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RESEARCH REPORT

Fluorophotometric Analysis of the Ocular Surface Glycocalyx in Soft Contact Lens Wearers

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ABSTRACT

Purpose: Unstable tear film characterized by shorting of tear break-up time (BUT) is associated with discomfort and dryness in contact lens wearers. The glycocalyx is thought to be crucial in maintaining the wettability and lubrication of the ocular surface. We evaluated the ocular surface glycocalyx in soft contact lens (SCL) wearers using a fluorescein-labeled wheat germ agglutinin (F-WGA) as a marker to demonstrate the ocular surface glycoconjugates *in vivo*.

Methods: Twenty experienced SCL wearers and 20 healthy volunteers with no history of CL wearing (controls) were enrolled in the study. After applying a 5% F-WGA solution to the eyes of study individuals, fluorescent intensities in their respective central corneas were measured by fluorophotometry. The relationship between F-WGA intensity in the corneal surface and clinical parameters associated with contact lens wear were analyzed.

Results: F-WGA fluorescence intensity in the SCL group was 418.5 ± 103.3, which was significantly lower than that of the controls (825.0 ± 179.8; $p < 0.0001$, Mann–Whitney test). F-WGA fluorescence intensity was not correlated with Schirmer's test values or age, whereas a statistically significant correlation between F-WGA fluorescence intensity and tear film BUT was observed ($r = 0.77$, $p < 0.0001$). The decrease in F-WGA fluorescence intensity could be reversed by discontinuation of SCL use.

Conclusion: Reduction and/or compositional alteration of ocular surface glycocalyx may be one of the causative factors of SCL-induced eye dryness.

Keywords: Contact lens, cornea, fluorescein, lectins, mucins

INTRODUCTION

Contact lens (CL) discomfort, particularly dryness sensation can cause some individuals to reduce the time they wish to wear CL and may render them intolerant of CL wear.[1–3] In a study examining the reasons for discontinuation of CL wear, 51% of subjects cited discomfort as the principal reason.[2] Ocular dryness is experienced by 33–50% of CL wearers.[3]

The dryness sensation experienced by CL wearers is complex and its causes appear multifactorial.[4] Several factors, including instability of the tear film, increased tear evaporation, deposition of proteins and lipids on contact lenses, and subclinical inflammatory changes in the ocular surface are thought to relate to dryness to some extent.[5] Of these, tear film instability appears to be the most notable issue in CL wearers.[6] It is well known that short precorneal tear break-up time (BUT) is common among CL wearers irrespective of

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symptoms.[7,8] Glasson and associates[6] reported that average non-invasive BUT in intolerant CL wearers was significantly shorter than that of tolerant CL wearers. Thus, unstable tear film characterized by shortening of BUT appears to be associated with CL wear and tolerance to wearing CL.

The measurement of BUT is usually performed when CL is taken out. Accordingly, a short BUT associated with CL wear is due to certain biochemical or structural changes in the ocular surface epithelia, rather than mechanical or biophysical properties of the CL itself. A possible mechanism responsible for unstable tear film is the change in wettability of the corneal epithelium. The glycocalyx, located on the apical portion of microplicae of the corneal and conjunctival epithelia, is thought to be crucial in maintaining the wettability and lubrication of the ocular surface.[9–11] Using scanning electron microscopy, Forte et al.[12] reported a significant reduction of epithelial mucus in CL wearers.

Ocular mucins are of secreted and membrane-associated types.[13–15] Membrane associated mucins, such as MUC1, MUC4 and MUC16, are identified as major components of the glycocalyx.[16–18] They form a hydrophilic surface over the hydrophobic plasma membrane to facilitate a formation of stable tear film. Secreted mucins, mainly MUC5AC, from the conjunctival goblet cells are thought to cover the ocular surface epithelia.[14,15] Therefore, both types of mucins are thought to play a crucial role on the ocular surface. The change in mucin levels in response to CL wear has been the subject of several studies but reported results are inconsistent.[19–23] Studies to date have shown that mucin content and production in CL wearers may be decreased or unaltered. Although recent advances in ocular surface mucins research are significant, the development of a simple and quantitative method to evaluate ocular surface glycocalyx would enable an improved understanding of the role of glycocalyx, including mucins, in the pathogenesis of ocular surface disorders.

We previously tested a lectin conjugate of fluorescein as a marker to demonstrate the presence of the ocular surface glycocalyx *in vivo*.[24] Lectins are a group of glycoproteins that specifically bind with carbohydrate residues of glycoconjugates.[25] Of these, wheat germ agglutinin (WGA) specifically binds to N-acetylglucosamine and N-acetyl neuraminic acid (sialic acid), which are often found in the non-reducing termini of mucous carbohydrate chains.[26–28] We reported that a WGA conjugate of fluorescein (F-WGA) appeared to predominantly bind to the glycocalyx of the ocular surface epithelium.[24] Hence, a fluorophotometry may be suitable for quantitative evaluation of the ocular surface glycocalyx *in vivo*.

In the present study, we evaluated ocular surface glycocalyx in soft contact lens (SCL) wearers using F-WGA. The relationship between F-WGA intensity on the corneal surface and clinical parameters associated with contact lens wear was analyzed.

TABLE 1 Demographic characteristics of study individuals.

	Control group	SCL group
N	20	20
Age in years (range)	30.7 ± 7.0 (23–48)	30.4 ± 6.4 (22–46)
Gender (male/female)	6/14	6/14
Length of SCL use in years (range)	NA	9.7 ± 5.7 (3–24)

SCL, soft contact lens. Age and length of SCL use are shown as mean ± SD (range). No statistical difference in age and gender was observed between the two groups (Mann–Whitney test and Chi-square test). NA = not applicable.

MATERIALS AND METHODS

Subjects

Twenty experienced SCL wearers (6 males and 14 females) aged 22–46 years (mean ± SD, 30.4 ± 6.5 years) were enrolled in the study (Table 1). Of these, six individuals were disposable SCL wearers and 14 were frequent replacement SCL wearers. All subjects wore their SCL on a daily basis with a mean wear time of 9.7 ± 5.6 years (range, 3–24 years). None of the individuals had significant complaints about their CL wear except for occasional dryness.

Twenty healthy volunteers (6 males and 14 females) aged 23–44 year (33.4 ± 6.8 years), with no history of CL wear or eye diseases except for refractive errors and receiving no topical drug therapy, served as controls.

At the screening visit, two of the authors (CS and MF) performed routine ocular examination of all subjects, followed by an examination of the ocular surface, including Schirmer's test and measurement of tear film BUT. Saline solution (2 μl) containing 1% fluorescein was used for vital staining. None of the subjects had apparent fluorescein staining of cornea and conjunctiva. In the control group, all subjects had more than 5 mm of Schirmer strip wetting, a tear film BUT greater than 5 s, and all were diagnosed as normal according to the Japanese criteria of dry eye syndrome.[29] Only the right eye of all subjects was used for the analysis. The following F-WGA analyses were performed on subsequent investigation visits.

The guidelines of the World Medical Association Declaration of Helsinki were followed. All study individuals received a full explanation of the procedures and provided their informed written consent for participation prior to the experiment. The protocol was approved by the institutional

review board of National Tokyo Medical Center (R10-022).

F-WGA Intensity Measurement on the Corneal Surface

WGA conjugate of fluorescein was purchased from Molecular Probes, Inc. (Eugene, OR). The dye has maximum absorption wavelength of 494 nm and an emission spectrum that peaks at 518 nm. A 5% F-WGA solution was prepared in sterile 0.067 M phosphate-buffered saline (PBS), pH 7.4.

As described in our previous report,[24] we beforehand tested the safety of F-WGA solution using rabbit and human eyes. No adverse reactions were detected either immediately or 24 h after instilling F-WGA solution. Concerning the staining characteristics, the F-WGA stained the corneal surface with a faint, diffuse pattern.[24] No apparent break-up was observed. The staining was too faint to detect the change of fluorescent intensities by a slit-lamp biomicroscope equipped with a blue-free barrier filter. Accordingly, fluorophotometry was adopted to evaluate the fluorescent intensity of F-WGA.

A slit-lamp fluorophotometer (Anterior Fluorometer FL-500, Kowa Co. Ltd., Tokyo, Japan) was used to quantify the fluorescent intensity of the corneal surface. The illuminating light was focused as a 2-mm-diameter circle on the corneal surface. The emitted light passed through a band interference filter centered on 565 nm (half bandwidth, 25 nm) and was directed to a photomultiplier tube with the band interference filter centered on a wavelength of 490 nm (half bandwidth, 30 nm).

The measurement was performed at least 15 min after CL removal. Study individuals were seated in front of the fluorophotometer, the instrument was focused on the central cornea, and the background fluorescence intensity was measured. Five microliters of 5% F-WGA solution was applied to the right eye using an Eppendorf micropipette. Five minutes later, the fluorescent intensity of the central cornea was measured.

F-WGA Intensity Alteration by SCL Wear

Five subjects in the SCL wearer group and five in the control group were selected for the next experiment to evaluate the effect of short-term SCL wear on corneal surface glycocalyx. Soft contact lens wearers were asked to stop wearing their lenses for 2 weeks before the experiment. F-WGA measurements were performed in the right eye of all subjects (day 0). Daily wear of SCL was resumed from the next day (day 1) to day 7 in the SCL group. Subsequently, study individuals again discontinued SCL wear from day 8 to day 10. F-WGA measurements were consecutively performed from day 0 to day 10 in both groups.

Statistical Methods

Data were analyzed using Prism 6 software (GraphPad Software, Inc.; La Jolla, CA). The results are provided as means with standard deviations (SD). The significance of the differences was analyzed using the Mann–Whitney test, Chi-square test, Wilcoxon's signed rank test or Spearman rank correlation coefficient. A probability (p) value of <0.05 was considered statistically significant.

RESULTS

F-WGA Intensity Measurement on the Corneal Surface

Results of Schirmer's tests, tear film BUT and fluorescent intensity on the corneal surface 5 min after the application of F-WGA are listed in Table 2. There were no statistically significant differences in Schirmer's test between the SCL group and normal controls ($p=0.79$, Mann–Whitney test). In contrast, tear film BUT in the SCL group was significantly shorter than that of normal controls ($p<0.0001$, Mann–Whitney test). F-WGA fluorescent intensity in the SCL group was 418.5 ± 103.3, which was also significantly lower than that of normal controls (825.0 ± 179.8; $p<0.0001$, Mann–Whitney test).

Spearman correlation coefficients were used to evaluate whether F-WGA fluorescence intensity was correlated with Schirmer's test values, tear film BUT and age of subjects. F-WGA fluorescent intensity was not correlated with Schirmer's test values or age ($r=0.24$, $p=0.14$; $r=-0.12$, $p=0.46$, respectively). However, as shown in Figure 1, there was a statistically significant correlation between F-WGA fluorescence intensity and tear film BUT ($r=0.77$, $p<0.0001$).

TABLE 2 Results of Schirmer's test, tear film break-up time (BUT), and fluorescent intensities on the corneal surface after the application of wheat germ agglutinin conjugate (F-WGA).

	Control	SCL group
N (eyes)	20	20
Schirmer's test (mm)	19.7 ± 8.0	19.7 ± 9.4
Tear film BUT (s)	14.7 ± 4.5	5.6 ± 2.9*
F-WGA fluorescent intensity	825.0 ± 179.8	418.5 ± 103.3*

SCL, soft contact lens. No statistical differences in Schirmer's test values were observed between the two groups (Mann–Whitney test). Tear film BUT and F-WGA fluorescent intensities in the SCL group were significantly lower than those of the controls ($p<0.0001$ and *$p<0.0001$, Mann-Whitney test).

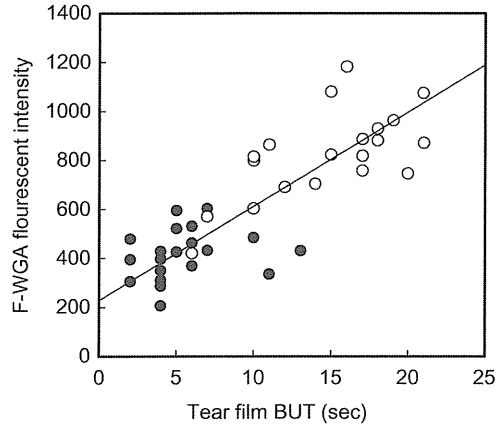

FIGURE 1 Correlation between tear film break-up time (BUT) and fluorescent intensity on the corneal surface after the application of wheat germ agglutinin conjugate (F-WGA). There was a statistically significant correlation between tear film BUT and F-WGA fluorescence intensity ($r=0.77$, $p<0.0001$). Open circle: control group, and closed circle: soft contact lens (SCL) wearers.

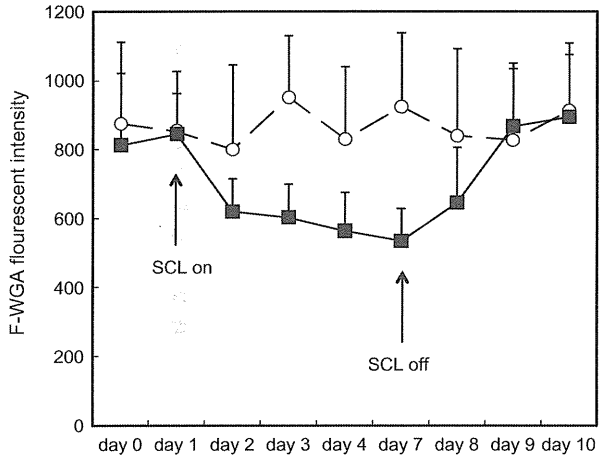

FIGURE 2 Plot of fluorescence intensities on the corneal surface after the application of wheat germ agglutinin conjugate (F-WGA). In control subjects (open circle), no significant differences in F-WGA fluorescence intensity throughout the experimental period were observed (Wilcoxon's singed rank test). In soft contact lens (SCL) group (closed circles), SCL wear was discontinued for 2 weeks prior to the experiment. SCL wear was resumed from the day 1 to the day 7 in SCL group, and then was discontinued again. F-WGA fluorescence intensity in the SCL group significantly decreased from the day 2 to the day 8 ($p<0.05$, Wilcoxon's singed rank test).

F-WGA Intensity Alteration by SCL Wear

Changes in F-WGA fluorescence intensity by SCL wear are shown in Figure 2. In control subjects (no SCL wear), there were no significant changes in F-WGA fluorescence intensity throughout the experimental period. In contrast, F-WGA fluorescence intensity decreased from day 2 to day 8; this decrease was statistically significant ($p<0.05$, Wilcoxon's singed rank test).

DISCUSSION

In the present study, we attempted to evaluate ocular surface glycocalyx in SCL wearers by fluorophotometric analysis of F-WGA staining. WGA, a kind of lectins, specifically binds to N-acetylglucosamine and sialic acid. Sialic acid is the terminal residue of various glycoproteins, not specific for mucins. It does not distinguish between mucin types. However, sialic acid is often found in the non-reducing termini of mucous carbohydrate chains.[26–29] Membrane-associated mucins are considered to be major components of the glycocalyx and glycoproteins.[16–18] From these backgrounds, we previously tested F-WGA as a marker to demonstrate ocular surface glycocalyx *in vivo*.[24]

As described before, ocular surface staining with F-WGA has several unique features.[24] Fluorescent intensities at the central cornea and the nasal bulbar conjunctiva did not decay with time, and remained constant at least for 30 min after the application of F-WGA. F-WGA fluorescent intensities were not diminished by saline instillation. We decided that fluorophotometric measurement was done 5 min after the application. Based on these observations and published histochemical studies that have investigated binding of lectins to the ocular surface, F-WGA was thought to primarily bind to the glycocalyx of the ocular surface epithelium.[24–29]

The most important finding in the current study is that F-WGA fluorescence intensity in SCL wearers was significantly lower than that of the controls. Our result is consistent with the observation of Forte et al.,[12] who showed a reduction of epithelial mucus in CL wearers by scanning electron microscopy. Versula and associates[27] also reported a significant reduction of glycosidic residues of conjunctival goblet cells in CL wearers by using the lectin-colloidal gold technique and transmission electron microscopy. These results suggest that quantitative or qualitative change of ocular surface glycocalyx may be induced by SCL wear, although the precise mechanism is not explored because of the methodological limitation.

There was no statistically significant difference in Schirmer's test values between the SCL group and the controls, but tear film BUT in the SCL group was significantly shorter than that of the controls. F-WGA fluorescent intensity was significantly correlated with tear film BUT. The decrease of F-WGA fluorescence intensity induced by SCL wear could be reversible. F-WGA fluorescence intensity decreased from the first day after resuming SCL wear and recovered to the baseline value the day after discontinuation. Thus, fluorophotometric analysis of F-WGA appears to be a

good indicator for the assessment of glycocalyx on the corneal surface.

Our results suggest that glycocalyx on the corneal surface is compromised by SCL wear, which may result in the reduction of corneal surface wettability; this could be explained by one or more of several plausible mechanisms. First, SCL wear increases the size of superficial epithelial cells in the cornea, which is identified as a consequence of the slowing of the epithelial renewal rate.[30–32] Cells that normally exfoliate remain attached longer while continuing to flatten and enlarge. Such old superficial cells are likely to lose their glycocalyx, or worsen in quality.[12,30] Second, CL wear causes mechanical friction, resulting in an inflammatory response in the ocular surface, even in the absence of apparent subjective symptoms or clinical signs of intolerance.[33–35] A significant increase of HLA DR and ICAM-1 positive cells in the conjunctiva[33] and a significant increase of several inflammatory mediators and cytokines in tear fluids of SCL wearers have been reported.[34,35] Blalock et al.[36] reported that the extracellular domains of MUC1, MUC4 and MUC16 were released from the corneal epithelial cells by treatment with inflammatory mediators, such as TNF-α, neutrophil elastase and MMP-7. Therefore, shedding of carbohydrate chains from membrane-associated mucins on the corneal surface may be facilitated by an inflammatory response induced by SCL wear. Third, tear exchange rate in SCL users is known to be extensively restricted.[37,38] In normal conditions, secreted mucins from conjunctival goblet cells are thought to form a thick and loose "mucous blanket" and cover the ocular surface epithelia.[13–15] When SCL are worn, the delivery of secreted mucins on the corneal surface may be substantially impaired because of restricted tear exchange under the SCL. We currently do not have additional data to judge valid interpretation, and further investigations are required to clarify these issues.

In conclusion, we examined the effect of SCL wear on the ocular surface glycocalyx using F-WGA. F-WGA fluorescence intensity in the SCL group was significantly lower than that of the controls and was significantly correlated with tear film BUT. Based on these observations, it is suggested that reduction and/or compositional alteration of the ocular surface glycocalyx may be one of the causative mechanisms of SCL-induced eye dryness.

DECLARATION OF INTEREST

The authors have no proprietary interest in any materials in this manuscript.

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ORIGINAL ARTICLE

Cost-utility Analysis of Screening for Diabetic Retinopathy in Japan: A Probabilistic Markov Modeling Study

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ABSTRACT

Purpose: To evaluate the cost-effectiveness for a screening interval longer than 1 year detecting diabetic retinopathy (DR) through the estimation of incremental costs per quality-adjusted life year (QALY) based on the best available clinical data in Japan.

Methods: A Markov model with a probabilistic cohort analysis was framed to calculate incremental costs per QALY gained by implementing a screening program detecting DR in Japan. A 1-year cycle length and population size of 50,000 with a 50-year time horizon (age 40–90 years) was used. Best available clinical data from publications and national surveillance data was used, and a model was designed including current diagnosis and management of DR with corresponding visual outcomes. One-way and probabilistic sensitivity analyses were performed considering uncertainties in the parameters.

Results: In the base-case analysis, the strategy with a screening program resulted in an incremental cost of 5,147 Japanese yen (¥; US$64.6) and incremental effectiveness of 0.0054 QALYs per person screened. The incremental cost-effectiveness ratio was ¥944,981 (US$11,857) per QALY. The simulation suggested that screening would result in a significant reduction in blindness in people aged 40 years or over (−16%). Sensitivity analyses suggested that in order to achieve both reductions in blindness and cost-effectiveness in Japan, the screening program should screen those aged 53–84 years, at intervals of 3 years or less.

Conclusions: An eye screening program in Japan would be cost-effective in detecting DR and preventing blindness from DR, even allowing for the uncertainties in estimates of costs, utility, and current management of DR.

Keywords: Cost-utility analysis, diabetic retinopathy, Japan, Markov model, screening

INTRODUCTION

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes mellitus (DM), and its prevalence is quite high. DR is a slow progressive disease and asymptomatic in its early stages, however, once it develops into vision-threatening DR, it has a substantial impact on quality of life.[1,2] A recent meta-analysis[3] revealed that 1 in 3 diabetic people have DR and 1 in 10 have vision-threatening DR defined as having either proliferative DR or diabetic macular edema (DME).[3]

DR is a good candidate for a screening program because it fulfills the necessary conditions for screening; there is a non-invasive economical fundus examination or photography to enable early detection and

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there is well-established evidence that early management of glucose levels and high blood pressure reduce the risk of development and progression of DR. Timely retinal laser photocoagulation and vitreous surgery is effective in preventing blindness or severe vision loss. Newer treatments with anti-vascular endothelial growth factor (anti-VEGF) agents for DME is even more promising, changing the target of DR treatment from "prevention of blindness" to "improving vision" which may further contribute to improvement in quality of life.

Since the number of people with DM in Japan has been increasing, the establishment of a screening program for DR has been of great interest. Optimal conditions for such a screening program are still being sought, and validation of its effectiveness in reducing blindness as well as its cost-effectiveness in the current medical situation is essential. Although there are studies showing that treatment of DR, including anti-VEGF treatment, is cost-effective,[4] it is still unclear whether the introduction of screening programs for DR remains cost-effective when new treatment modalities for DR and DME are routinely performed.

We therefore examined whether a comprehensive screening program for DR in Japan would reduce blindness due to DR and be cost-effective based on updated epidemiological data, the natural course of disease development and progression, and current treatment modalities for DR/DME.

MATERIALS AND METHODS

Research Design

We developed a Markov state-transition model simulating natural history and treatment of DR, integrating screening opportunity, treatment outcomes (i.e. visual acuity), treatment costs, complications and mortality. The model simulated a hypothetical Japanese cohort (50,000 people) without any ophthalmic care for any eye conditions at the age of 40 years. The model compared the effect of the screening program on the rate of detecting DR, preventing blindness and costs of the management of DR. All costs were calculated in Japanese yen (¥), and converted into US dollars (2012) using Federal Reserve historical foreign exchange rates for 2012 (US$1 = ¥79.82).[5] We assumed that each cycle through the model was 1-year long, and in each one, costs and utilities were tabulated for each cohort. We assumed a perspective of entire payers (payment by the National Health Insurance and copayment by DR patients), a lifetime horizon (40–90 years old), and a discount rate of 3% per year for both health benefits and costs. We assumed that subjects in the simulation cohort had no history of other eye diseases (Supplementary Tables S1–S5 – online only).

Proposed Screening Strategy for Diabetic Retinopathy

We compared two strategies: (1) no screening program, which represents the current situation, and (2) a screening program for DR, which would be provided by ophthalmologists using dilated fundus examination. In the strategy with no screening program, we assumed that opportunities to identify patients with DR were available through incidental diagnosis, the national screening program for lifestyle-related diseases in Japan (providing 1-field non-stereo non-mydriatic 45° photograph for those with high risk of cardiovascular disease with metabolic syndrome), annual fundus examinations recommended for patients with DM, or clinic visits for those with severe vision loss caused by advanced stage DR (Supplementary Table S6 – online only). Our model assumed that a fixed proportion of patients with other eye conditions (e.g. presbyopia) or advanced stage DR with visual symptoms (e.g. visual acuity, VA, <0.2) would be visiting an ophthalmologist and would therefore have a chance of being diagnosed with DR.

Markov Model

Figure 1 shows a schematic of the model. States of diabetes and DR were defined in terms of severity of disease: normal, impaired glucose tolerance or prediabetes, DM, non-proliferative diabetic retinopathy (NPDR), severe NPDR, proliferative retinopathy (PDR), high-risk PDR, clinically significant macular edema (CSME; low VA or high VA), stabilized DR (low VA or high VA), and blindness. Progression was assumed to follow fixed annual transition probabilities[6–9] as shown in Supplementary Table S2. Progression of DR was determined using the transition probability extracted from the literature[2,6–8] until they died or reached 90 years of age (age-specific background mortality based on the 2009 Japan abridged life tables[10]). For each model parameter, mean values were used for the base-case analysis, as well as ranges for the possible values as shown in Supplementary Tables S1–S5.

Incidence and Prevalence of Diabetes (Supplementary Tables S1 and S2)

Where patients with DM were medically managed, a fixed proportion of 30% was subtracted from the value, to assume risk reduction following successful

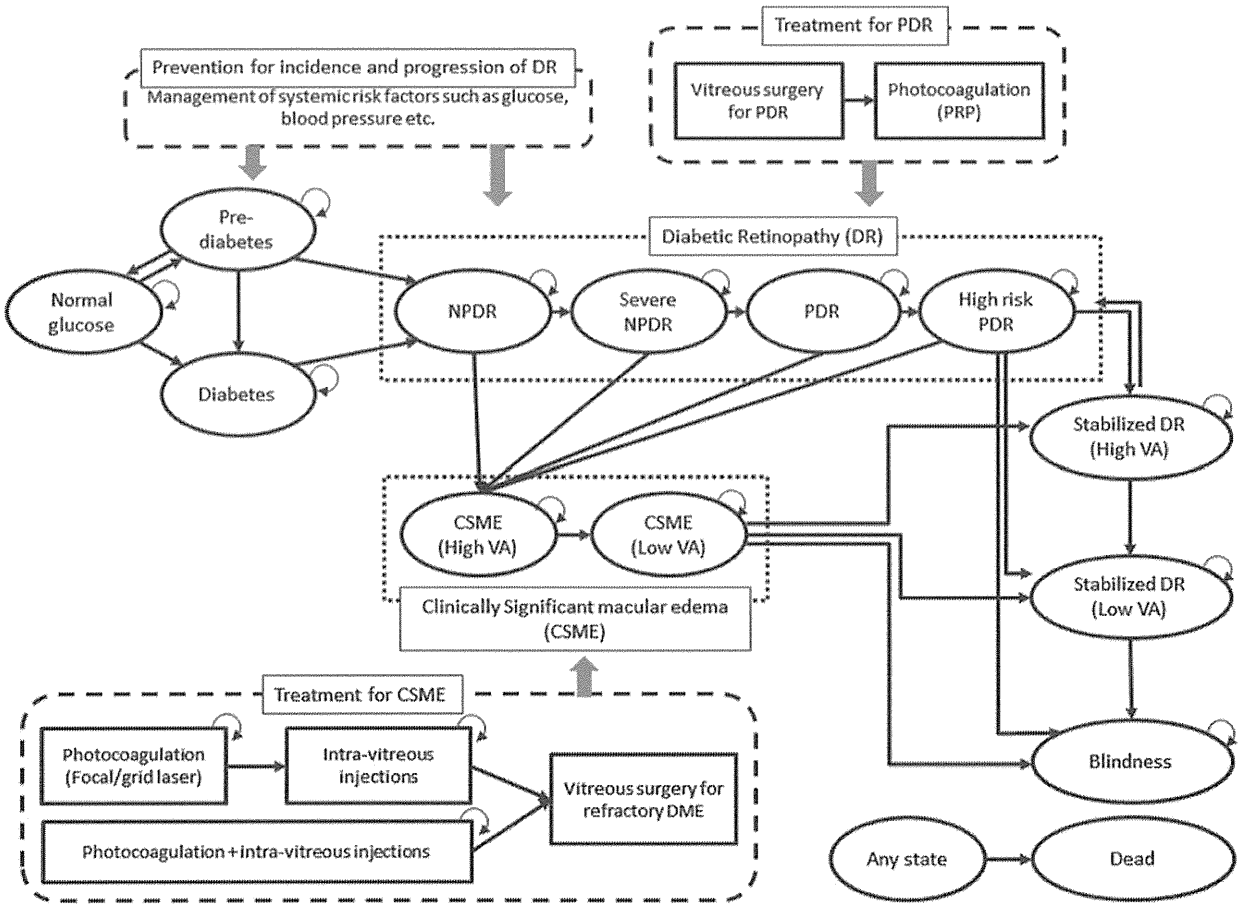

FIGURE 1. Markov model with a simplified transition state diagram for a diabetic retinopathy eye screening program (DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; CSME, clinically significant macular edema; VA, visual acuity; DME, diabetic macular edema.

intervention and management of high glucose, blood pressure and lipids.

Examination Rate (Supplementary Table S3)

Data from annual reports regarding the national screening program[10] and follow-up examination rates at medical institutions were extracted from the 2002 National Diabetes Survey, Japan.[11] The proportion of those who underwent fundus examinations was extracted from the Organization for Economic Co-operation and Development (OECD) report.[12] We hypothesized fixed rates of incidental diagnoses (e.g. subjects with presbyopia[13] or visual symptoms related to advanced stage DR). The base case of the proposed screening protocol was defined as being conducted once every 5 years between the ages of 50 and 90 years.

Rates of Dropout (Supplementary Table S3)

Lack of symptoms in the initial stages of diabetes or the mild stage of DR may lead patients to drop out from the regular management program for diabetes or DR.[14] Our model assumed that 10% of patients would drop out from the recommended management schedule. Patients who dropped out were returned to the initial state, without treatment, and we modeled possible return to the management of diabetes and DR through other diagnostic opportunities.

Treatment of DR and Prognosis (Supplementary Table S4)

Treatment for DR was assumed as below:

(1) NPDR stages were to have periodic follow-up ophthalmic examinations once a year, and for those with severe NPDR, every 4 months until the development of CSME or PDR;
(2) PDR and high-risk PDR stages were treated with pan-retinal laser photocoagulation first, then with vitrectomy;
(3) Treatment for DME was assumed to be performed at the CSME stage with focal/grid laser photocoagulation, with or without intravitreal injection of anti-VEGF, then multiple anti-VEGF

intravitreal injections. Finally, vitrectomy for CSME was added when repeated anti-VEGF treatment was not successful.

The probability of complications and further surgery was also estimated, as shown in Supplementary Table S4.[15–22] Treatment success was defined as patients acquiring VA $\geq$ 0.5, then those with a successful outcome shifted to stabilized retinopathy or a state prior to onset; those with unsuccessful outcomes moved to a state of progression. Vitreous surgery would be repeated up to 3 times.

Costs

Estimates of direct medical costs were determined from the perspective of entire payers (Supplementary Table S5). All medical costs were uniformly standardized by a social medical insurance system in Japan; medical costs associated with DR treatment were calculated based on the official medical fee tariffs in Japan. Costs relating to the national screening program for lifestyle-related diseases, detailed examinations undertaken for a definitive diagnosis of DM, and annual costs of DM treatment were not included because they are currently ongoing as part of a public screening program in Japan. The cost of detailed fundus examinations performed by ophthalmologists was included in the calculations for the strategy with screening for DR.

Utility Scores

The utility scores of visual function of both healthy subjects and DM patients without DR and any other eye diseases were set at "1". Although studies reporting that utility scores are decreased by having DM or by aging, we adopted the value "1" because our primary aim was to model vision-specific utility based on VA determined by severity of DR. We adopted the vision and related time-trade off (TTO) data[23] derived from Japanese patients with visual impairment, with cataract used as a main source of the tariff converting VA to utility values, given that there was no significant difference in the utility values between patients with cataract and DR,[24] and ethnicity-specific data was preferred.[25] Additional adjustment was based on report from patients with diabetes with or without DR; in cases of DR with relatively good VA (VA $\geq$ 0.5), utility data were extracted from a study of diabetic patients, because utility scores in people with cataract tend to be lower even when VA is good[26] (Supplementary Table S7 – online only). We measured health benefits in quality-adjusted life years (QALYs) gained. The incremental cost-effectiveness analysis compared the no screening strategy with the screening strategy. We calculated the incremental cost-effectiveness ratio (ICER) of DR screening as the additional cost of the latter divided by its additional benefit, compared with no DR screening strategy. It was calculated using the following formula:

$$\mathrm{ICER} = \frac{Cost_s - Cost_{ns}}{QALY_s - QALY_{ns}} = \frac{\Delta \mathrm{Cost}}{\Delta \mathrm{osLY}}$$

Sensitivity Analysis

Several sensitivity analyses were undertaken to assess the known variability that exists in, among others, estimates of cost, utility, examination rate, risk reduction rate under management of diabetes, and transitions from one state with vision loss to another. In total, 87 parameters were examined in the sensitivity analyses. Univariate sensitivity analysis was performed by varying single parameter values according to the ranges described in Supplementary Tables S1 to S5 and repeating the analytical solution of the model. We then conducted a probabilistic sensitivity analysis (PSA) to examine the effect of uncertainty in multiple variables.[27,28] We used a Monte-Carlo simulation in the PSA; the triangular distribution was used in PSA where the individual probability distribution was not available. This process of resampling and recalculating the incremental costs and effects of 50,000 patients from the model was repeated 10,000 times to generate a distribution of the estimated ICER. Uncertainty intervals were estimated from the simulated data by taking the 2.5 and 97.5 percentile values to represent the end points for a 95% confidence interval (CI), and cost effectiveness acceptability curves were constructed. All analyses were performed using TreeAge Pro Suite 2009 software (TreeAge software, Williamstown, MA, USA).

Model Validation

We tested external validity of the model by comparing prevalence of DR in persons 40 years or older, incidence of blindness due to DR in persons 40 years or older, and number of vitrectomies for PDR. The prevalence of DR in the simulated cohort was 20.1%, which was comparable to that reported in international meta-analysis as 19.9%.[3] The cumulative incidence of blindness due to DR was 0.026% in the simulated cohort, which approximated estimates of 0.02% reported by the Japan Ophthalmologists Association in 2007. The number of eyes undergoing vitreous surgery for macular edema was 31,326 cases in the simulated cohort, which approximated estimates of 43,104 cases reported by the survey of medical care activities in public health insurance.[29]

TABLE 1. Simulated number of events with or without a diabetic retinopathy eye screening program in Japan.

Factors (simulation with $N = 50,000$)	With screening program (A), *n* (%)	Without screening program (B), *n* (%)	(A) − (B), *n* (%)
Persons with DR	5324 (100)	5324 (100)	–
Persons with confirmed diagnoses of DR	4781 (89.8)	4398 (82.6)	+383 (+7.2)
Modalities for diagnosis			
Screening program	1301 (27.2)	–	+1301 (+27.2)
Annual fundus screening following the standard guidelines	1690 (35.3)	1967 (44.7)	−277 (−9.4)
Specific health checkup program	1202 (25.1)	1618 (36.8)	−416 (−11.7)
Opportunistic screening for visual symptoms other than DR	452 (9.5)	554 (12.6)	−102 (−3.2)
Symptoms with advanced DR	136 (2.8)	259 (5.9)	−123 (−3.0)
Persons with blindness	41	47	−6
Blindness over all persons with DR	0.770%	0.883%	−0.113% (−12.8%)
Blindness over all persons with confirmed diagnosis of DR	0.858%	1.069%	−0.211% (−19.7%)

DR, diabetic retinopathy.

RESULTS

Base-case Analysis

The base-case analysis results are shown in Table 1. In our simulation of 50,000 subjects, the number of people with diabetes was estimated as 5324. With a screening program in place, an additional 383 people with DR (+7.2%) were estimated to be diagnosed than when there was no screening program (4781 people compared with 4398). Of the 4781 people with DR, 1301 (27.2%) were likely to be identified through the proposed screening program. The number of people being diagnosed with advanced stage DR with symptomatic visual disturbance, was estimated to decrease from 259 (5.89%) to 136 (2.84%); the number of people with blindness was also estimated to decrease from 47 to 41 (−12.8%; Figure 2).

The screening program would result in incremental costs of ¥5,147 (US$65) and incremental effectiveness of 0.0054 QALYs compared to not having a screening program. ICER was ¥944,981 (US$11,857) per QALY.

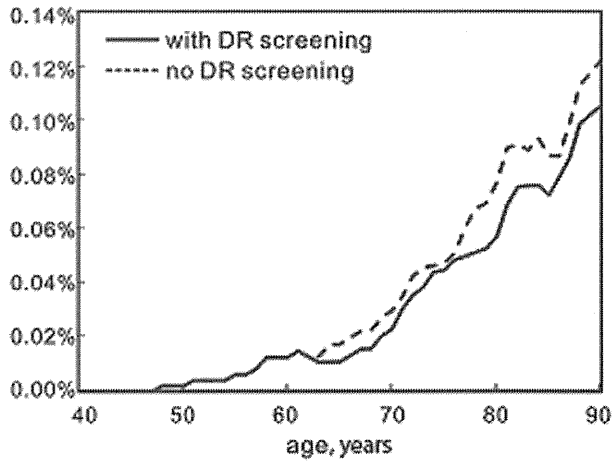

FIGURE 2. Simulated risk of blindness due to diabetic retinopathy (DR) with or without an eye screening program in Japan.

Evaluation of DR Screening Protocol

ICER was calculated to simulate for possible variations in DR screening initiation age, interval of screening, and conclusion age comparing the screening and non-screening strategies. The minimum ICER value was −¥50,041,774 (−US$512,198) per QALY (starting at age 50, every 4 years, ending at age 60), and the maximum was ¥79,537,292 (US$997,958) per QALY (starting at age 40, every 9 years, ending at age 80). When we compared 130 screening programs by changing the value of initiation age, screening interval, and conclusion age, we identified the most cost-effective and effective screening program enabling reducing blindness was one: (1) starting at age 53, (2) with a screening interval of <5 years, and (3) concluding at age 84. It is also suggested that the shorter the average screening interval, differences between screening and no screening in the cumulative number of cases of blindness increased.

Sensitivity Analysis and Monte-Carlo Simulation

A 1-way sensitivity analysis was conducted on the 87 parameters, and the top 15 most influential parameters are shown in Table 2. The most influential parameter in the model was the risk reduction rate obtained by management of glucose control, and the second most influential parameter was follow-up rate by ophthalmologists. The incremental cost and incremental utility of all parameters did not become negative and the maximum value of ICER did not exceed willingness-to-pay (WTP) of ¥5,000,000 (US$62,735) per QALY; these results indicate the robustness of the proposed model of the DR screening program.

TABLE 2. One-way sensitivity analysis of a diabetic retinopathy eye screening program in Japan (top 15 most influential parameters to ICER of 87 parameters shown).

	ICER, JP¥/QALY	
	Lower limit value	Upper limit value
Reduction in DR by glucose management	861,436.0	4,078,079.9
Follow-up examination rate by ophthalmologists	811,438.4	2,517,488.6
Drop-out from ophthalmic care	944,980.7	1,989,356.5
Cost of eye screening procedure	431,930.6	1,458,030.9
Progression from severe NPDR to PDR	944,980.7	1,891,218.1
Participation in the national screening program	663,741.6	1,526,220.2
Number of pan-retinal photocoagulation to high-risk PDR	107,151.5	944,980.7
Number of pan-retinal photocoagulation to PDR	944,980.7	1,491,243.3
Prevalence of CSME	861,106.2	1,602,679.8
Prevalence of diabetes mellitus	642,753.2	1,371,809.9
Prevalence of DR	944,980.7	1,508,483.0
Persons with diabetes at age 40 years	620,459.2	1,306,949.7
Sensitivity of eye screening program	812,825.0	1,437,714.5
Sensitivity of eye screening in the national screening program	650,503.8	1,132,834.3
Discount rate	555,598.3	1,346,925.2

DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; CSME, clinically significant macular edema; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; JP¥, Japanese yen

Supplementary Figure S1 (online only) shows the joint distribution of incremental costs and effectiveness generated in 10,000 Monte-Carlo simulations on the cost-effectiveness plane. The circle represents the 95% confidence ellipsoid. The slope of the line represents the WTP of ¥5,000,000 (US$62,735) per QALY, the hypothetical threshold line of Japanese WTP for one additional QALY gained.[30] Of the 10,000 simulations, 76.3% was in the right side from the dashed line, meaning that the majority of the simulated ICERs indicate that an eye screening strategy is more effective than the hypothetical upper limit of the ICER of ¥5 million in Japan. The cost-effectiveness acceptability curves for the simulation results are shown in Supplementary Figure S2 (online only). This figure indicates that the probability of the screening strategy being more cost-effective than the no DR screening strategy was >50% (53.5%) and >75% (76.3%) at the threshold values of ¥2 million and ¥5 million, respectively.

Optimal Conditions of Screening Scenario

We examined multiple screening scenarios to explore when to start, screening intervals, and when to cease the screening program. We calculated the average values from the screening scenarios meeting the conditions "ICER $\leq$ WTP" and "cumulative number of people with blindness < base case" ($n = 70$) compared to other scenarios not meeting either efficacy or cost-effectiveness. The optimal screening program is suggested to screen those aged from 52.8 ± 1.25 years to 84.4 ± 1.63 years, at intervals of 3.3 ± 0.3 years or less in our model (Figure 3A–C).

DISCUSSION

We found that a DR screening program in Japan is cost-effective compared to the current situation of no systematic screening, and has the potential to reduce blindness and low vision by 16% and 5%, respectively. It was cost-effective even allowing for the uncertainty of the known variability that exists in estimates of costs, utilities, and complication rates.

Prevention of diabetes and its complications, including DR, is one of the goals for the National Health Promotion program in Japan.[31] However, the proportion of those who underwent fundus examinations on a regular basis is reported to be 37%, the lowest in the OECD report.[12] There is an urgent need to provide a systematic screening program rather than solely depend on opportunistic screening. Although there is no formal standard set by the Japanese government regarding the cost-effectiveness for acceptance of screening programs, our result of ICER ¥944,981 (US$11,857) per QALY is a strong reason to advocate implementing a screening program for DR in Japan. Given that the WTP, which is considered to be the hypothetical upper limit of the ICER, is ¥5,000,000 (US$62,735) in Japan,[30] screening for DR in Japanese adults was found to be likely to be cost-effective.

Uniqueness of our study should be noted though when interpreting our results of cost-utility of a DR screening program is far superior to those reported in different contexts.[32,33] Considering that there is an ongoing nation-wide screening program for cardiovascular risk, including diabetes, in Japan, our results should be interpreted such that additional DR screening added to the ongoing screening program for DM

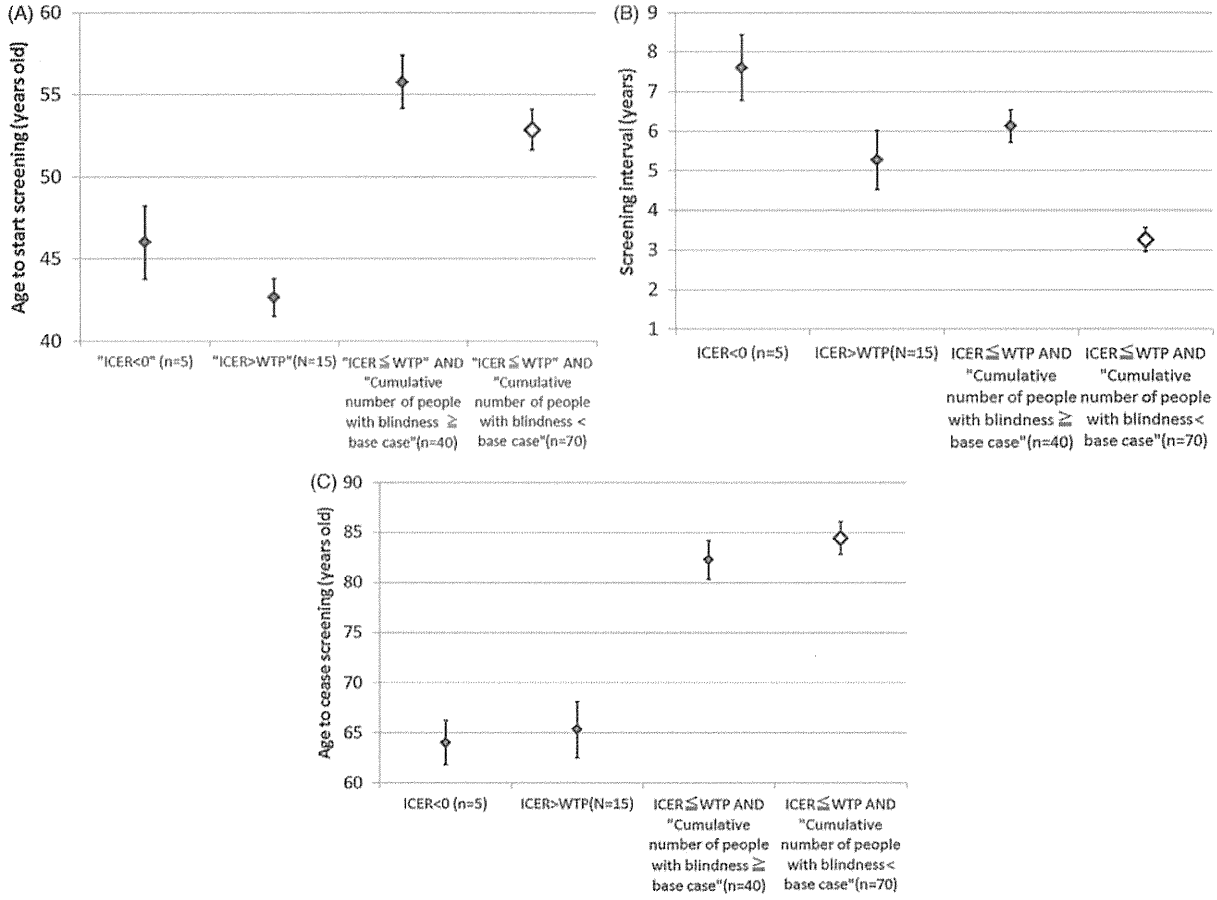

FIGURE 3. Average values of (A) age to start screening, (B) screening interval, and (C) age to cease screening from the scenarios meeting the conditions for optimal screening in a model for screening for diabetic retinopathy in Japan (ICER, incremental cost-effectiveness ratio; WTP, willingness-to-pay).

is beneficial for prevention of blindness with cost-effectiveness standard. Similarly, simulating population-based screening starting from a non-diabetic population might also contrast our results compared to other studies starting from a diabetic population because earlier intervention may prevent progression to an advanced stage of DR.

In the present study, we simulated a model for a screening interval longer than 1 year to evaluate comprehensive management of both DR and DME. The strength of this study was to include comprehensive interventions to DR and DME, i.e. from systemic management of glucose and blood pressure, standard laser treatment, vitreous surgeries, to newer treatment of anti-VEGF treatment based on parameters reflecting real world management of patients with DR and DME. Detailed sensitivity analyses were performed to evaluate the precision and robustness of our simulation. We also found that the optimal screening program suggested by our simulation was to screen between the ages of 53 and 84 years, with a screening interval of 5 years or less.

It should be emphasized that this study represents the current management and treatment of DR and DME in Japan. To date, various studies have shown that DR screening is cost effective in a variety of contexts. Jones and Edwards reported a systematic review of 29 studies and concluded that "systematic screening for DR is cost-effective in terms of sight years preserved compared with no screening".[33] However, there have been no previous studies that incorporated current treatment modalities or detailed newer treatment modalities into the model of screening for DR. Therefore, we covered in this analysis from standard care of laser treatment to vitreous surgery, and more recent treatment options of anti-VEGF treatment for DME. Considering rates of successful treatment, drop-outs from follow-up, side effects or surgical complications of each treatment into the model make our simulation reflect real-world management of DR. Although there was a concern that direct costs for a screening program may increase by adopting current costly treatment modalities, we found that the proposed screening program would remain very cost-effective, even with sensitivity analysis varying a wide range of parameters.

Now that studies have shown that a systematic DR screening program is cost-effective, establishing the

optimal screening interval is the next key issue. Jones and Edwards pointed out that there is controversy over which interval is optimal for screening. An interval of annual screening has been widely adopted in guidelines and there is no doubt complying with this would maintain highest effectiveness. However, alternative screening intervals have been shown to be more cost-effective. For example, Vijan and colleagues proposed a possibility that variable screening intervals of every other year depending on the patient's glycemic control level can be an alternative option.[32] They discussed strategies such as annual screening for all diabetic patients especially people with poor glycemic control, but offering a longer screening interval of 2 or 3 years to those with good glycemic control without DR who are at low risk of blindness.[32] Based on the model in this study, the interval for screening should be less than 5 years; however, we must emphasize that our simulation is not intended to replace guideline recommendations for patients with diabetes, that is, annual screening is recommended for all patients with diabetes. We consider having a nationwide screening program for DR provided at either annual basis or less frequent interval up to 5 years may play an important role in uptake among those who are not under regular monitoring for DR in the current situation. It may contribute to fill in the gap between the current recommendation of annual screening and the real-world situation of low compliance to regular screening.

Another important aspect when considering a screening program is compliance to recommendations or guidelines after screening. Although annual screening for DR is advised for patients with diabetes in multiple guidelines for the management of diabetes, only 37% are reported to have such screening in Japan.[12] In our univariate sensitivity analysis, good glycemic control for diabetes and a high regular follow-up rate after the screening program were the two most influential factors associated with variation in ICER. By assuming undesirable conditions such as risk reduction by glycemic control of 0% (i.e. assuming no reduction in risk of DR because of not having good glycemic control) or drop-out between screening and follow-up examination as high as 30.0%, ICER can become high, up to ¥4,078,080 (US$51,168) per QALY; though these numbers still remain lower than WTP of ¥5,000,000 (US$62,735) per QALY.[30]

A number of limitations should be noted when interpreting our study results. First, there are some assumptions in parameter values used in the model. While we were able to obtain reasonable estimates of costs, utility, and transition state probabilities for the variables included from the literature, information on several parameters needed to be estimated or assumed based on expert opinion, since insufficient evidence was available for all parameters. To confirm our findings, we performed sensitivity analyses to examine the impact of changing the assumptions on the findings; we confirmed that our findings are robust against a wide range of possible parameter values. Second, measurements of cost-utility estimates are based solely on TTO utility. TTO incorporates quality of life directly into the utility measure, which some researchers believe makes it a preferred method of measurement.[34,35] TTO utility was chosen because it is reproducible and reliable on a test-retest basis over a prolonged period of time. It also has excellent intra-observer and inter-observer reliability.[34,36] For classifying utility in persons with DR by its severity, we used the TTO utility value corresponding to VA derived from cataract patients in Japan. Though the level of reduced vision is related to utility values rather than the specific disease process causing reduced vision,[24] utility values for patients with DR by the visual stratification levels in Japan should be a topic for further research. Third, we did not include indirect costs in our model because there have been no reliable sources of estimates for social and productivity costs related to DR in Japan. This was because our primary aim was to perform cost-utility analysis from a health-care perspective rather than a social perspective. This was also to avoid including enormous uncertainties into our model by estimating indirect cost due to the fact that mortality from this condition is not high and longer duration after visual consequence is not uniform. Last, we adopted triangular distributions in our PSA which might limit the range for possible values at both lower and higher ends even though the number of observations is increased. This was useful for avoiding extreme values by adopting other forms of distributions in our model where parameters could be varied due to the fact that parameters were determined by multiple sources. Also, with limited data sources for some parameters, we adopted triangular distributions due to its simplicity to fit. However, lack of detailed statistical characteristics of this distribution might cause limited probabilistic analyses.

In conclusion, our study suggests that the proposed eye screening program in Japan is likely to be cost-effective, even allowing for uncertainty of the known variability that exists in estimates of costs, utilities, and complications rate based on sensitivity analyses. The optimal screening program is suggested to screen those aged from 53 to 84 years, at intervals of 3 years or less in this model.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary Material Available Online
Supplementary Tables 1–7
Supplementary Figures 1 & 2

原著論文 / 臨床研究

先天角膜混濁の超音波生体顕微鏡所見と臨床診断および眼圧の関係

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要 約

目 的：超音波生体顕微鏡(UBM)を用いて先天角膜混濁症例の前房隅角所見を観察し，臨床所見との関連を明らかにする．

対象と方法：2001年9月から2009年1月までの間に京都府立医科大学附属病院眼科にて加療した小児先天角膜混濁症例10例19眼を対象にUBM検査を実施し，細隙灯顕微鏡所見，眼圧，臨床診断と比較，検討した．

結 果：UBM所見はPeters奇形7例13眼，強膜化角膜3例6眼のそれぞれにおいて，部分的隅角閉塞を10眼(77%)，5眼(83%)，Descemet膜欠損を13眼(100%)，6眼(100%)，虹彩からの索状物の立ち上がりを12眼(92%)，6眼(100%)に認めた．Peters奇形のうち5例9眼(69.2%)に緑内障の合併を認め，強膜化角膜では明らかな高眼圧を認めなかったが2眼(33.3%)で角膜径の拡大傾向を認めた．

結 論：UBMによりPeters奇形と強膜化角膜の前房隅角形状の類似性が判明した．一方，緑内障合併の有無とUBM所見に関連を認めず，隅角の機能的異常に関してさらなる検討を要すると考えられた．(日眼会誌 119：16-21，2015)

キーワード：先天角膜混濁，Peters奇形，強膜化角膜，超音波生体顕微鏡(UBM)，発達緑内障

Original Article / Clinical Science

Ultrasound Biomicroscopy in Infants with Congenital Corneal Opacity and its Correlations with Clinical Diagnosis and Intraocular Pressure

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Abstract

Purpose：Ultrasound biomicroscopy (UBM) can be used to investigate the appearance of the anterior chamber in infants with congenital corneal opacity. This study investigated the association between the UBM-obtained clinical imaging of anterior chamber morphology and the clinical diagnosis in infants with congenital corneal opacity.

Subjects and methods：This study involved 19 eyes of 10 consecutive infants with congenital corneal opacity, 13 eyes with Peters anomaly (PA, 7 cases) and 6 eye with sclerocornea (SC, 3 cases), recruited at the Kyoto Prefectural University of Medicine, Kyoto, Japan between September 2001 and January 2009. In each subject eye, UBM findings were compared with the clinical diagnosis based on slit-lamp findings and intraocular pressure (IOP).

Results：UBM findings revealed partial angle closure in 10 PA eyes and in 5 SC eyes, absence of Descemet's membrane in 13 eyes and 6 eyes, and funicular fiber from the iris in 12 eyes and 6 eyes. All 6 eyes with SC showed normal IOP, while 9 eyes with PA were diagnosed as glaucoma.

Conclusion：Similarities in UBM appearance were observed between PA and SC. PA had a higher incidence of glaucoma；however, there was no relation between IOP and the UBM images.
Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 119：16-21, 2015.

Key words：Congenital corneal opacity, Peters anomaly, Sclerocornea, Ultrasound biomicroscopy (UBM), Congenital glaucoma

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I 緒　言

先天角膜混濁はまれな疾患であり，発症率は出生10万人に3人程度，約80%が両眼性，緑内障の合併率は50～70%との報告がある[1)~8)]．一般診療で遭遇する機会が少ないが，角膜の白濁が開眼で分かるため，出産直後に保護者および医療関係者が気づき早期に眼科に受診する疾患である．Shigeyasuら[9)]は，日本での先天角膜混濁を伴う前眼部形成異常139例220眼の臨床像について検討し，Peters奇形160眼(73%)，強膜化角膜14眼(6%)はいずれも小児の重篤な視覚障害の原因となることを報告している．

これらの疾患は角膜混濁のために角膜透見性が不良であり，細隙灯顕微鏡検査を用いた前房隅角所見の把握は困難である．このような場合，超音波生体顕微鏡(ultrasound biomicroscopy：UBM)を利用することで，角膜混濁のため観察困難な角膜厚，前房深度，隅角部の情報を得ることができ，さらには通常の細隙灯顕微鏡検査では観察不可能な虹彩後面，毛様体形状の評価が可能になる．先天角膜混濁症例に対するUBM所見の報告は，海外ではNischalら[10)]が臨床所見上Peters奇形，強膜化角膜と診断した症例(計16眼)を比較し両者の前房隅角形状が類似していることを報告した．また，Shigeyasuら[9)]は日本での先天角膜混濁(前眼部形成異常)220眼を対象に，角膜混濁の部位，視力などを検討している．しかし，UBM所見については詳細には検討されていない．ほかには國原ら[11)]がPeters奇形に類似した前眼部形成不全のUBM所見を1例，朴ら[12)]が強膜化角膜のUBM所見を1例，症例報告しているのみである．

そこで今回我々は，2001年9月から2009年1月までの間に京都府立医科大学附属病院眼科(以下，当科)を受診した先天角膜混濁症例に対して，UBMを用いて前房隅角所見を観察し，眼圧を含む臨床所見とUBM所見との関係を検討したので報告する．

II 対象と方法

2001年9月から2009年1月までの間に当科にて診断および加療した小児の先天角膜混濁症例のうち，経過中にUBM検査が可能であった10例19眼〔男性2例4眼，女性8例15眼，初診時年齢1か月～3歳11か月(平均値±標準偏差：7.8±13.9か月)〕を対象とした．経過観察期間は2か月～7年4か月(27.1±31.5か月)である．

全例において細隙灯顕微鏡検査を行い，また可能な限りiCare® tonometer(Icare Finland Oy, Helsinki, Finland)，Perkins圧平眼圧計(Haag Streit USA and Reliance Medical Products, Mason, Ohio, USA)，およびTONO-PEN® XL(Medtronic Solan, Jacksonville, Florida, USA)を用いて眼圧を測定した．測定困難な場合および信頼性に乏しいと判断される場合には触診(tactile measurement)を併用した．触診にて20 mmHg以下程度と判断したものは，Tension normal(Tn)とし，20 mmHg台前半程度と判断したものをTn+1，20 mmHg台後半以上と判断したものをTn+2とした．触診での眼圧は角膜を専門とする医師1名，緑内障を専門とする医師1名が行い，その後に測定可能であったiCare®，Perkins圧平眼圧計，TONO-PEN® XLなどの測定眼圧と比較し，整合性を確認した．眼圧測定時，啼泣にて測定困難な場合は入眠するまで待つか，またはトリクロホスナトリウム(トリクロリールシロップ®)を内服させ入眠したのちに測定した．入眠せず，器機を用いて測定困難な場合には触診のみでの測定とした．

角膜混濁の診断および鑑別については，細隙灯顕微鏡検査において角膜中央が混濁・菲薄化しており，周辺角膜の透明性が保持されているものをPeters奇形，強膜

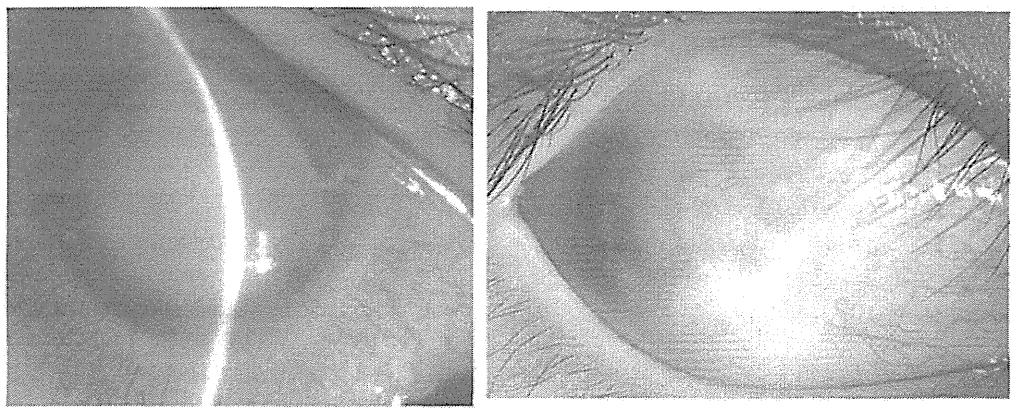

図1　前眼部所見．
A：Peters奇形(症例4)では角膜中心部の混濁と角膜周辺部の透明性を認める．
B：強膜化角膜(症例9)では，強膜と角膜の境界が不明瞭である．

表 1 疾患別の初診時・最終観察時所見

症例	性別	患側	初診時所見 初診時年齢(か月)	合併症(眼以外)	眼圧(mmHg)	角膜径(垂直 mm×水平 mm)	前医からの抗緑内障点眼薬(剤)	経過観察時 最高眼圧(mmHg)	最終観察時所見 眼圧(mmHg)	緑内障手術回数(回)	緑内障点眼薬(剤)	経過観察期間(か月)
Peters 奇形												
1	女	右	4	水腎症，心房中隔欠損症	Tn+1	13.5×13.5	1	30[i]	30[a]	2	0	80
		左			Tn	14.0×13.0	1	30[i]	30[a]	0	2	
2	女	右	2	なし	19[i]	6.0×7.0	0	19[t]	Tn	0	0	13
		左			23[t]	6.0×7.0	0	23[t]	Tn	0	0	
3	男	右	3	なし	34[p]	11.0×10.5	2[*]	34[p]	10[i]	0	2	10
		左			34[p]	14.0×15.5	2[*]	34[p]	11[i]	1	2	
4	女	左	3	なし	25[p]	10.0×16.0	2[*]	25[p]	10[i]	0	1	10
5	男	右	4	なし	Tn	NA	1	18[i]	10[i]	0	1	9
		左			Tn	NA	1	16[i]	6[i]	0	1	
6	女	右	4	なし	Tn	NA	0	16[t]	測不	0	0	7
		左			Tn	NA	0	12[t]	測不	0	0	
7	女	右	1	多発奇形[注1]	Tn+2	NA	3	18[t]	14[p]	1	3	2
		左			Tn+2	NA	3	26[t]	19[p]	1	3	
強膜化角膜												
8	女	右	8	なし	Tn	測不	0	35[n]	測不	0	0	88
		左			Tn	測不	0	26[n]	16[n]	0	1[注3]	
9	女	右	47	多発奇形[注2]	Tn	測不	0	23[t]	16[t]	0	0	14
		左			Tn	測不	0	30[i]	22[i]	0	0	
10	女	右	2	精神発達遅延，足指癒着	Tn	測不	0	33[i]	16[i]	0	1	38
		左			Tn	測不	0	17[i]	15[i]	0	1	

*：合剤1剤使用のため2剤として換算，g：Goldmann 圧平眼圧計，n：ノンコンタクトトノメーター，p：Perkins 圧平眼圧計，i：iCare®，t：TONO-PEN®

注1)：動脈管開存症，脳梁発育不全，右膀胱尿管逆流症，左多嚢胞腎．

注2)：喉頭軟化症，脳梁欠損，心房中隔欠損症，てんかん，染色体異常(21モノソミー)．

注3)：抗緑内障点眼薬が開始されているのは角膜移植後の眼圧上昇のためであり，発達緑内障のためではない．

グレーの網掛け：発達緑内障．

NA：カルテ記載なし，測不：測定不能．

から角膜にかけての境界を同定できず，角膜全体が混濁しているものを強膜化角膜と判断した(図1)．

また，通常，角膜混濁のない発達緑内障の合併については，眼圧，視神経乳頭の形状，角膜径の拡大傾向，角膜浮腫の有無などから判断されるが[5)13)]，先天角膜混濁の症例では眼底の観察ができず，角膜径の拡大傾向と眼圧値が重要な情報となる．小児では成長とともに角膜径は増大し，新生児の角膜径はおおよそ9.5～10.5 mmであり，生後2年頃までに10.8～11.5 mmに増加すると報告されている[14)15)]．今回，我々が検討を行った先天角膜混濁の症例は，全例において眼底の観察が不可能で視神経乳頭の形状が確認できなかった．そこで，眼圧の推移，緑内障点眼薬の有無，角膜径の拡大傾向の有無などを総合的に判断して緑内障を診断した．

全症例でUBM(トーメーコーポレーション社製，UD-6000UBM)を用いて，Descemet膜欠損，虹彩からの索状物の立ち上がり，虹彩前癒着，部分的隅角閉塞，無虹彩，前房深度，前房隅角異常の有無を判定し，前眼部所見，眼圧，臨床経過とUBM所見との関係を比較，検討した．得られた結果の数値記載については，すべて平均値±標準偏差で記載した．

Ⅲ 結 果

全例(10例19眼)が他院からの紹介患者であった．Peters奇形は男児2例4眼，女児5例9眼，初診時の平均年齢は3.0±1.2か月，平均経過観察期間18.7±27.2か月であった．強膜化角膜は男児0例，女児3例6眼，初診時の平均年齢19.0±24.4か月，経過観察期間46.7±37.8か月であった．Peters奇形7例中の6例が両眼性であり，強膜化角膜は全例が両眼性であった．

Peters奇形の初診時の眼圧はPerkins圧平眼圧計またはiCare®にて測定可能であった3例5眼では平均眼圧が27.0±6.7 mmHgとやや高値であり，測定不可であった4例のうち触診Tnが3例5眼，Tn+1が1例1眼，Tn+2が1例2眼であった．一方，強膜化角膜の3例6眼は初診時に眼圧を測定できず，触診にてすべて

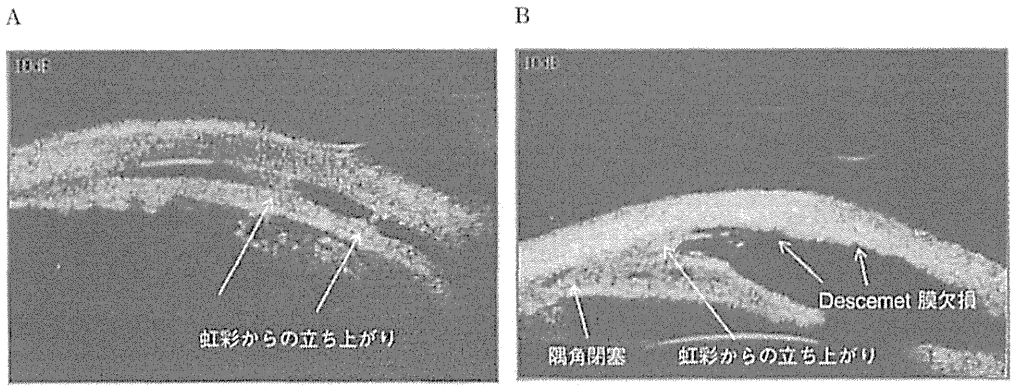

図 2　超音波生体顕微鏡(UBM)所見.
A：Peters 奇形(症例 6)では，虹彩から角膜後面に向かう索状物の立ち上がりを認める.
B：強膜化角膜(症例 10)では，隅角閉塞，虹彩から角膜後面に向かう索状物の立ち上がり，Descemet 膜欠損を認める.

Tn と判断された．角膜径の拡大傾向を伴った症例を緑内障に分類すると，緑内障の合併が Peters 奇形で 5 例 9 眼(69.2%)にみられたのに対して，強膜化角膜では 1 例 2 眼(33.3%)であった(表 1)．これらの緑内障合併例では初診時に紹介元ですでに緑内障の診断がされていた．緑内障合併の Peters 奇形は，当院受診前より緑内障点眼薬が使用されていた(表 1 の症例 1，3〜5，7)．一方，緑内障合併の強膜化角膜は点眼なしの状態で紹介され，当院経過観察中に緑内障点眼薬を開始した(表 1 の症例 10)．

Peters 奇形の UBM 所見は，前房深度が 1.40±0.84 (range 0.30〜2.40) mm，中心角膜厚が 0.63±0.32 (0.46〜0.77) mm，であり，特徴として，角膜中央部を中心とした Descemet 膜欠損，虹彩から角膜内皮面に向けての索状物の立ち上がり，虹彩前癒着，部分的隅角閉塞が顕著にみられた(図 2，表 2)．一方，強膜化角膜の UMB 所見は，前房深度が 1.89±1.02 (1.52〜2.33) mm，中心角膜厚が 0.83±0.46 (0.64〜1.14) mm であり，Peters 奇形と同様に，角膜中央部を中心とした部分的 Descemet 膜欠損，虹彩から角膜内皮面に向けての索状物の立ち上がり，虹彩前癒着，部分的隅角閉塞を認めた(図 2，表 2)．

Peters 奇形は強膜化角膜に比べて緑内障合併率が高かったにもかかわらず，UBM 所見において両者の隅角所見に明らかな違いを認めなかった．

Ⅳ　考　　按

今回の検討では全体の 57.9% に緑内障の合併を認めた．病型別では，Peters 奇形 7 例 13 眼中，5 例 9 眼(69.2%)，強膜化角膜 3 例 6 眼中，1 例 2 眼(33.3%)と，Peters 奇形の半数において緑内障の合併を認めた．海外の報告によると Peters 奇形の緑内障合併率は 50%〜70% であり[1〜8]，当院での検討結果も過去の報告と類似であった．先天角膜混濁では白濁した角膜を主訴に受診されることが多く，眼圧を測定せずに紹介される例もあるが，常に眼圧上昇や角膜径の拡大について注意が必要である．強膜化角膜 3 例のうち 1 例で角膜径の拡大傾向を認めたため緑内障を疑い，抗緑内障薬を開始したが，本症例は精神発達遅延があり常に指で両眼を押す動作がみられたため，その影響を否定できない．

UBM 所見は全症例で Descemet 膜欠損，虹彩前癒着を認め，Peters 奇形 1 例 1 眼を除いた 9 例 18 眼で虹彩から立ち上がる索状物を認めた．部分的隅角閉塞は Peters 奇形の 5 例 10 眼，強膜化角膜の 3 例 5 眼で認められた．Peters 奇形と強膜化角膜との間に特に明らかな違いが見出せなかったことより，今回の症例においては UBM 所見からの病型の診断は難しいと考える．

UBM で測定した前房深度は Peters 奇形，強膜化角膜ともに，既報にある正常な小児の前房深度[16][17]と比較して浅い結果であった．ただし，浅前房を伴う 6 眼(表 2 の症例 3 右，4 左，6 右左，7 右，9 左)のうち，緑内障と診断された症例は 3 眼(表 1 の症例 3 右，4 左，7 右)であった．緑内障の合併の有無と UBM 所見に関連を認めず，UBM では検出できない隅角の機能異常により眼圧上昇を来すことが推測された．

正常乳幼児の角膜厚の平均は測定対象の人種や測定条件などの違いにより異なり[18〜20]，本邦では山本ら[21]が正常乳幼児の角膜厚の平均を報告している(0 歳：0.488 mm，1 歳：0.510 mm，2 歳：0.515 mm，3 歳：0.529 mm，4 歳：0.521 mm)．今回，角膜厚を測定できた Peters 奇形 5 例 9 眼，強膜化角膜 2 例 4 眼のうち Peters 奇形は 6 眼で 0.6 mm を超え，強膜化角膜は 4 眼で 0.6 mm を超えていた．そこで，これらの中心角膜厚が眼圧に影響している可能性を考え，Suzuki ら[22]の眼圧補正式〔補正眼圧値＝測定眼圧値－0.012(中心角膜厚＜μm＞－520)〕で今回得られた眼圧を補正してみたが，初診時角

表 2 疾患別 UBM 所見

症例	性別	患側	Descemet 膜欠損	虹彩からの索状物の立ち上がり	虹彩前癒着	部分的隅角閉塞	無虹彩	浅前房	中心角膜厚(mm)	前房深度(mm)
Peters 奇形										
1	女	右	+	+	+	+	+	−	測不	測不
		左	+	+	+	+	+	−	測不	測不
2	女	右	+	+	+	+	−	−	0.77	1.61
		左	+	+	+	+	−	−	0.73	1.84
3	男	右	+	+	+	−	−	+	0.53	1.21
		左	+	+	+	−	+	−	0.62	1.45
4	女	左	+	−	+	−	−	+	0.48	1.39
5	男	右	+	+	+	+	−	−	0.46	2.40
		左	+	+	+	+	−	−	0.64	1.67
6	女	右	+	+	+	+	−	+	0.70	0.30
		左	+	+	+	+	−	+	0.72	0.74
7	女	右	+	+	+	+	−	+	測不	測不
		左	+	+	+	+	−	−	測不	測不
所見の該当率(%)			100(13/13)	92(12/13)	100(13/13)	77(10/13)	23(3/13)	38(5/13)		
強膜化角膜										
8	女	右	+	+	+	+	−	−	測不	測不
		左	+	+	+	+	−	−	測不	測不
9	女	右	+	+	+	−	−	−	1.14	2.33
		左	+	+	+	+	−	+	0.84	1.70
10	女	右	+	+	+	+	−	−	0.64	2.02
		左	+	+	+	+	−	−	0.70	1.52
所見の該当率(%)			100(6/6)	100(6/6)	100(6/6)	83(5/6)	0(0/6)	17(1/6)		

測不：測定不能.

膜厚を考慮しても眼圧は高かった.

今回検討した症例の中には，初診時眼圧は正常範囲であっても，経過中に眼圧が上昇し角膜径が拡大傾向となったために，検討期間を過ぎてから点眼が開始される症例があった(症例 9)．眼圧が上昇傾向にある場合，角膜径の拡大傾向が生理的な成長を上回る場合などは，こまめに診察をしていくことが重要である．角膜混濁の程度，眼圧，角膜径(垂直，水平)，観察できる場合には視神経乳頭陥凹比の推移を記録し，角膜混濁の程度については写真などでも記録，追跡することが望ましい.

Nischal ら[10]は先天角膜混濁 13 例 22 眼について臨床診断，UBM 所見，移植した 13 眼の病理所見を比較，検討し，5 眼において UBM 後に臨床診断を変更，UBM 所見と病理所見が一致することを報告した．今回検討した 10 例のうち，移植を行ったのは症例 8 のみであり，臨床診断と病理所見は強膜化角膜で合致した[23]．しかし症例 8 は他院で Peters 奇形の診断を受けており，両疾患の鑑別は難しいといえる.

今回，小児先天角膜混濁症例の眼圧，臨床所見と UBM 所見の検討を行った．UBM 所見により，Peters 奇形と強膜化角膜の前房隅角形状の類似性が判明した．Peters 奇形は強膜化角膜よりも緑内障合併率が高かったが，緑内障合併の有無による UBM 所見の相違を認めなかった．先天角膜混濁における隅角の機能異常については，さらなる検討を要する.

利益相反：利益相反公表基準に該当なし

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