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ORIGINAL ARTICLE

Long-term outcome of cataract surgery in patients with idiopathic hypoparathyroidism and its relationship with their calcemic status

Soma Saha[1] · Shiva Prasad Gantyala[2] · Sameer Aggarwal[1] · Vishnubhatla Sreenivas[3] · Radhika Tandon[2] · Ravinder Goswami[1]

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Abstract Cataract is a cardinal manifestation of hypoparathyroidism. Although patients with hypoparathyroidism require cataract surgery at a younger age than individuals without hypoparathyroidism, there is limited information on the outcome of this surgery. We assessed long-term complications of cataract surgery in patients with idiopathic hypoparathyroidism (IH) and its relationship with their clinical and biochemical parameters. Twenty-seven patients with IH and 25 nonhypoparathyroid controls with a minimum follow-up of 2 years after cataract surgery were assessed for visual acuity, intraocular pressure, lens centricity, Nd:YAG laser capsulotomy, and the severity of posterior capsular opacification (PCO) and anterior capsular opacification. High-resolution optical slit-lamp images were analyzed by an ophthalmologist. Patients with IH had cataract surgery at a younger age than controls (34.0 ± 16.4 years vs 58.0 ± 11.2 years, $P < 0.001$). A higher proportion of IH patients had dense white PCO (75.0 % vs 39.4 %, $P = 0.004$), Nd:YAG laser capsulotomy (44.2 % vs 10.0 %, $P = 0.001$), anterior capsular opacification (97.7 % vs 84.2 %, $P = 0.03$), and a decentric lens (28.3% vs 2.6 %, $P = 0.001$) at a comparable time after surgery (8.6 ± 6.1 years vs 8.7 ± 6.8 years, $P = 0.85$). On regression analysis, the severity of PCO in IH correlated only with male sex and not with other factors, including serum total calcium and inorganic phosphorus levels at the baseline and during follow-up. To conclude, patients with IH are likelier than individuals without IH to develop PCO and to require Nd:YAG laser capsulotomy after cataract surgery. Proper precautions should be taken during surgery to minimize this complication in IH.

Keywords Hypoparathyroidism · Complications · Cataract · Calcium

Introduction

Association of hypoparathyroidism and cataract was first described in 1880 [1]. Cataract is considered a cardinal clinical manifestation of hypoparathyroidism. In a series of 69 patients with hypoparathyroidism, Pohjola [2] observed a 58 % prevalence of cataract, mostly of the posterior subcapsular type. In our previous studies, cataract was present in 51 % of patients with idiopathic hypoparathyroidism (IH), and its presence correlated with the duration of hypocalcemic symptoms and basal ganglia calcification [3, 4]. Clark [5] reported decreased deposition of calcium in pig lenses immersed in calcium chloride solution following addition of parathyroid hormone (PTH). However, the mechanism of opacification of the lens in a chronic hypocalcemic and hyperphosphatemic milieu of hypoparathyroidism is not clear. Posterior capsular opacification (PCO) is the most frequent long-term complication in patients with senile or age-related cataract, manifesting itself in up to 50 % of them 2–3 years after surgery [6, 7]. Nd:YAG laser capsulotomy is a standard procedure to treat PCO [8].

✉ Radhika Tandon
radhika_tan@yahoo.com

✉ Ravinder Goswami
gosravinder@hotmail.com

[1] Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi 110029, India

[2] Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi 110029, India

[3] Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Metabolic abnormalities in patients with hypoparathyroidism often remain inadequately controlled despite calcium and vitamin D therapy [9]. Such patients are also prone to develop calcifications in the basal ganglia region, spine and hip joint. These ectopic calcifications correlate with their lower serum calcium to inorganic phosphorus ratio [3, 4, 10]. Hypoparathyroidism is a rare disorder with a prevalence of 37 cases per 100,000 person-years in the USA and 22 cases per 100,000 person-years in Denmark [10]. We have a large cohort of patients with IH in our follow-up since 1998 [11–18]. These patients are being investigated for the etiopathogenesis and unique clinical features of the disease [13–18]. Several of them were observed to have dense cataract that required surgery and subsequently Nd:YAG laser capsulotomy for PCO. There is no information on the outcome of cataract surgery in hypoparathyroidism. Here, we report the long-term outcome of cataract surgery in patients with IH and its relationship with their clinical profile, including their serum calcium and inorganic phosphorus levels at the baseline and during follow-up.

Materials and methods

The study was performed in accordance with the tenets of the Declaration of Helsinki after permission had been obtained from the Ethics Committee of the All India Institute of Medical Sciences, New Delhi. Study participants were patients with IH being followed up in the endocrine clinics of the All India Institute of Medical Sciences. The essential selection criteria were a history of cataract surgery and a minimum follow-up of 2 years after cataract surgery. The criteria used to diagnose IH were essentially the same as described before [9, 18]. Briefly, diagnosis of hypoparathyroidism was based on clinical and biochemical features of hypocalcaemia, hyperphosphatemia, and normal blood urea, normal serum creatinine, and low serum PTH levels. None of the patients had features of autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome and serum cortisol and adrenocorticotropic hormone levels were normal in all patients. Patients with postsurgical hypoparathyroidism were excluded. All these patients were given a daily dose of 1–2 g of elemental calcium and 0.5–3.0 μg of 1α-hydroxyvitamin D. They were followed up every 3 months to monitor serum total calcium level, serum inorganic phosphorus level, and urinary calcium excretion. The therapy was adjusted to maintain their serum calcium level between 2.0 and 2.1 mmol/L and their calcium excretion at approximately 100 mg/day.

Controls were patients with type 2 diabetes mellitus attending endocrine clinics and their relatives who had undergone cataract surgery at least 2 years previously and who were willing to participate in the study. None of them had hypoparathyroidism and their serum total calcium, inorganic phosphorus, and PTH levels were within the normal range.

All the participants underwent a detailed examination by an ophthalmologist before and after mydriasis caused by 1 % tropicamide eye drops. Parameters noted included the duration after cataract surgery, best corrected visual acuity, intraocular pressure (Goldmann tonometer), type of intraocular lens implant, lens centricity, evidence of previous Nd:YAG laser capsulotomy, and presence of PCO and anterior capsular opacification (ACO). The severity of PCO and that of ACO were recorded with use of a predesigned proforma with use of an adaptation of the semiquantitative clinical score [20]. Briefly, PCO of fibrotic type was classified into two categories: mild (translucent) and severe (opaque/dense white). The proliferative type of PCO was categorized as mild when the number of Elschnig pearls

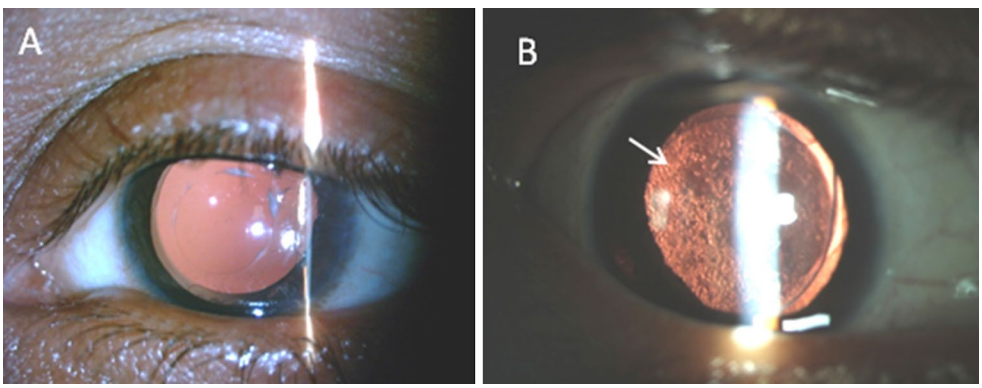

Fig. 1 Slit-lamp images of the posterior capsule after cataract surgery in two patients with hypoparathyroidism: **a** a patient with mild posterior capsular opacification with occasional Elschnig pearls; **b** a patient with severe Posterior capsular opacification and innumerable Elschnig pearls (*arrow*) requiring Nd:YAG laser capsulotomy for restoration of vision

could be counted and as severe when these were numerous or uncountable. Figure 1 shows representative slit-lamp images of mild and severe PCO. The severity of PCO and ACO was assessed by (1) its circumferential extent, with 360° as the maximum possible spread, and (2) our noting the density of the opacification.

Images of the anterior and posterior segments were captured in JPEG format with 24-bit depth and 72–96-dpi resolution with use of an LED-powered high-resolution coaxial optical slit lamp (BQ 900, Haag-Streit, Koeniz, Switzerland), under slit, diffuse, retroillumination, and reflected light conditions (imaging module 900, Eye Suite) These images were transferred to another computer with a high-resolution 19-in. monitor. The digital images of both patients and controls were arranged alphabetically by the initials of the names and were analyzed serially by the ophthalmologist, who was blinded to the endocrine status of the patients.

To determine the relationship between the severity of PCO and serum total calcium and inorganic phosphorus levels maintained during follow-up, the mean serum total calcium and inorganic phosphorus levels were recorded for each of the hypoparathyroid patients. The number of measurements available in follow-up was 17 per patient (median 13, interquartile range 9–31).

Biochemical analysis

Serum total calcium, inorganic phosphorus, and alkaline phosphatase were measured by standard procedures with a Modular P 80 autoanalyzer (Roche Diagnostics, Mannheim, Germany; normal ranges of 2.0–2.60 mmol/L, 0.81–1.45 mmol/L, and 80–240 IU/L respectively; intra-assay and interassay coefficients of variation 3.5–5.0 %). Serum intact PTH was measured by an immunoradiometric assay until 2006 (DiaSorin, minimum detection 0.7 ng/L; normal range 13–54 ng/L) and thereafter by a chemiluminescence assay (Elecsys; Roche, Mannheim, Germany; normal range 15–65 ng/L) in the clinical endocrine services laboratory [9, 19].

Statistical analysis

Data are presented as the mean and standard deviation and frequencies as a percentage. Parametric and nonparametric tests were used as appropriate. The differences in the frequency of abnormalities between patients and the control group were assessed by the chi square test. Multiple regression was used to determine variables associated with the severity of PCO. A two-tailed P value less than 0.05 was considered significant. All the analyses were done with Stata 12.1.

Results

During 2014–2015, 101 patients with IH presented for follow-up in the endocrine clinics. Twenty-seven of them had a history of cataract surgery with postsurgery follow-up of 2 years or more. Thirteen of them had already undergone cataract surgery when they first presented to us and others had this surgery while they were being followed up. Twenty-one of them had cataract surgery in both eyes and six had it in only one eye. Their male-to-female ratio, mean age at surgery and at ophthalmic assessment, body mass index (BMI), and duration of disease since the onset of hypocalcemia symptoms were 14:13, 34.0 ± 16.4 years, 44.1 ± 17.0 years, 22.9 ± 3.8 kg/m^2, and 14.1 ± 8.3 years respectively. Intracranial calcification was present in 23 of them. Their baseline mean serum calcium, inorganic phosphorus, and intact PTH levels were 1.3 ± 0.28 mmol/L, 2.3 ± 0.39 mmol/L and 6.1 ± 7.0 ng/L (median 4.1 ng/L, interquartile range 1.2–7.4 ng/L) respectively.

During the study period, 32 nonhypoparathyroid controls were identified. Seven of them were excluded [clinically overt diabetic nephropathy ($n = 1$), traumatic cataract following accidental chemical injury ($n = 1$) and those with primary concern of dimness of vision following cataract surgery ($n = 5$)]. Twenty-five controls were finally used for evaluation. Seventeen of them had cataract surgery in both eyes and eight had it in one eye. Eleven of them had type 2 diabetes mellitus. Their mean age at ophthalmic assessment (65.5 ± 8.11 years), male-to-female ratio (9:16), and body mass index (28.0 ± 5.7 kg/m^2) were different from those of the hypoparathyroid group. The mean age of the controls at the time of cataract surgery was significantly greater than that of the hypoparathyroid patients (58.0 ± 11.2 years vs 34.0 ± 16.4 years, $P < 0.001$). The median interval between cataract surgery and the ophthalmologic assessment was comparable between the IH and control groups [6.5 years (interquatile range 4.0–12.9 years) vs 6.0 years (interquartile range 3.9–11.3 years) respectively, $P = 0.85$].

Postoperative complications

The final analysis for the long-term complications after cataract surgery was done for 48 eyes in the IH group and 42 eyes in the control group (Table 1).

Posterior capsular opacification

A significantly higher proportion of participants in the IH group as compared with the controls had undergone Nd:YAG laser capsulotomy for PCO (44.2 % vs 10.0 %, $P = 0.001$) and seven of them had had it performed in both

Table 1 Mean values (and standard deviations) and frequencies of long-term complications after cataract surgery in eyes of patients with hypoparathyroidism and controls

Complications	Hypoparathyroid patients	Controls	*P*
Posterior capsule			
Evidence of Nd:YAG laser capsulotomy for PCO	19/43 (44.2 %)	4/40 (10.0 %)	0.001
Patients with current evidence of PCO	43/46 (93.5 %)	39/40 (97.5 %)	0.38
Severity of PCO			
Circumferential extent (°)	222 ± 103	161 ± 114	0.02
≤90°	6/39 (15.4 %)	16/32 (50.0 %)	<0.01
>90°	33/39 (84.6 %)	16/32 (50.0 %)	
Opacity of PCO			
Translucent margins	10/40 (25.0 %)	20/33 (60.6 %)	<0.01
Opaque	30/40 (75.0 %0	13/33 (39.4 %)	
Number of Elschnig pearls			
Countable	13/39 (33.3 %)	21/33 (63.6 %)	0.01
Uncountable	26/39 (66.7 %)	12/33 (36.4 %)	
Circumferential extent of pearls (°)	222 ± 113	217 ± 116	0.86
Anterior capsule			
Presence of any ACO	43/44 (97.7 %)	32/38 (84.2 %)	0.03
Circumferential extent of ACO (°)	267 ± 114	220 ± 130	0.11
Severity of ACO			
Translucent margins	20/40 (50.0 %)	15/29 (51.7 %)	0.80
Opaque	20/40 (50.0 %)	14/29 (48.3 %)	
Lens-related complication			
Decentric position of the lens	13/46 (28.3 %)	1/39 (2.6 %)	0.001
Lens deposits	4/48 (8.3 %)	0/40 (nil)	0.12
Intraocular pressure	14.6 ± 3.11	14.3 ± 2.49	0.68
Visual activity (decimal points)	0.67 ± 0.31	0.62 ± 0.28	0.46
Impaired visual acuity (<6/6)	30/44 (68.2 %)	31/41 (75.6 %)	0.48
Type of lens			
PMMA	30/46 (65.2 %)	5/35 (14.3 %)	<0.001
Hydrophobic acrylic	10/46 (21.7 %)	28/35 (80.0 %)	
Others	6/46 (13.0 %)	2/35 (5.7 %)	

ACO anterior capsular opacification, *PCO* posterior capsular opacification, *PMMA* poly(methyl methacrylate)

eyes. The prevalence of Nd:YAG laser capsulotomy was high (61.1 %) in IH patients who had undergone cataract surgery before 25 years of age.

Although the total number of the participants with PCO (with and without capsulotomy) was similar in the IH and control groups ($P = 0.71$), PCO was severer in the IH group as indicated by (1) circumferential spread, (2) opacity, and (3) Elschnig pearls (Table 1, Fig. 1). The mean circumferential spread of the PCO and proportion of patients with PCO affecting more than one quadrant (more than 90°) were significantly higher in the IH group than in the control group (84.6 % vs 50.0 %, $P < 0.01$). Similarly, a significantly higher proportion of patients in the IH group than among the controls had dense white opaque PCO (75.0 % vs 39.4 %, $P = 0.004$) and innumerable Elschnig pearls (66.6 % vs 38.7 %, $P = 0.02$).

Anterior capsular opacification

The prevalence of ACO was higher in the IH group than in the control group (97.7 % vs 84.2 %, $P = 0.03$). However, the severity of the ACO as indicated by its circumferential spread and opacity was comparable between the two groups (Table 1).

Opacity and decentralization of the lens implant and other parameters

The position of the intraocular lens implant was decentric in a significantly higher proportion of hypoparathyroid patients as compared with the controls (28.3 % vs 2.6 %, $P = 0.001$). Evidence of crystallization in the lens implant was present in two hypoparathyroid patients as compared

with none of the controls. There was no significant difference in the mean intraocular pressure and number of individuals with impaired visual acuity (less than 6/6) between the IH and control groups (Table 1). A significantly higher proportion of individuals in the IH group as compared with the controls had a poly(methyl methacrylate) lens.

Univariate and multivariate regression for PCO with clinical and calcemic characteristics of hypoparathyroid patients

Table 2 shows the intergroup differences in the clinical and biochemical characteristics of hypoparathyroid patients with and without a history of Nd:YAG laser capsulotomy ($n = 12$ and 15 respectively). The mean age at ophthalmic assessment, age at cataract surgery, total duration since the first onset of hypocalcemic symptoms until cataract surgery, duration of follow-up after cataract surgery, and mean serum total calcium, inorganic phosphorus, and albumin levels at the baseline and during follow-up were not significantly different between the two groups. However, the capsulotomy group had a significantly higher proportion of males. The baseline mean serum total calcium level tended to be lower in the capsulotomy group than in the noncapsulotomy group (1.2 ± 0.22 mmol/L vs 1.7 ± 0.39 mmol/L, $P = 0.12$). A similar trend was noticed for the serum calcium to inorganic phosphorus ratio (0.68 ± 0.17 vs 0.82 ± 0.25, $P = 0.10$). There were no significant differences in the mean serum total calcium and inorganic phosphorus levels or their ratio between these two groups of IH patients during follow-up. On regression analysis, the severity of PCO in IH correlated only with male sex ($P = 0.03$) and not with age, body mass index, duration after cataract surgery, type of intraocular lens implant, or serum total calcium and inorganic phosphorus levels and their ratio at the baseline and during follow-up.

Discussion

There is a paucity of information on cataract in hypoparathyroidism in the endocrine as well as the ophthalmic literature [2, 21]. The only systematic description available is by Pohjola [2], who in 1962 reviewed ocular manifestations in 69 patients with hypoparathyroidism. Cataract, papilloedema, corneal changes, and alopecia of the eyebrows were observed in 58, 11, 10, and 7 % of the cases respectively. Although Pohjola documented secondary cataract after initial surgery in a case of hypoparathyroidism, no details were given in the report [2].

Currently, phacoemulsification with intraocular lens implant is the standard procedure for cataract surgery. The procedure leaves the posterior capsule and a margin of the anterior capsule intact and a lens is implanted between the two. Posterior capsular fibrosis manifesting itself as opacification is a well-known long-term complication of cataract surgery and can occur even after an uneventful

Table 2 Clinical and biochemical characteristics of patients with hypoparathyroidism requiring Nd:YAG laser capsulotomy after cataract surgery

Parameters	Capsulotomy		*P* value
	Capsulotomy done ($n = 12$)	Capsulotomy not done ($n = 15$)	
Male-to-female ratio	9:3	5:10	0.03
Age at ophthalmic assessment (years)	42.2 ± 19.43	45.5 ± 15.30	0.63
Age at cataract surgery (years)	32.3 ± 18.62	35.9 ± 14.5	0.59
Total duration since the onset of hypocalcemic symptoms until cataract surgery (years)	6.6 ± 7.5	5.5 ± 4.3	0.76
Median duration since the onset of hypocalcemic symptoms until cataract surgery (years)[a]	4.5 (0.6–10.1)	5.0 (1.3–8.6)	
Duration of follow-up since cataract surgery (years)	10 ± 6.88	7.6 ± 5.2	0.53
Serum total calcium level at diagnosis (mmol/L)	1.2 ± 0.22	1.4 ± 0.30	0.12
Serum albumin level at presentation (gm/dL)	4.3 ± 0.63	4.5 ± 0.46	0.26
Serum inorganic phosphorus level at diagnosis (mmol/L)	2.4 ± 0.49	2.2 ± 0.28	0.28
Serum calcium to inorganic phosphorus ratio at diagnosis	0.68 ± 0.17	0.82 ± 0.25	0.10
Follow-up serum total calcium level (mmol/L)	1.8 ± 0.21	1.83 ± 0.15	0.35
Serum albumin level at ophthalmic assessment (gm/dL)	4.8 ± 0.30	4.7 ± 0.42	0.43
Follow-up serum inorganic phosphorus level (mmol/L)	1.9 ± 0.34	1.8 ± 0.20	0.65
Follow-up serum calcium to inorganic phosphorus ratio	1.3 ± 0.38	1.3 ± 0.23	0.69

Serum total calcium, 1.0 mmol/L = 4.0 mg/dL; serum inorganic phosphorus, 1.0 mmol/L = 3.09 mg/dL

[a] The interquartile range is given in parentheses

procedure [6, 7]. It is also known as "secondary/after cataract." Its prevalence can increase by up to 50 % or more with increasing duration of follow-up [6]. Patients with dense PCO require a corrective procedure such as Nd:YAG laser capsulotomy. Similarly, ACO is another long-term complication of cataract surgery. The mechanism of PCO is not clearly known. However, proliferation, migration, and differentiation of epithelial cells of the residual lens into myofibroblasts is implicated in its pathogenesis. The molecular basis of these processes has been linked to release of cytokines such as transfoming growth factor β, IL-1, and Il-6, metalloproteinases, and hepatocyte, epidermal, fibroblast growth factors in experimental studies [22–24]. These cytokines released by the epithelial cells of the lens and melanocytes from the iris act as autocrine and paracrine factors on epithelial cells of the residual lens that line the anterior and posterior capsule, leading to ACO and PCO respectively. A similar process in the equatorial region of the capsular bag leads to proliferative Elschnig pearl formation. Patients with diabetes mellitus and myotonic dystrophies are prone to develop cataract and PCO [25–27].

The results of the present study showed that patients with IH required cataract surgery two decades earlier than the controls. After a similar duration of postoperative follow-up (8–10 years), they had a higher prevalence of ACO and PCO than the nonhypoparathyroid controls. PCO was severer in patients with IH; almost half of them had already undergone Nd:YAG laser capsulotomy, unlike only 10 % of the controls. The extent of PCO, the density of opacification, and the number of Elschnig pearls were also significantly greater in the IH group. These factors increase the likelihood of repeated Nd:YAG laser capsulotomy later.

In the present study, patients with IH had received different types of lenses and a significantly higher proportion of them as compared with the controls had a poly(methyl methacrylate) lens implant. Since, the need for Nd:YAG laser capsulotomy may vary with the type of lens implant, this factor was also included in the regression analysis [28]. However, the type of lens did not predict the severity of PCO. The observations of high prevalence and severity of capsular opacification in IH have practical implications as these indicate a need for novel measures to prevent and reduce the occurrence of PCO [29].

The reasons for the increased prevalence and severity of PCO after cataract surgery in IH are not clear. However, associated factors such as chronic hypocalcemia, hyperphosphatemia, and younger age at surgery might predispose them to this complication. Ten of the 27 patients in the IH group had undergone cataract surgery before 25 years of age, in contrast to none of the controls. Young age is a known risk factor for the occurrence of PCO [30]. The incidence of Nd:YAG laser capsulotomy was also high (61.1 %) in hypoparathyroid patients who had surgery before 25 years of age. The present study also revealed a trend of lower mean calcium to inorganic phosphorus ratio in patients who had undergone Nd:YAG laser capsulotomy, indicating that a low calcium level coupled with a high inorganic phosphorus level could contribute to PCO. This trend is similar to that observed for the progression of calcification in the basal ganglia region in IH [4]. That the trend of lower calcium to inorganic phosphorus ratio did not reach statistical significance as a predictor of PCO in IH could be related to the limited sample size. With the observed differences in the calcium to inorganic phosphorus ratio, 50 hypoparathyroid patients operated on for cataract would be required in each group (i.e., with and without capsulotomy) to attain statistical significance with 90 % power and 90 % confidence. Despite our having a large cohort of patients with IH in our follow-up since 1998, we could not attain the required sample size because of the rarity of the disease and the limitation of including patients with a long follow-up after cataract surgery. Multicenter studies are required to investigate this aspect. An increased level of local or circulating fibroblast growth factor implicated in the pathogenesis of PCO might also contribute to increased susceptibility to PCO in IH. Serum fibroblast growth factor 23 levels have been observed to be higher in patients with hypoparathyroidism with chronic hyperphosphatemia [31, 32]. Since the present study was not designed to investigate the causes of increased prevalence and severity of PCO in IH, the present discussion on these aspects is at best speculative. A prospective study with serial biochemical monitoring beginning before and continued after cataract surgery could address these questions.

To conclude, patients with IH are likelier than individuals without IH to develop PCO and require Nd:YAG laser capsulotomy after cataract surgery. They should be regularly followed up after cataract surgery even if the procedure was uneventful so as to detect PCO at an early stage. Endocrinologists and ophthalmologists should both be aware of the high prevalence of this long-term complication after cataract surgery in patients with hypoparathyroidism. Proper precautions should be taken during surgery to minimize the occurrence of PCO in these patients.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

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