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Gradients of refractive index in the crystalline lens and transient changes in refraction among patients with diabetes

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Abstract: Transient hyperopic refractive shifts occur on a timescale of weeks in some patients after initiation of therapy for hyperglycemia, and are usually followed by recovery to the original refraction. Possible lenticular origin of these changes is considered in terms of a paraxial gradient index model. Assuming that the lens thickness and curvatures remain unchanged, as observed in practice, it appears possible to account for initial hyperopic refractive shifts of up to a few diopters by reduction in refractive index near the lens center and alteration in the rate of change between center and surface, so that most of the index change occurs closer to the lens surface. Restoration of the original refraction depends on further change in the refractive index distribution with more gradual changes in refractive index from the lens center to its surface. Modeling limitations are discussed.

OCIS codes: (330.4460) Ophthalmic optics and devices; (330.7326) Visual optics, modeling.

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1. Introduction

It has long been known that patients suffering from diabetes mellitus may experience transient visual blur. This is usually caused by changes in their refraction [1], although neural factors may also be involved [2]. In addition, there may be systematic long-term differences between the biometric parameters of the eyes of diabetic and non-diabetic individuals, e.g., [3–7], but these chronic effects will not be considered here.

There is little doubt that the transient changes in refraction are associated with variations in blood glucose levels but the nature of the relationship between the two parameters remains in doubt. Some authors claim that increased blood sugar leads to a myopic shift and others that the change is in the hyperopic direction [8]. However, more recent work suggests that, at least in the majority of cases, when therapy is instituted to control hyperglycemia and blood glucose levels fall, the refractions first change in the hyperopic direction on the timescale of a few days or weeks and then gradually return to their baseline values on the timescale of a few weeks or months [9–14]. Effects are similar in the two eyes of the same individual. Figure 1 shows typical data for an individual patient: note particularly that the same level of refraction is found at both high and low levels of fasting plasma glucose level, so that, at least on the timescale of weeks, there is no simple linear correlation between blood glucose and refraction.

Although Saito *et al*. [9] claimed that some lens swelling occurred, most later authors (e.g., [10,12–14] agree that the acute refractive changes are not accompanied by changes in curvatures or separations of the corneal and lenticular surfaces, or in the axial length or lens position. The retinal thickness appears also to be constant [15]. It is therefore inferred that

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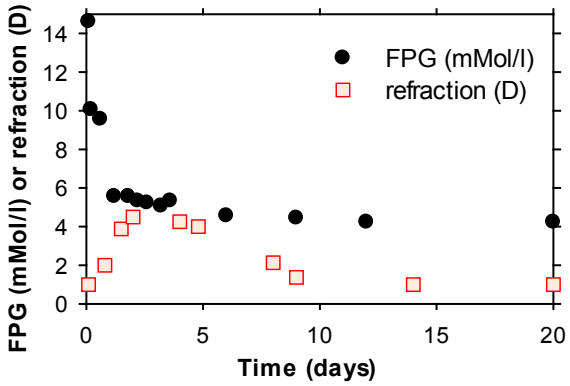

Fig. 1. Example of the changes in fasting plasma glucose (FPG) levels and the mean spherical refraction, the latter given as the average for both eyes, after initiation of blood sugar control. Based on Fig. 1 of Saito *et al*. [9].

changes in refractive index, probably in the lens, must be the source of the refractive change, although this has yet to be demonstrated experimentally.

Okamoto *et al.* [10] concluded from their data on 14 patients (28 eyes) that there is a moderate correlation between the magnitude of the initial hyperopic change and the initial pre-treatment plasma glucose concentration, and that the times to reach the peak of the refractive change and to recover from the changes both increase with the magnitude of the refractive shift (and hence with the initial glucose concentration). Figure 2 illustrates the general trends found: the quasi-asymptotic return of the refraction towards its original value and the limited sampling in time (Fig. 1) means that the recovery time is not well defined.

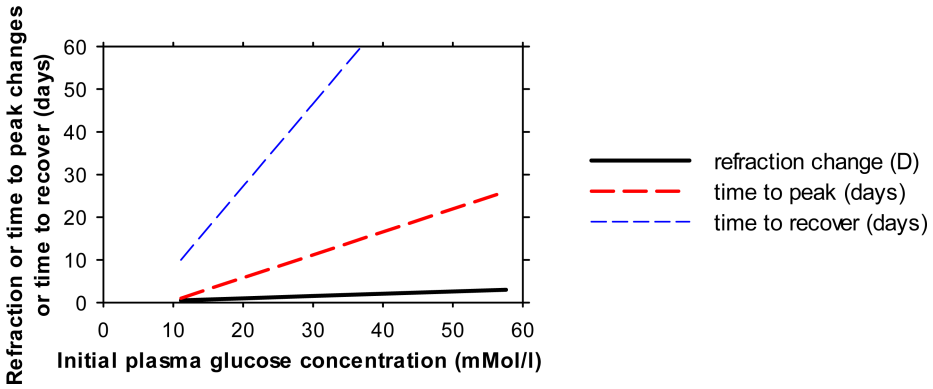

Fig. 2. Fits to data from Okamoto *et al*. [10] for the peak changes in refraction and the times after initiation of glycemic control at which they occur and decay, as a function of the plasma glucose level on admission. Blood glucose levels of all the patients exceeded 16 mMol/l).

It is clear from Figs. 1 and 2 that the refractive changes are relatively slow, generally occurring over several weeks, and that the transient nature of the changes implies that two mechanisms may be involved, one relatively rapid which leads to a hyperopic change and then a slower process which approximately restores the original refractive state. It may be remarked that it is difficult to reconcile the slow timescale of these changes with the much more rapid changes in refraction, occurring within minutes, with blood sugar level found by Gwinup and Villareal [16] after the injection of glucose in diabetic subjects.

As noted earlier, the absence of systematic changes in axial separations or surface curvatures of the optical components of the eye at the time that refraction is changing suggests that changes in refractive index must be involved. An analysis of the sensitivity of refraction to change in each biometric parameter supports the view that it is the equivalent refractive

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index of the lens that is the most important factor [17], and this varies with the form of the gradients of refractive index within the lens.

The aim of the present paper is to attempt to understand the nature of the changes in the lenticular index gradients that could be responsible for transient refractive changes of the type illustrated in Figs. 1 and 2 and to suggest possible physiological mechanisms to cause these.

2. Optical characteristics of the lens in normal and diabetic subjects

The basic characteristics of the lens have been reviewed by Bron *et al.* [18,19]. Lens thickness increases throughout adulthood in both normals and diabetics but at any age is slightly thicker in Type 1 diabetic patients. Surface curvatures are greater in eyes of diabetics than in normals, but the equivalent refractive index is lower so that lenticular powers are similar [6,7].

The refractive index gradients in the normal lens have been studied in several ways but the most useful measurements appear to be those made using magnetic resonance imaging (MRI [20,21], since these are free of assumptions about the optical or ultrasonic parameters of the various media. They show a smooth increase in index from the lens surface to the center, with the gradient being highest near to the surface. However, although in younger lenses the index continues to increase until the lens center is reached, in the older lens the index remains almost constant within the nuclear region, the gradient being mainly confined to the outer layers. As yet no analogous measurements appear to have been made of the lenses of diabetic patients, but if their equivalent refractive indices differs from that of normals of similar age [6], their gradient must also differ in some way.

The age-dependence of the lenticular index-gradients suggests that transient changes in refraction might also be age-dependent, although no attempt has been made in the literature to analyze observational evidence in these terms.

3. Optical modeling of possible origins of transient refractive changes in diabetic patients

3.1. Changes in the refractive index of the aqueous

In principle, changes in the glucose concentration within the aqueous could directly cause refractive change. The refractive index of glucose solution changes by about 2.7×10^{-5} per 1 mM (or per 1 mMol/L) of glucose [22], although the exact figure varies with temperature. If we assume that aqueous concentrations parallel those in the blood, and that blood glucose increases of the order of 10 mMol/L (180 mg/dL) occur in hyperglycemia, the corresponding index increases in the aqueous would be about 0.0003; the figure is lower if aqueous glucose levels are lower than those in the blood [23]. Aqueous humor index changes of this magnitude would, if occurring in isolation, produce a myopic refractive shift, but of too small a magnitude (<0.01 D) to be reliably detectable [17]. Thus it seems much more likely that an induced change in the equivalent index of the lens is the major factor (see also [24]).

3.2. Changes in the refractive index distribution of the lens

From the purely optical point of view, we need to gain insight into the possible changes in the normal lenticular refractive index distribution that could bring about first a fall in lens power, to produce a hyperopic refractive shift, and then a return to base level (see Fig. 1).

The power of the lens arises from the contributions of its surface powers, which depend upon the index changes across the lens boundaries, and the power conferred by the index distribution within the lens. In principle, an infinite number of different types of index distribution could occur within the lens. However, it is reasonable to argue that the physiological diffusive and other processes that are involved within the eyes of diabetics will produce smooth gradations of index, rather than abrupt discontinuities within the lens. Thus we assume here that the effect of changes in the aqueous glucose levels is to modify the normal smooth index gradients, rather than to produce gradients of totally different form, e.g., containing abrupt discontinuities.

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Kasthurirangan *et al.* [21] found that their data for the axial index distribution of normal lenses were well fitted by an equation of the form proposed by Smith *et al* [25], which, following Bahrami and Goncharov [26], we write as

$$n(\xi) = n_c + (n_s - n_c)(\xi^2)^p \qquad (1)$$

where ξ is the normalized distance from the center of the lens, ranging from −1 at the anterior surface to +1 at the posterior surface, and n_s and n_c are the refractive indices at the lens surface and center, respectively. The parameter p describes the shape of the index distribution: for low values of p the refractive index falls steadily from the lens center whereas with high p most of the changes occur relatively close to the lens surface, as in older lenses. According to Kasthurirangan *et al.*, for the axial index profile p is about 2.45 for unaccommodated young (ca. 23 years) lenses and 3.35 for older (ca. 64 years) lenses. Normalized index distributions for these and some other p values are shown in Fig. 3.

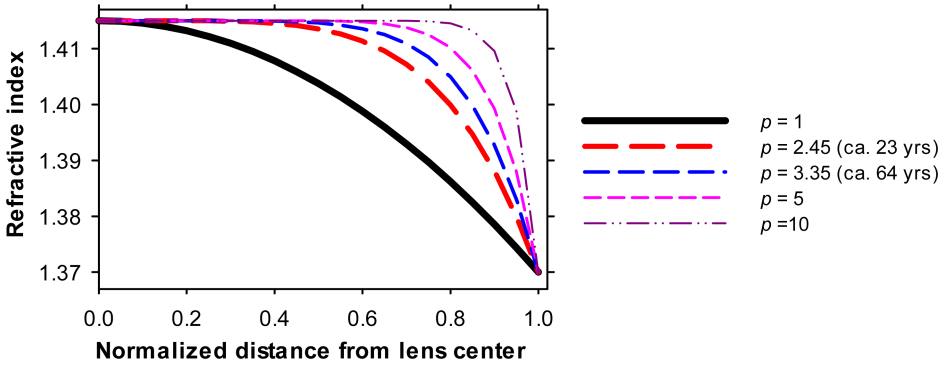

Fig. 3. Gradient index profiles according to Eq. (1) with $n_c = 1.415$, $n_s = 1.37$ and with different values of p. The axial distance from the lens center to the surface has been normalized to unity.

Bahrami and Goncharov [26] used Eq. (1) as the basis for the development of a geometry-invariant lens model, in which the iso-indicial contours always mimic the external shape of the lens, so that the normalized index profile is the same in all directions from the lens center. They gave details of how to calculate the optical characteristics of any lens with this index gradient, combined with conicoidal surfaces, and provided open source code for carrying out the calculations. In this model, in the absence of shape or thickness changes, the power of the lens can vary as result of changes in any one or in any combination of the three parameters n_s, n_c and p.

We use the Bahrami and Goncharov [26] model to explore the effects of changes in the three parameters, on the assumption that these might change as a result of changes in the blood glucose levels. We take the basic lens parameters and refractive indices of surrounding media from the default values of the Bahrami and Goncharov program (Table 1), together with the p value used by Bahrami and Goncharov as typical of a 40 year-old eye. The other ocular parameters are those of the Le Grand model eye [27]. The use of these baseline parameters leads to a hyperopic model eye (refraction + 2.47 D). We have not adjusted the eye parameters to give an emmetropic model, since the effects under consideration apply whatever the initial ametropia. Numerical results are shown in Table 2 and more extended sets are given in Figs. 4 and 5.

It can be seen from Table 2 that an increase in surface index n_s by 0.005 increases the surface powers as a result of the increased change in refractive index across the lens boundaries. However, this is accompanied by a decrease in gradient index (GI) power due to the decrease in the overall range of index values within the lens. Correspondingly, a decrease in n_s will reduce the surface powers but increase the GI power. Thus the overall power of the lens and the final refraction of the eye are relatively insensitive to changes in n_s.

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Table 1. Assumed baseline values of the lens for the eye model

Parameter	n
Aqueous and vitreous index	1.336
Anterior radius (mm) and asphericity	11, –2
Posterior radius (mm) and asphericity	–7.5, –3
Anterior semi-thickness (mm)	2.1
Posterior semi-thickness (mm)	1.4
n_s	1.37
n_c	1.415
p for 40 year-old	3.13

Table 2. Effect of changes in each of the parameters of the lenticular refractive index gradient on the surface (F_1, F_2), gradient index (GI) and total lens powers (Diopters), together with the resultant ocular refraction

Condition	Anterior surface power F_1 (D)	Posterior surface power F_2 (D)	GI power (D)	Lens power (D)	Ocular refraction (D)	Change in refraction (D)
Baseline	3.09	4.53	11.93	19.41	+2.47	
n_s increases from 1.37 to 1.375	3.55	5.20	10.61	19.20	+2.61	+0.14
n_c decreases from 1.415 to 1.410	3.09	4.53	10.61	18.10	+3.31	+0.84
p increases from 3.13 to 4.00	3.09	4.53	11.46	18.94	+2.78	+0.31

The surface powers are unaffected by changes in the center index n_c, since this does not affect the index change across the lens surfaces. Thus, when n_c is reduced by 0.005 to 1.410, the surface powers remain the same as those at baseline but the GI power is reduced by 1.3 D because the overall range of index change is reduced. Note, however, that the GI power is the same as that found for a 0.005 increase in n_s, since the total surface-to-center range of refractive index is the same in both cases (0.04). A reduction in n_c, if n_s remains fixed, causes a fairly substantial drop in lens power and hence a marked hyperopic shift in refraction (+0.84 D for a reduction of 0.005 in n_c).

An increase in p, from 3.13 to 4, has no effect on the surface powers but reduces the GI power and, in turn, the total lens power. This shifts the refraction in the hyperopic direction.

Figure 4 shows changes in powers and refraction with changes in the refractive indices at the surface and center of the lens. For modest index changes in the range –0.005 to +0.005, the lenticular powers vary linearly. Note that the GI power changes are the same in both plots, except that the gradients of the regression lines are opposite in sign. As noted earlier, ocular refraction is more sensitive to changes in n_c than to those in n_s.

Figure 5 shows how p affects the lens powers and overall ocular refraction. Evidently a hyperopic shift requires a higher p value, corresponding to a wider central plateau of near-constant refractive index (see Fig. 3), and is enhanced if n_c also reduces. However an increase of p to 6 and a reduction of n_c to 1.41 yield a hyperopic change of only 1.4 D (Fig. 5), much less than the observed shift of around 4 D illustrated in Fig. 1. To obtain a 4D hyperopic shift from the baseline refraction of 2.47 D, i.e., a refraction of +6.47 D, would require that, if p became very large so that the refractive index was nearly constant through the volume of the lens, the central (and near-surface) indices would have to have a value of about 1.395.

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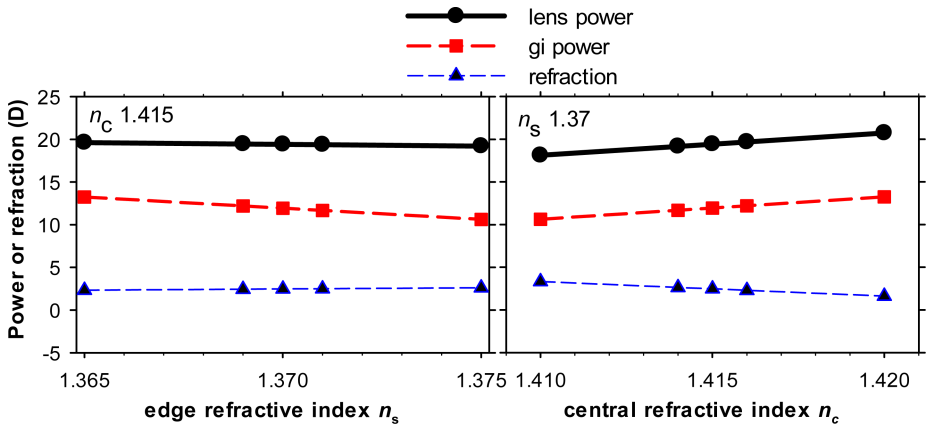

Fig. 4. Effects of varying n_s (left) and n_c (right) on lens power, GI power and refraction. Other parameters are held constant.

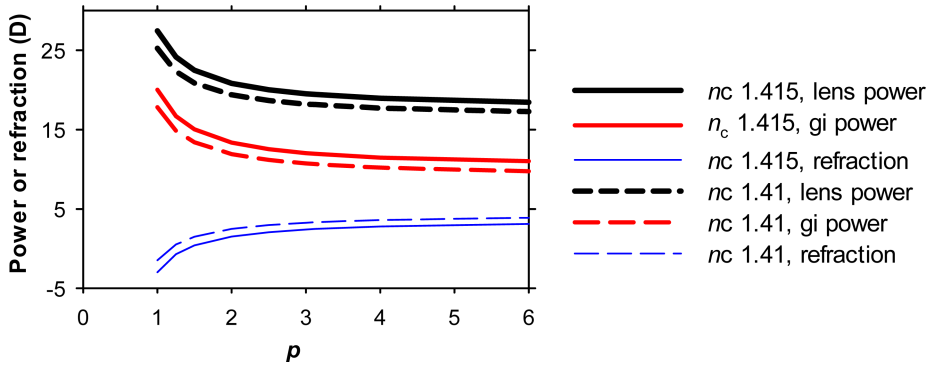

Fig. 5. Effect of changes in p on lens power, GI power and refraction for central refractive index values of n_c = 1.41 and 1.415. Surface refractive index n_s is 1.37.

Overall, these results suggest that a hyperopic shift in the refraction of the eye is most likely to be caused by a reduction in the central index of the lens, enhanced by a flattening of the index gradient over the nuclear region. Such a process might be initiated by the changes in osmotic pressure across the lens boundary induced by the abrupt fall in the glucose concentration in the aqueous. It has been speculated that water might be drawn into the lens and that permeability of the lens membranes to glucose, fructose and other molecules would be affected [18]. The nuclear region, with its relatively higher index would be more vulnerable to such changes. Initially, then, the nuclear index n_c would fall and the p-value of the index gradients would increase, with a wider index plateau developing (Fig. 6). The extent of these index changes, and the associated hyperopic shift, would depend upon the magnitude of the change in blood glucose levels following therapy. With the nuclear region depleted of mobile molecules, those in the surface layers would continue to move out of the lens, making the index gradient less steep in the outer part of the lens and moving the refraction back in the myopic direction, until a new equilibrium index distribution was established. This would have a lower p value than the original index distribution, with lower central values of refractive index. Undoubtedly the nature of the biochemical and other changes is much more complex than is sketched here (e.g., [18,19,28]) and we offer no explanation for their timescale but, optically, the general nature of the changes envisaged appears plausible.

The suggestion that, during hyperopic shifts related to diabetes, the refractive index distribution becomes more uniform may be supported by observations by Huggert [29] and Planten [30], who noted that the slit-lamp appearance of the optical section of the lens during

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refractive shifts tended to show less internal structure, perhaps because the refractive index differences between different regions of the lens were reduced.

Figure 6 illustrates the general nature of the suggested changes in the lenticular index profile. In the absence of suitable experimental measurements, the parameter values are chosen to illustrate effects that might be involved. It is assumed that initially (black solid curve) the lens has the parameters given in Table 1, including n_s = 1.37, n_c = 1.415 and p = 3.13, yielding a refraction of +2.47 D. When the glucose concentration is reduced, the already-low surface index of the lens is unlikely to fall very far towards the aqueous index of 1.336, since the integrity of the lens demands a reasonable protein concentration: for simplicity, n_s is therefore assumed to remain constant. The major effect of a fall in aqueous glucose concentration is on the refractive index in the central regions of the lens, n_c, which in Fig. 6 is assumed to reduce to 1.400 over the central region (red medium dashed curve). This process changes the value of p to 5, with most of the index change occurring near the lens surface, and the refraction to +5.30 D, i.e., a hyperopic shift of +2.83 D. Further internal changes and molecular exchanges between the lens and aqueous smooth the index profile (blue short dashed curve) to give p = 1.5, when the refraction changes to +3.63 D, i.e., a myopic shift of −1.63 D.

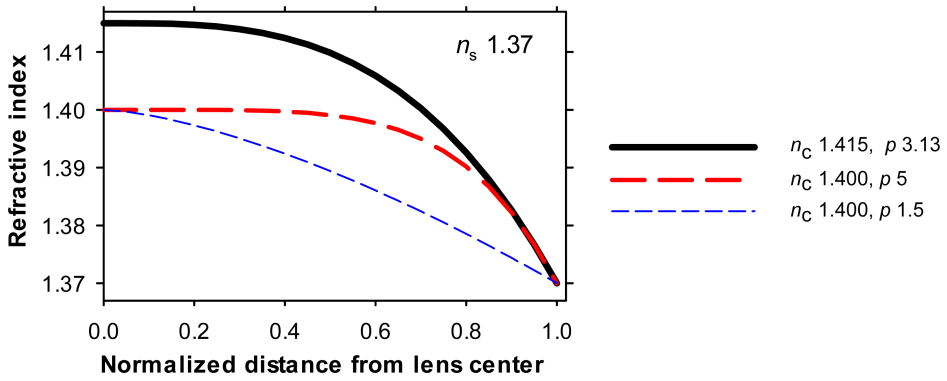

Fig. 6. Illustration of the changes in index profile that could bring about first a hyperopic change and then a myopic change.

The assumptions used in Fig. 6 mean that the initial hyperopic shift is incompletely compensated by the subsequent changes in the direction of myopia. Further adjustments in index parameters of the model could be made to yield complete compensation, but we do not feel that such an exercise is justified at present, in view of the uncertainties about the initial index profiles in the lens of a patient who in experiencing hyperglycemia. Additionally, it can reasonably be argued that the assumption that the original index profile is "normal" is unlikely to be correct and that the *refraction* of the diabetic patient with hyperglycemia has already shifted in the myopic direction as a result of the high blood glucose levels. Such a change might be caused by an increase in the refractive index of the more superficial layers of the lens as a result of glucose penetration. This would increase surface power and, if accompanied by a decrease in p would lead to a change of refraction in the myopic direction. For example, an increase of n_s from 1.37 to 1.375 accompanied by a decrease in p to 2 would lead to a change in *refraction* from +2.47 D to +1.77 D. The picture is complicated by the observation that the surface curvatures are steeper and the thickness is greater in the lenses of diabetics than in normals [6,18], although in fact ocular refraction is not very sensitive to changes in these parameters [17]. In any case, the exact effects are likely to depend upon the age, biometric parameters and other characteristics of the individual eye.

4. Discussion

The present results are obviously limited by the assumptions of the lens model used and the uncertainties over the initial distribution of refractive index within the lens of the eye of the

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diabetic patient during hyperglycemia and prior to treatment. Nevertheless, the important finding is that it appears possible to account for observed hyperopic refractive shifts after the initiation of therapy for hyperglycemia, and the subsequent recovery, on the basis of physiologically-plausible changes in the distribution of refractive index within the lens.

Progress in understanding the exact nature of these lenticular changes depends on better information on how the lens of the diabetic patient differs from that of a normal individual of the same age (e.g., [3–7]). As noted earlier, no information is available on the internal index gradients of DM lenses, although Wiemer *et al.* [6] found that the lenses of a group of patients with DM type 1 were significantly thicker and more convex than those of a control group and that their equivalent refractive index was also significantly lower. These differences increased with the duration of DM. On the other hand no differences in lens parameters were found between DM type 2 patients and controls.

One problem with some existing lens data is that estimates of true lens thickness and its changes may be affected by the assumptions made during in its estimation. In particular a uniform lens refractive index or a constant ultrasound velocity is usually assumed, and these assumptions may be of limited validity for the inhomogeneous lens. For example, estimates based on partial coherence interferometry (PCI) are affected by changes in index gradients. PCI instruments measure the optical path through a lens and convert this to a true thickness using an assumed constant average refractive index n_{av}. For axial gradients of the form assumed previously, the normalized optical path [OP] from the lens center to the surface is

$$[OP] = \int_0^1 n(\xi)d\xi = \int_0^1 [n_c + (n_s - n_c)(\xi^2)^p]d\xi = \left[n_c\xi + (n_s - n_c)\xi^{2p+1}/(2p+1)\right]_0^1$$
$$= n_c + (n_s - n_c)/(2p+1) = n_{av}$$

since the normalized true path is 1.0 (see also Eq. (16) in Ref. [26]).

Figure 7 shows the dependence of this "ideal" average index as a function of p for the baseline case assumed earlier where $n_c = 1.415$ and $n_s = 1.37$.

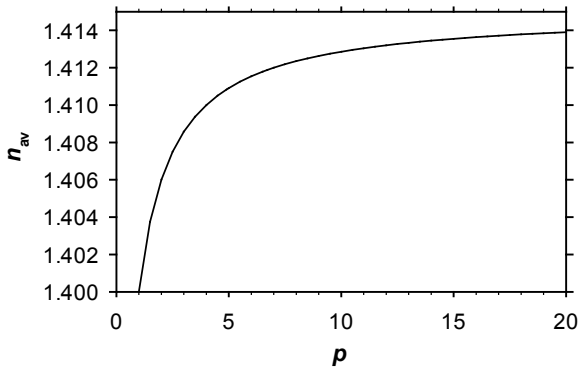

Fig. 7. Average refractive index that must be used to obtain the correct lens thickness from a measurement of optical pathlength as a function of the refractive index parameter p.

It is clear that, to get the correct true thickness, the assumed average index has to be appropriate to the value of p. For example, a lens with a true thickness of 3.5 mm (Table 1) would have an optical thickness of 3.5 x 1.4076 = 4.9266 mm when p is 3, but 3.5 x 1.4119 = 4.9417 mm if p is 10. Should the n_{av} value appropriate to p = 3 be applied to the p = 10 pathlength, the estimate of true thickness is 4.94165/1.4076 = 3.5107, an error of 11 μm. Analogous effects occur when a constant "standard" ultrasound velocity is assumed, although details of the distribution of acoustic impedance within the lens do not appear to be available. To illustrate the order of magnitude of the effects, however, it has been suggested that, in conventional A-scan work, a velocity of about 1630 m/sec is appropriate for the cataractous lens in comparison to about 1640 m/sec for the normal lens [31], leading to errors of around

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20 microns if the inappropriate velocity is used: such a systematic error is small in comparison with the reliability of the method (around 100 micrometers).

There is clearly a need for further in vitro and in vivo measurements of the index distribution of the lenses in the eyes of patients with diabetes. Magnetic resonance imaging techniques such as those employed by Jones *et al.* [20] and Kasthurirangan *et al.* [21] would appear to be particularly useful here, since these are free of the assumptions about constant refractive indices and velocities inherent in PCI and ultrasonic techniques. However, the applicability of the calibration process to diabetic lenses remains to be validated and volumetric resolution is limited. It may be that PCI methods as at present applied to in vitro studies [32] can be further developed for in vivo work.

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