

Vitamin D deficiency and posterior subcapsular cataract

Craig J Brown¹
Faical Akaichi²

¹The Eye Center, Fayetteville, AR, USA; ²Scotland's Rural College, Edinburgh, UK

Purpose: To evaluate risk factors associated with posterior subcapsular cataract (PSC) development and the relationship between vitamin D deficiency and etiology of PSC.

Methods: Of 195 consecutive patients from a private ophthalmology practice, diagnosed with PSC, serum vitamin D₃ (25-OH D) levels were obtained for 175, and associations among risk factors, comorbidities, and PSC were assessed.

Results: In all 175 PSC patients, mean 25-OH D levels were low (24 ng/mL ±11 SD) compared with age/sex-matched standards. Significant differences in 25-OH D levels were noted between PSC subjects taking/not taking calcium supplements, systemic steroids, osteoporosis medications, etc. Alone, smoking status and calcium channel blockers and/or topical steroids use made no significant difference in PSC subjects 25-OH D levels, but two or more of these factors were associated with lowered levels of 25-OH D ($P < 0.001$). Low vitamin D was correlated with female sex, autoimmune disease, and non-skin cancer diagnosis, but not with age, or other comorbidities or medication use. In five early-stage PSC patients taking 5,000 IU of 25-OH D daily for vitamin D deficiency, there was resolution of their cataracts during the 2-year follow-up period.

Conclusion: Vitamin D levels for most PSC patients fell below the 30 ng/mL calcium homeostasis threshold. Some comorbidities and non-ophthalmic interventions are associated with the development of PSC at less depressed levels of 25-OH D. In this series, vitamin D deficiency was associated with PSC cataract, suggesting that raising the level of vitamin D intake may reduce PSC incidence.

Keywords: posterior subcapsular, cataracts, vitamin D deficiency, risk factors, hypocalcemia, case report

Introduction

Posterior subcapsular cataract (PSC) is clinically common and known to be visually debilitating, having a high societal burden in terms of lost work and need for early surgical intervention. Prolonged corticosteroid use can lead to the development of PSC.¹⁻³ Although other described risk factors⁴ include myopia,⁵ various skin disorders,⁶ diabetes,⁷ intraocular inflammation or trauma,⁸ retinitis pigmentosa,⁹ and smoking,¹⁰ the majority of PSCs have an unknown etiology.¹¹ PSC resembles the hypocalcemic cataract described in the endocrine and veterinary literature, and can be reproduced in vitro or in vivo by incubating clear excised lenses in hypocalcemic media or by feeding animals diets deficient in calcium or in severe vitamin D deficiency states.¹²⁻¹⁶ It was noted by one of the authors that within a large series of PSC cases, patients frequently presented with vitamin D insufficiency or deficiency. A retrospective examination of other risk factors was undertaken to establish any possible interactions with vitamin D deficiency as causative mechanisms of PSC formation, supporting the validity of the hypocalcemic animal model in humans.

Correspondence: Craig J Brown
The Eye Center, 594 E Millsap Road,
Fayetteville, AR 72073, USA
Tel +1 479 442 2020
Email cjbrown1234@sbcglobal.net

Methods

This study comprised 195 of 1,585 consecutive cataract patients seen in a private practice ophthalmology clinic between June 1, 2008 and June 1, 2010, and diagnosed with PSC/anterior subcapsular cataract (ASC) alone or mixed cataract PSC/ASC combined with nuclear or cortical opacities. Histories and risk factors were recorded by the senior author including steroid use, use of calcium supplements or osteoporosis medications, prior trauma, autoimmune or skin cancer disorders, diabetes, cancer diagnosis, or cardiopulmonary disease. The use of concomitant medications for their control was taken from the chart record (Table 1). Levels of 25-OH D were obtained or available for 175 of 195 PSC patients using either the DiaSorin LIAISON® Immunochemiluminometric assay or the QuestAssureD™ liquid chromatography, tandem mass spectrometry. Both methods,

Table 1 Patient demographics, cataract types, comorbidities, and risk factors

Demographics, cataract types, and risk factors	Total number of patients	Percentage of patients	Standard deviation
Sex			
Women	109	62.3	
Men	66	37.7	
Age, years			
<50	16	9	
51–70	108	62	
>71	51	29	
Cataract components with PSC			
ASC	173	16	0.36
Nuclear	175	95	0.22
Cortical	175	85	0.36
Concomitant medications			
Ca ²⁺ supplements	172	22	0.41
Systemic steroids	175	25	0.43
Topical steroids	175	13	0.34
Ca ²⁺ channel blockers	172	19	0.39
Antidepressants	173	27	0.45
Osteoporosis drugs	173	9	0.28
Comorbidities, risk factors			
Ocular trauma, prior surgery, inflammation	173	25	0.44
Autoimmune disease	175	44	0.5
Cardiovascular disease	173	28	0.45
Hypertension	173	53	0.5
Asthma/COPD	173	9	0.28
Non-skin cancer history	173	14	0.35
IDDM/NIDDM	174	24	0.42
Smoking history	165	20	0.40
Retinitis pigmentosa	174	1	0.08

Abbreviations: PSC, posterior subcapsular cataract; ASC, anterior subcapsular cataract; COPD, chronic obstructive pulmonary disease; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus.

as performed by commercial laboratory testing services, had an analytical sensitivity of at least 4 ng/mL. Associations between risk factors and comorbidities and the presence of PSC were then assessed. A *t*-test for independent samples was used to determine whether the differences of 25-OH D levels in PSC subjects with and without risk factors and concomitant medications were statistically different from zero. In addition, a linear regression analysis was carried out to model the relationship between the level of 25-OH D and variables such as age, sex, autoimmune disease, hypertension, skin cancer, and antidepressant use. Access to anonymized clinical records by nonclinical personnel was approved by the Washington Regional Medical Center Institutional Review Board. All patients had received routine medical and surgical care. Patients whose cataracts interfered with daily vision function were scheduled for cataract surgery. Those whose cataracts were minimally symptomatic or asymptomatic were followed without surgery. Patients in this interval of care newly diagnosed with low levels of vitamin D were treated and referred to their primary care physician for follow up. This was a retrospective chart review study, and all patients received routine care with no experimental intervention.

Results

All eyes were examined in the dilated state. Anterior and posterior subcapsular opacities were identified with the slit lamp set for retroillumination, spanning a range from axial retrodots to dense fibrotic plaques involving the capsule and immediately adjacent degenerating cortical lens fibers. In this study, all degrees of PSC and ASC were included. Lens Opacity Classification System III¹⁷ grades P1–P5 represented the majority of subcapsular cataracts. Additionally, some PSCs were greater than P5, involving the entire posterior capsule, and some patients had predominantly anterior subcapsular opacities identical to posterior subcapsular opacities, except for anterior location and more severe functional visual disturbance. Of 1,585 unique cataract patients seen during the study period, 12.3% had PSC (195/1,585), while 27.6% of patients who received cataract surgery had a PSC component (164/595). Vitamin D levels were evaluated for 175 (most bilateral; 62.3% female, 37.7% male; most were Caucasian) PSC patients (76% confirmed after diagnosis by serum testing, 24% as lab values were obtained from history/referral chart). Mean 25-OH D level of PSC cataract patients was on the low normal end of the spectrum (24 ng/mL ± 11SD) compared to age/sex-matched national standards for vitamin D levels.¹⁸ This serum 25-OH D level has been defined by some authorities as vitamin D insufficiency.¹⁹

Table 2 Significantly different 25-OH vitamin D levels in PSC subjects with and without risk factors and concomitant medications

Variables	N ^a	Mean (ng/mL)	P-value	Standard deviation
All PSC	175	24	NA	11
Risk factors				
PSC taking Ca ²⁺ supplements	37	28	0.01	11
PSC not taking Ca ²⁺ supplements	135	23		10
PSC taking systemic steroids	43	30	<0.001	12
PSC not taking systemic steroids	132	22		9
PSC taking osteoporosis medications	15	28	0.05	14
PSC not taking osteoporosis medications	158	24		10

Notes: ^aN<175 total. Information on all variables not available or not collected for all PSC subjects. Some patients declined to share their past medical histories or their current medications.

Abbreviation: PSC, posterior subcapsular cataract.

Significant differences in 25-OH D levels were noted between PSC subjects with and without certain risk factors and variables, including with or without calcium supplementation (28±11 vs 23±10 ng/mL; *P*=0.01), systemic steroids exposure (30±12 vs 22±9 ng/mL; *P*<0.001), or taking osteoporosis medications or not (28±14 vs 24±10 ng/mL; *P*=0.05) (Table 2). Smoking, use of calcium channel blockers, or topical steroid use alone showed no significant difference in 25-OH D levels between PSC patients with that variable or without it. However, marginally significant lower levels of vitamin D were noted when two or more variables were present compared with none of the variables (23±11 vs 25±11 ng/mL; *P*=0.06) (Table 3). Linear regression analysis showed that 25-OH D levels also correlated with female sex (*P*=0.042), autoimmune disease (*P*<0.001), (non-skin) cancer diagnosis (*P*=0.016), but not with age, hypertension, eye trauma or inflammation (not shown), cardiopulmonary disease (not shown), diabetes (not shown), or antidepressant use (Table 4). Five patients with early-stage multiple axial posterior or anterior subcapsular water cleft cysts and retro dots who began taking 5,000 IU of vitamin D₃ (25-OH D) daily, completely resolved their early-stage cataracts.

Discussion

Low vitamin D status is extremely common worldwide when the cut point of <30–32 ng/mL is applied. In the USA, vitamin D levels have fallen over the last few decades due to fewer work and recreation-related outdoor activities, including more air conditioning in homes and offices, television viewing, computer use, and intentional sun avoidance (ie, sun screen use).²⁰ Milk fortification and dietary supplement have not closed the gap. The National Health and Nutrition Examination Surveys conducted between 1988 and 1994 compared with those conducted between 2001 and 2006 showed a mean decrease in age-specific 25-OH D levels of 5–10 ng/mL for Caucasian men and 2–6 ng/mL for Caucasian women. Other racial groups typically exhibited lower vitamin D levels even in the reference decades. Comorbidities on the rise due to lifestyle diseases or the aging demographic, including diabetic nephropathy and bone and mineral metabolism defects, may also be associated with vitamin D insufficiency or deficiency.^{21,22} Several agencies and guides now categorize serum 25-OH D levels <10.0 ng/mL as very deficient with impaired bone mineralization (rickets/osteomalacia), <20 ng/mL as deficiency, 20–29 ng/mL as insufficiency, and above 30 ng/mL vitamin D as normal

Table 3 Similar 25-OH vitamin D levels in PSC subjects with and without other risk factors and concomitant medications

Variables	N ^a	Mean (ng/mL)	P-value	Standard deviation
Smoker PSCs	32	23	0.23	11
Non-smoker PSCs	133	25		11
PSC taking topical steroids	23	23	0.30	10
PSC not taking topical steroids	152	24		11
PSC taking Ca ²⁺ channel blockers	31	23	0.27	10
PSC not taking Ca ²⁺ channel blockers	141	24		11
With one or more risk factors	74	23	0.06	11
Without one or more risk factors	90	25		11

Notes: ^aN<175 total. Information on all variables not available or not collected for all PSC subjects. Some patients declined to share their past medical histories or their current medications.

Abbreviation: PSC, posterior subcapsular cataract.

Table 4 Linear regression analysis of additional covariates associated with vitamin D levels in PSC subjects

25-OH D ₃ variable ^a	Coefficient of variation	Standard error	t-test value	P-value	95% confidence interval	
Constant	14.70876	4.834603	3.04	0.003	5.162234	24.25529
Age	0.1325422	0.0748039	1.77	0.078	-0.0151675	0.2802519
Sex	3.384471	1.651817	2.05	0.042	0.1227512	6.64619
Autoimmunity	-5.876174	1.631045	-3.60	<0.001	-9.096875	2.655473
Hypertension	-3.978292	1.548215	-2.57	0.011	-7.035436	0.921148
Non-skin cancer	5.08325	2.091757	2.43	0.016	0.952815	9.213685
Antidepressant use	2.734565	1.626064	1.68	0.095	-0.4763008	5.945432

Notes: ^aExplanatory variables used in the regression include age expressed as a continuous variable expressed in the number of years; all others expressed as dummy variable that takes the value 1 if patient sex is male and 0 if female; or 1 with disease or medication characteristic or 0 without characteristic.

Abbreviation: PSC, posterior subcapsular cataract.

serum levels. The Institute of Medicine recently revised the Recommended Dietary Allowances of vitamin D in order to maintain serum 25-OH D at or above 50 nM (20 ng/mL) to sustain bone density and calcium absorption and minimize the risk of osteomalacia and rickets.²³ But because vitamin D insufficiency seems to be associated with a number of adverse health effects, scientists and health professionals are advocating increasing vitamin D status to above 75 nM (30 ng/mL) 25-OH D.²⁴ Furthermore in a large cohort study, the association of serum 25-OH D levels with all-cause mortality was shown to be a nonlinear inverse association with risk increasing slightly at 25-OH D concentrations, <75 nM (30 ng/mL) and was most strongly increased in subjects with vitamin D deficiency.²⁵ In this series, the mean 25-OH D level for many more PSC patients was below this value (Figure 1).

Vitamin D is the chief regulator of systemic calcium as well as calcium levels in the serum and aqueous humor. Serum levels of vitamin D are negatively ($P<0.01$) correlated with parathyroid (PTH). There is a stable plateau for serum PTH levels as long as serum 25-OH D levels remain above 31 ng/mL, but increase when 25-OH D levels drop below 31 ng/mL.²⁶ Historic observations also suggest that PSC can be associated with PTH disorders.^{27,28} Disruption of calcium homeostasis in the lens has been shown experimentally to produce lens opacification via several mechanisms, including lens protein aggregation, enhanced migration of lens epithelial cells (LECs) onto the posterior capsule, abnormal differentiation of LECs into fibrocytes, lens fiber gap junction uncoupling, and loss of activity of calcium channels.^{29,30} Paradoxically, both hypocalcemia

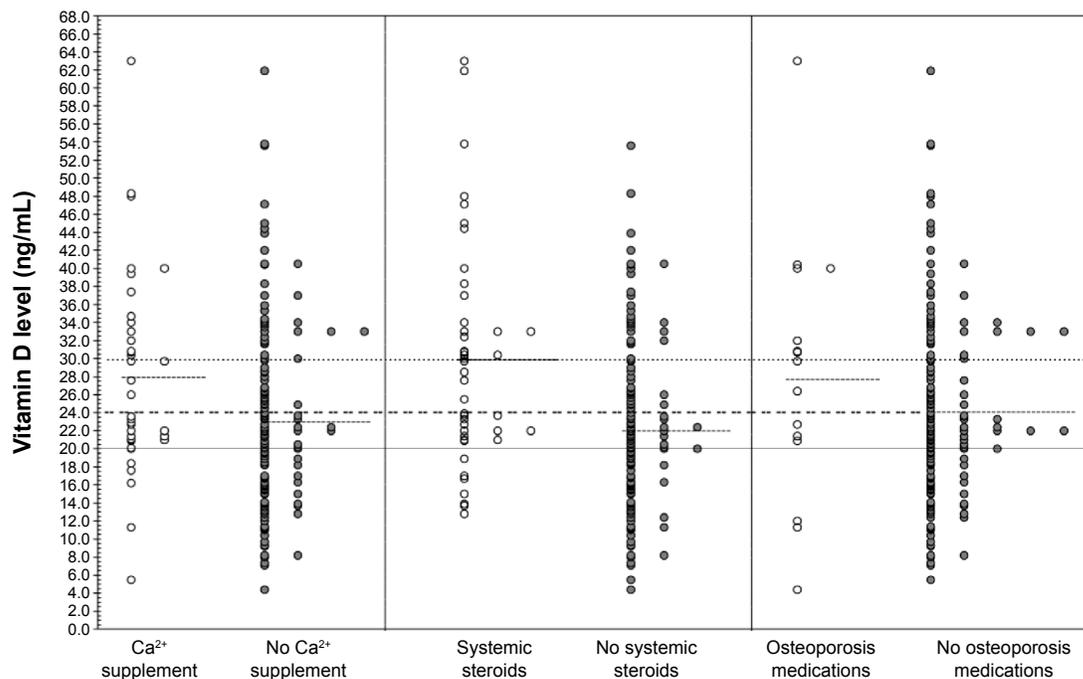


Figure 1 Individual PSC patient serum 25-OH D₃ levels and associated concomitant medications.

Notes: - - - - - Mean vitamin D₃ level, overall for 175 patients (24 ng/mL). ----- Individual subgroup means vitamin D₃ levels. Ca²⁺ supplements vs no Ca²⁺ supplements ($P=0.01$) and systemic steroids vs no systemic steroids ($P<0.001$). Vitamin D insufficiency/deficiency level, Heaney and Holick recommendation²⁴ (<30 ng/mL). Vitamin D insufficiency/deficiency level, Institute of Medicine recommendation^{18,23} (<20–12 ng/mL).

Abbreviation: PSC, posterior subcapsular cataract.

and hypercalcemia have been observed in association with experimental cataract models and in other forms of human cataract.³¹ It is possible that causative factors for PSC cataracts fall into a bimodal distribution pattern for vitamin D levels, where one class of PSC cataracts develops in subjects with 25-OH D levels above 28–32 ng/mL and the other in subjects with lower levels. The group with levels below 28–32 ng/mL may have no other known risk factors for PCS except systemic hypocalcemia/low aqueous calcium. The group above ~30 ng/mL may have known risk factors such as systemic steroid exposure, use of calcium supplements, or a need for osteoporosis medications.

PSC patients in the series reported here who were or had been using systemic steroids (but not topical steroids) showed a mean level of 25-OH D of 30 ng/mL, significantly higher than PSC subjects without systemic steroid exposure whose mean level was 22 ng/mL (Table 2 and Figure 1). Several studies have noted the association between the use of inhaled or oral corticosteroids and the long-term cataract risk.³² Several cataractogenic mechanisms of action have been suggested for steroids, including modulation of LEC migration³³ and downregulation of LEC fibroblast growth factor receptor and β -crystallin protein.³² LECs exhibit a steroid-binding membrane protein whose activities are mediated in part by calcium.³⁴ Administration of a calcium-containing compound can reverse the cataract-inducing activity of steroids in an animal model.³⁵ The failure to find an association between vitamin D levels in individuals with PSC, and comorbidities such as asthma and chronic obstructive pulmonary disease where steroid use would be expected, may be a result of their use of other management medications, insufficient duration of steroid use, or just a sample size limitation. The involvement of calcium signaling in PSC formation appears complex, given that individuals taking calcium supplements and osteoporosis medications appeared to have higher 25-OH D levels despite PSC formation. In the instance of patients on Ca^{2+} supplements, usually for incipient osteopenia or a diagnosis of osteoporosis, these supplements often include vitamin D in the formulation contributing to their elevated 25-OH D level. It has been shown that as long as vitamin D levels are adequate, calcium intake need be no higher than 800 mg/day³⁶ for osteoporosis. Those taking calcium channel blockers had similar levels of vitamin D to those not using these medications. Because Ca^{2+} channel blockers are prescribed for hypertension, also not strongly correlated with vitamin D deficiency, this may also not be unexpected.

In the early stage of ASC and PSC, vitamin D deficiency affects the calcium metabolism of the LEC, causing cell junctions to separate and creating cystic vacuoles that are visible

as water cleft cysts. With time, the lens tissue becomes cloudy and distorted with calcium deposition; microscopically, the clear LECs turn into cloudy fibrocytes, eventually breaking down and depositing Ca^{2+} on the capsule forming white lens retrodots.³⁷ In five patients in this series with evidence of early axial subcapsular water cleft cysts,³⁸ their lenses unexpectedly normalized after taking 5,000 IU of vitamin D_3 taken to treat their low vitamin D level.

Although 25-OH D is available in the human diet, it can also be synthesized from ultraviolet irradiation of 7-dehydrocholesterol, a precursor present in mammalian skin. Following cutaneous production or intestinal absorption from nutritional sources, it is metabolized to 25-OH D_3 in the liver by cytochrome P450 (CYP) 27A1. CYP27B1 in the kidney then converts this compound to the physiologically active hormone, $1\alpha,25$ -dihydroxyvitamin D (calcitriol).³⁹ Calcitriol binds to the intracellular vitamin D receptor (VDR), which heterodimerizes with retinoic X receptor and binds DNA. The protein transcription thus initiated regulates calcium metabolism. The gene for VDR has variant polymorphisms in a fraction of American population with various diseases.⁴⁰ Patients with the E420A mutant form of VDR are known to have vitamin D-resistant rickets, requiring vitamin D supplementation at doses up to 100,000 IU daily to maintain adequate blood levels.⁴¹ It is suspected that less severe forms of VDR impairment make it harder for some individuals to maintain adequate vitamin D_3 levels without supplementation. It is hoped that with increasing and inexpensive gene testing methods, other haplotype VDR variations may be characterized to help identify patients who could benefit from additional vitamin D supplementation and thereby reduce their risk of PSC cataract formation and other allied disorders.

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Disclosure

The authors report no conflicts of interest in this work.

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