mm^2\ [deg^2/sr]$$

Discussion

Hydrophobic acrylic IOLs are not all made from the same polymers. We found in five of the six IOL models a varying tendency to form glistenings and demonstrated that glistenings may cause an increase of straylight to a level that is considered functionally important. This increase is proportional to the number of glistenings and occurs irrespective of the IOL model.

In an overview of the historical development of straylight measurement, van den Berg[25] described how disability glare was defined in the early 20th century as “the negative effect on visual function of a bright light located at some distance in the visual field”. At angles larger than 1º the functional effect corresponded precisely to the effect of a light with a luminosity equal to that of the light that is perceived spreading around such a bright source. This perceived spreading of light was called straylight and by international standard disability glare became defined as identical to straylight which today is recognized by ophthalmologists as an important aspect of the quality of vision.[25]

In a normal eye, straylight increases with age as the crystalline lens ages.[25,34,35] A young lens shows a low scattering level which has little effect on visual performance. In 60% of the IOLs in the present study, straylight values were below values for the young lens (Figure 3). In IOLs, such a low scattering level corresponds to a low glistening number, or an absence of glistenings. A large number of glistenings, however, may increase straylight to the level associated with a 70- and 80-year-old crystalline lens and we found this elevated number in 20% of the IOLs: an average straylight parameter of 18.1 deg^2/sr. Michael et al.[36] examined the relationship between lens opacity and intraocular straylight, VA and CS in European drivers aged between 20 and 89 years and reported that 15.8 deg^2/sr was associated with “extreme difficulties” while driving and values higher than 20 deg^2/sr would be associated with “self-limiting driving” behavior[36] which can be related to increased sensitivity to high-intensity glare sources, such as oncoming car headlights or a low sun.[25,37,38] In a different study, van der Mooren et al.[26] demonstrated that an increase of straylight by 19.0 deg^2/sr (0.40 log(s)) is associated with a 76% increase in halo size and a serious loss in luminance detection threshold (by 2,130%). This straylight elevation was also associated with decreased CS function with and without the presence of a glare source in the visual scene. The authors concluded that increased straylight can significantly impair these patients' visual function, particularly have an impact on their driving performance.[26] Thus, the presence of glistenings in IOLs may adversely affect the patient's quality of vision and affect everyday visual tasks, like driving, by inducing photopic phenomena.

The relation between straylight and glistenings found in pseudophakic patients has been described in two papers.[10,11] Colin and Orignac[10] measured straylight in patients with IOLs that were graded based on the glistening severity as grade 0 (absence), grade 1 (moderate) and grade 2 (dense). Although straylight was not significantly associated with the glistening grades, the mean log(s) value of grade 2 was increased as compared to a normal pseudophakic eye.[39] In the grade-2 group straylight was on average 1.3 log(s) in subjects at 65 years of age. The normative data for the straylight increase in normal pseudophakic eyes[39] shows a value of 1.2 log(s) at the age of 65 years in groups with lower grades. Hence, the reported increased straylight in the grade-2 group, although not statistically significant, could have resulted from the presence of dense glistenings in the Colin and Orignac's[10] patients. In contrast, Henriksen et al.[11] did find a statistically significant correlation between straylight and the quantification of glistening severity. The density of glistenings and their scattering effects reported by Henriksen et al.[11] was later found to be in agreement with the results of Łabuz et al. from an *in vitro* model.[22] Straylight elevation has also been confirmed in in IOLs with glistenings that had formed *in vivo* in the eye and were evaluated *in vitro* after explantation. Increased straylight levels were found by van der Mooren et al.[13] in two patients where the presence of glistenings was given as the primary reason for IOL explantation. In another analysis, Łabuz et al.[30] took a random sample of IOLs that were extracted from autopsy donor eyes, and identified alterations to the IOL material. One of the reported IOL complications was the presence of glistenings.[30] A mean straylight value of 1.7 deg^2/sr in 1-piece yellow-tinted IOLs and 5.4 deg^2/sr in 3-piece IOLs was measured[30] these are very close to the results we present here: 1.15 deg^2/sr in the SN60WF and 5.95 deg^2/sr in the MA60AC. The highest value found by Łabuz et al.[30] was measured from a 3-piece IOL at 13.8 deg^2/sr.[14] Again this is close to the 12.2 deg^2/sr measured in one of the MA60AC group, indicating that scattering effects of *in vitro* induced glistenings can be compared to glistenings that form *in vivo* in the eye.

This study indicates that the same proportional relationship between the number of microvacuoles and straylight holds for different IOLs, although there are differences in glistening size and IOL material. In a previous report,[22] two IOL models made of AcrySof material were found to have a slope of 0.0046 for the glistening number vs. straylight relationship, showing a good agreement with clinical and experimental data found in the literature.[22] In the current study, we also included those earlier results, which yielded a small adjustment of the slope by 0.0002. Although 5 different IOL models were used, R^2 remained at a high level (0.95) demonstrating strong correlation despite existing differences between the IOLs. This finding indicates that our numerical model can be used to predict the scattering effect of glistenings independently of the IOL model.

Glistening formation has been most often studied in lenses of AcrySof material.[6,7,10,13,22,32] We, however, compared the response to the accelerated aging procedure in 6 different hydrophobic-acrylic models. Five of the 6 IOLs developed glistenings, but their total number differed between the IOL groups. Intriguingly, significant differences were also reported between IOLs of the same group. The highest intragroup variability was found in the MA60AC with a range of 136 to 1312 MV/mm^2. Why there should be such variability remains to be elucidated and the question should best be addressed to the manufacturer. We also demonstrated that glistenings may vary in size depending on the material. The PY-60AD and Aktis lenses showed microvacuoles with a diameter of 5.2µm and 5.4µm, respectively, but in the other IOLs it was 8.0µm for the SN60WF, 8.4µm for the CT Lucia, and 10.2µm for the MA60AC. The reported size range of glistenings appears to be in agreement with that found in the literature. A 3-piece and a 1-piece AcrySof IOL were studied by Gregori et al.[40] They reported mean values of 13.4µm and 6.3µm with a larger diameter found in the 3-piece IOL.[40] This is in accordance with what we also found - smaller glistenings in the SN60WF than in the MA60AC. In another laboratory study, van der Mooren et al.[21] found a mean size of 5.2µm and 6.2µm in the iSymm (Hoya) and AcrySof (Alcon) respectively. These values are also close to the size of glistenings found in our PY-60AD and SN60WF groups. The measurement of glistening size *in vivo* is quite challenging in that it requires high-quality image recording equipment and specialized knowledge about image processing.[4,11] In the two studies that have been published, the size ranged from 1µm to 20µm reported by Werner[4] and from 6µm to 36µm by Henriksen et al.[11], so the mean sizes we found *in vitro* do lie within the clinical range.

Four IOL models showed a typical pattern of peak density of microvacuole distribution in the IOL optic center. However, the reverse pattern was found in the Aktis, where glistenings were not observed in the central area but accumulated in the lens periphery. The whitish appearance of these lenses (Figure 3) may suggest the presence of subsurface nano-glistenings,[41,42] given that the gross examination did not reveal visible microvacuoles in the lens centre. Nano-glistenings are submicron water vacuoles of 33nm to 190nm size that accumulate just underneath the lens surface.[42] Although very small, nano-glistenings can scatter light, producing a white discoloration of the IOL.[41] Despite the presence of increased diffuse light scattering, the straylight of the Aktis IOLs remained low but this this could have been expected, as there are reports that nano-glistenings do not have a significant straylight effect.[41,43]

Since IOL manufacturers acknowledged the problem of glistening formation, some materials have been improved and this is especially well described for the Alcon Acrysof.[4,32,44] Thomes and Callaghan[32] reported that when the SN60WF IOL was subjected to an accelerated-aging protocol (identical to the one we described here) they found a significantly lower glistening number in IOLs that were manufactured in 2012 compared to those manufactured in 2003.[33] The mean glistening number (±SD) of the improved SN60WF IOLs was 40±35 MV/mm^2, and this is in line with 61±33 MV/mm^2

what we found. However, although a clear improvement can be seen for the SN60WF, the MA60AC IOLs showed that glistenings may still exist in other AcrySof lenses, also those manufactured after 2012 (De Soyza J, et al. RANZCO 2017, Abstract number: S1902).[15,45] This problem may be resolved by the new Clareon material introduced by Alcon, which was shown to be glistenings-free in preclinical *in vitro* studies (Auffarth GU, ESCRS 2017).

In conclusion, we found glistenings in the majority of the IOLs (5 of the 6 IOL models) we studied, but only in 20% did the induced light scattering reach levels that have the potential to hinder visual performance. We showed that glistenings' morphology differs depending on the IOL models, but the proportional straylight increase with the glistening number holds regardless of those differences. Although less severe, the glistening problem persists and needs to be addressed by the IOL manufacturer through either introduction of new materials or by continuous improvement of the manufacturing process used to make lenses in a current material.

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Figures

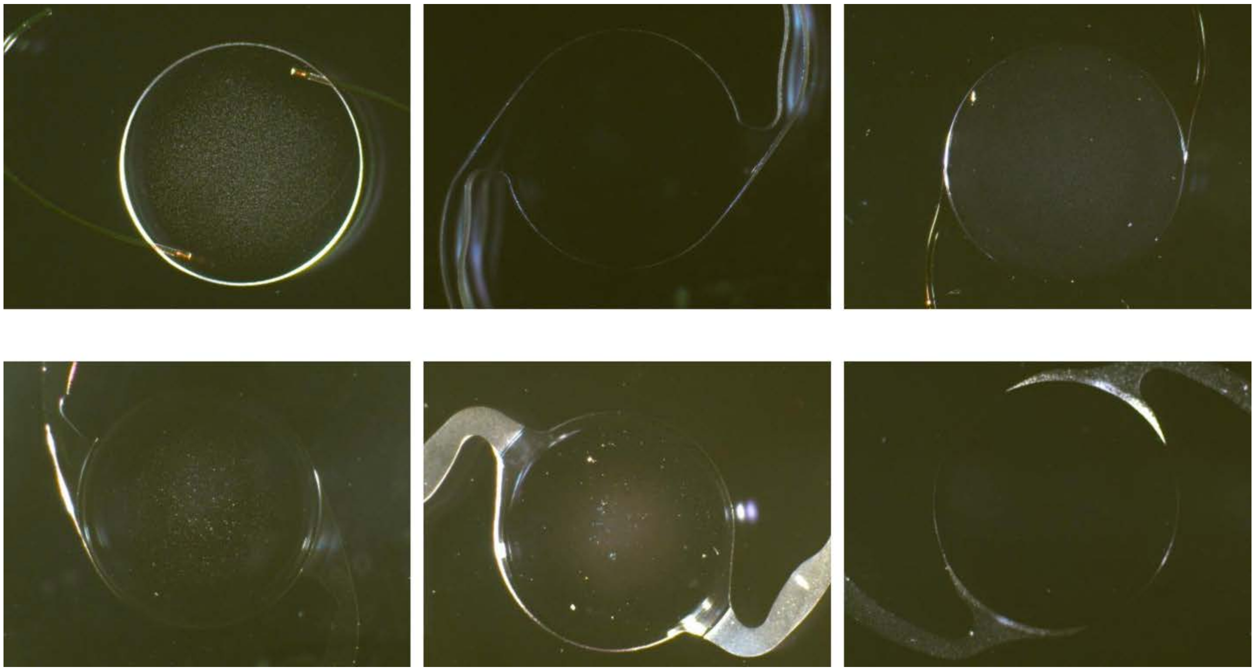
Figure 1. Microscopic images of the intraocular lenses after glistenings induction. Top Left: MA60AC (Alcon), Top Middle; SN60WF (Alcon); Top Right; PY60AD (Hoya), Bottom Left; CT Lucia 601P (Zeiss), Bottom Middle; Aktis SP NS-60YG (Nidek), Bottom Right; Avansee (Kowa).

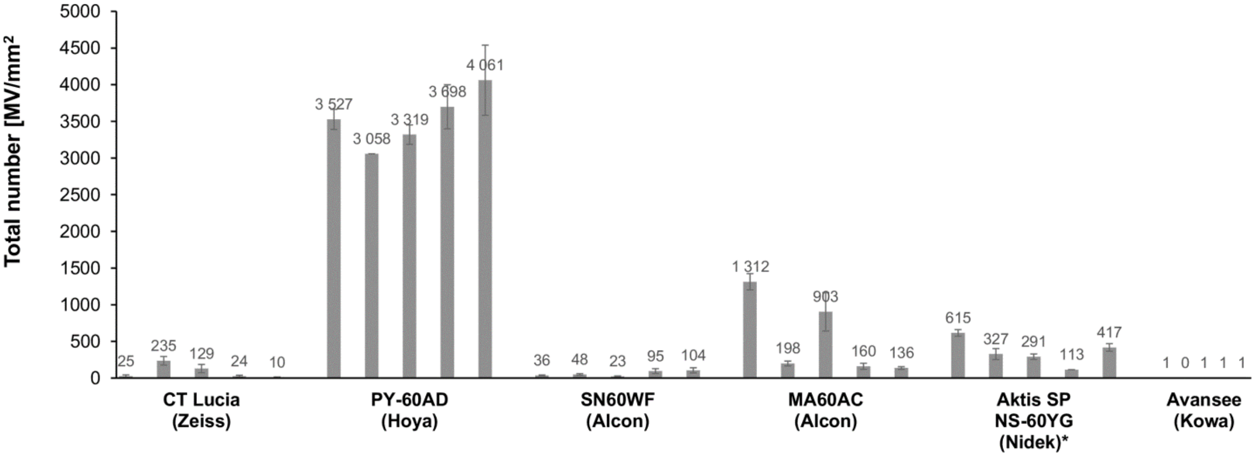
Figure 2. Mean glistening numbers in each studied intraocular lense. Error bars = standard deviation.

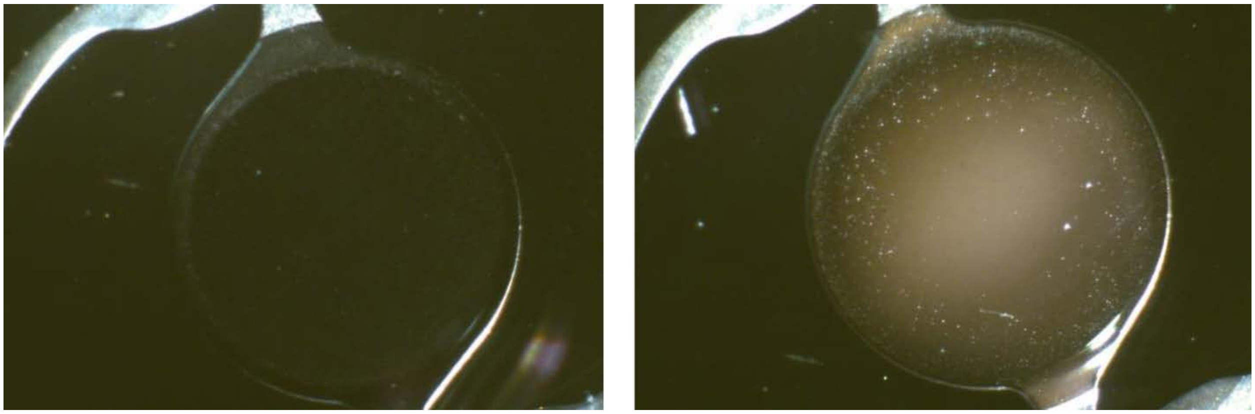
Figure 3. Photographs of an Aktis SP NS-60YG (Nidek) before (Left) and after (Right) the aging procedure. Note a white discoloration of the IOL lens following aging.

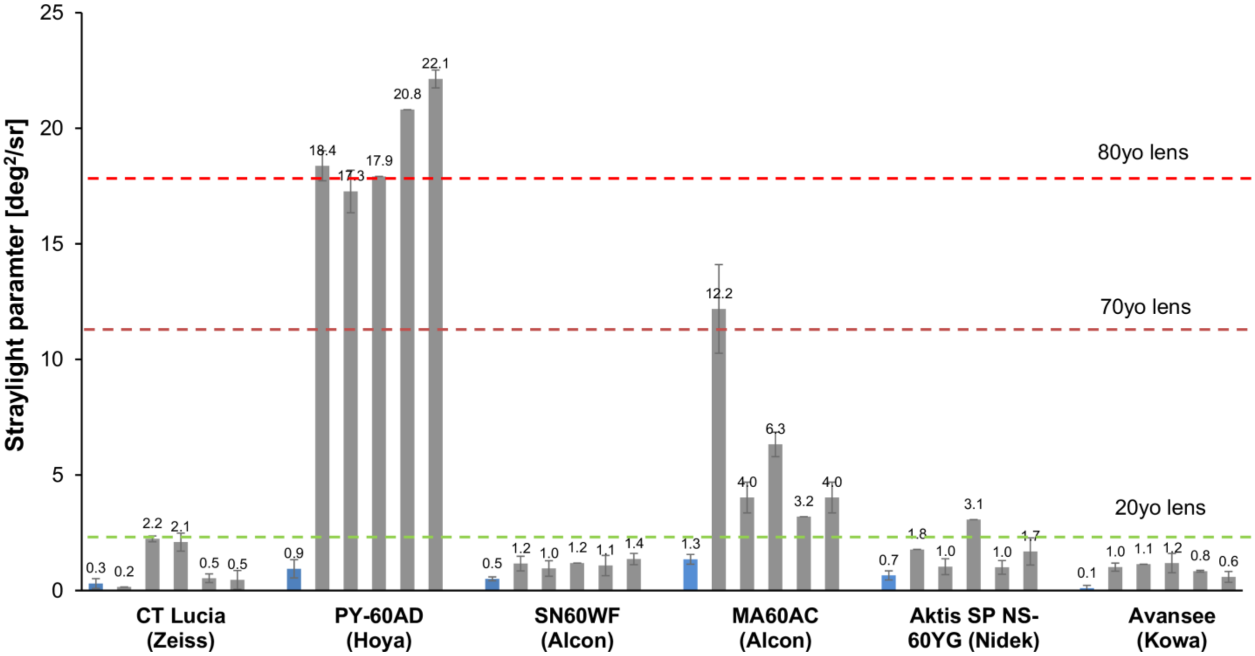
Figure 4. Mean straylight parameter across the studied intraocular lens (IOL) groups. The blue bars indicate straylight before IOL aging (control IOLs). The grey bars show straylight values of lenses after the aging procedure. The green line refers to a straylight level of a 20-year-old crystalline lens. The brown and red lines indicate straylight of the crystalline lens of age 70 and 80 years respectively. Error bars = standard deviation.

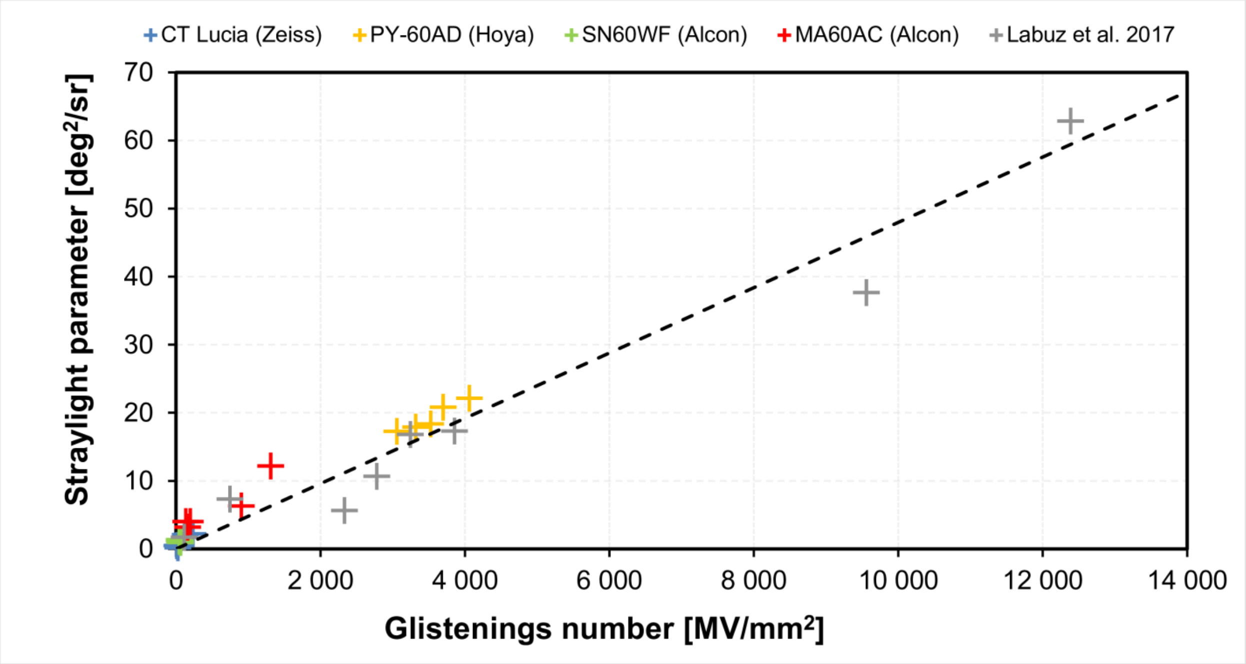
Figure 5. A proportional relationship between the straylight parameter and the glistening number in different lens models.




Total number [MV/mm²
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
25
235
129
24
10
3 527
3 058
3 319
3 698
4 061
36
48
23
95
104
1 312
198
903
160
136
615
327
291
113
417
1 0 1 1 1
CT Lucia (Zeiss)
PY-60AD (Hoya)
SN60WF (Alcon)
MA60AC (Alcon)
Aktis SP NS-60YG (Nidek)*
Avansee (Kowa)




Straylight paramter [deg²/sr]
25
20
15
10
5
0
80yo lens
70yo lens
20yo lens
0.3
0.2
2.2
2.1
0.5
0.5
0.9
18.4
17.3
17.9
20.8
22.1
0.5
1.2
1.0
1.2
1.1
1.4
1.3
12.2
4.0
6.3
3.2
4.0
0.7
1.8
1.0
3.1
1.0
1.7
0.1
1.0
1.1
1.2
0.8
0.6
CT Lucia (Zeiss)
PY-60AD (Hoya)
SN60WF (Alcon)
MA60AC (Alcon)
Aktis SP NS-60YG (Nidek)
Avansee (Kowa)


CT Lucia (Zeiss)
PY-60AD (Hoya)
SN60WF (Alcon)
MA60AC (Alcon)
Labuz et al. 2017
Straylight parameter [deg²/sr]
70
60
50
40
30
20
10
0
0
2 000
4 000
6 000
8 000
10 000
12 000
14 000
Glistenings number [MV/mm²]

Manufacturer	Optic material composition	Blue-light filter	Refractive index	Lens Design	Optic design	Pre-loaded	Haptic material	M
Carl Zeiss Meditec	*Coppolymer of butyl acrylate, ethyl methacrylate and N-benzyl-N-isopropylpropenamide* *Heparin Coated Surface*	No	1.49	1-piece	Aspheric	Yes	See optic material	
Hoya Surgical Optics	Copolymer of phenylethyl methacrylate and n-butyl acrylate, fluoroalkyl methacrylate	Yes	1.52	3-piece	Aspheric	Yes	Polymethyl methacrylate	
Alcon, Inc.	Copolymer of phenylethyl acrylate and phenylethyl methacrylate, cross-linked with butanediol diacrylate	Yes	1.55	1-piece	Aspheric	No	See optic material	C
		No		3-piece	Spherical		Polymethyl methacrylate	
Nidek	Copolymer of n-butyl acrylate, n-butyl methacrylate and phenoxyethyl acrylate	Yes	1.52	1-piece	Aspheric	Yes	See optic material	
Kowa	Crosslinked copolymer of 2-phenoxyethyl acrylate and ethyl acrylate	Yes	1.52	1-piece	Aspheric	Yes	See optic material	C

Table 1. Characteristics of the studied intraocular lenses (IOLs).

IOL models	Pattern of glistening formation	Glistenings number [MV/mm²]	Mean glistening size [µm]
CT Lucia 601P (Zeiss)	central	85 ± 86	8.4 ± 0.4
PY60AD (Hoya)	central	3532 ± 340	5.2 ± 0.4
SN60WF (Alcon)	central	61 ± 33	8.0 ± 0.6
MA60AC (Alcon)	central	542 ± 480	10.2 ± 1.4
Aktis SP NS-60YG (Nidek)	peripheral	352 ± 164	5.4 ± 0.6
Avansee (Kowa)	no glistenings	<1	-

Table 2. Glistening characteristics in the studied intraocular lens (IOL) models (mean value ± standard deviation). MV; microvacuoles.