Risk Factors For Posterior Vitreous Detachment: A Case-Control Study

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• PURPOSE: To identify possible risk factors for the development of posterior vitreous detachment (PVD).
• DESIGN: Retrospective case-control study.
• METHODS: A total of 138 cases with PVD and 114 age-matched controls were accrued from two different sites. Demographic, medical, ocular, and lifestyle data were obtained through chart review, questionnaires, and clinical examination. A 108-item semiquantitative food frequency questionnaire was also used to estimate macro- and micronutrient intake. Univariate and multivariate regression analyses were employed to identify variables significantly associated with the main outcome measure of PVD. Subgroup analysis of gender-specific variables was performed.
• RESULTS: Among all patients, multivariate regression analysis demonstrated female gender (odds ratio [OR] = 2.01, $P = .016$), myopic refraction (OR = 4.32, $P < .0005$), and higher intake of vitamin B6 (OR = 2.61, $P = .001$) to be associated with PVD after controlling for age. In the subgroup analysis of women, menopause (OR = 18.2, $P < .0005$), myopic refraction (OR = 3.42, $P = .01$), and higher intake of vitamin B6 (OR = 3.92, $P = .005$) were associated with PVD. Specifically, there was a significant association between vitamin B6 and PVD amongst premenopausal women but not amongst postmenopausal women.
• CONCLUSIONS: An association between PVD and menopause has not been documented previously. We suspect that high estrogen levels seen in premenopausal women may be protective against PVD and that hormonal changes associated with menopause may lead to changes in the vitreous, predisposing to PVD. Higher levels of intake of vitamin B6 were also associated with the development of PVD in premenopausal women possibly through an anti-estrogen effect. These findings should be investigated further with prospective studies. (Am J Ophthalmol 2006;142:931–937. © 2006 by Elsevier Inc. All rights reserved.)

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POSTERIOR VITREOUS DETACHMENT (PVD) IS A RELATIVELY common occurrence wherein the vitreous cortex physically separates from the internal limiting lamina (ILL) of the retina. Complications following PVD include retinal tears,[1] rhegmatogenous and tractional retinal detachments,[2,3] macular holes,[4] and epiretinal membrane formation. The incidence of retinal complications in symptomatic PVD can be as high as 24%.[5–7]

Despite its serious complications, only a limited group of risk factors have been evaluated with respect to the development of PVD. Age,[8] gender,[9–12] myopia,[13] ethnic background,[14] and retinitis pigmentosa[15] have been studied. Of these, increased age, female gender, and myopia have been associated with PVD. Systemic factors, such as diet and hormonal influences, have not been investigated in the context of PVD.

A better understanding of risk factors for PVD is needed to define the population most at risk of developing this condition and its subsequent retinal complications. The purpose of this current case-control study was to broadly investigate demographic, systemic, lifestyle, and dietary risk factors for PVD.

METHODS

• SELECTION OF CASES AND CONTROLS: Participants were selected from patients attending two referral-based retinal practices: (1) at the University of British Columbia/Vancouver General Hospital Eye Care Centre in Vancouver, Canada and (2) at the Royal Bournemouth Hospital,

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Bournemouth, United Kingdom. Subjects were enrolled between January 2001 and August 2002. Prior to beginning this study, the protocol was approved by the University of British Columbia and Vancouver General Hospital Ethics Committees.

All patients with acute PVD presenting to the study centers within the enrolment period were eligible to be cases in the study and were offered participation. The presence of acute PVD was diagnosed in all patients using 90 diopters (D) biomicroscopy and B-scan ultrasonography. Participants had to be 35 years of age or older. Exclusion criteria included a history or physical findings consistent with prior PVD, retinal detachment, retinal tear, or macular hole in either eye. Patients with acute symptoms who were thought to have anomalous PVDs, defined as PVD in the setting of underlying ocular pathology such as intraocular inflammation, trauma, or hereditary vitreo-retinopathy, were excluded. Individuals who presented with acute retinal pathology because of a new PVD were included.

Control subjects were selected randomly using a computer-generated random number table and enrolled concurrently with cases from the same referral-based retina practices in Vancouver and Bournemouth. An eligible age-matched (within five years) control was identified from the same center for every case enrolled in the study. If this control declined to participate, a second eligible age-matched control was contacted; however, no further participants were identified if the second control declined participation. Eligible controls were ≥35 years of age and with no known PVD, retinal tears, retinal detachment or macular hole formation in either eye at the time of enrolment. They were approached by one of the authors (J.Y.C., T.Y.Y.L., J.D.R., S.P.M.) in clinic or contacted by a letter detailing the nature of the study. The lack of PVD in the participants was confirmed with 90 D biomicroscopy and B-scan ultrasonography at the time of enrollment. Sample size was calculated roughly for a risk factor present in 40% of cases to detect an odds ratio (OR) of greater than 2.5, with a power of 90% and an alpha of 0.05. Assuming that cases would be easier to recruit than controls, we determined that 125 cases and 100 controls were needed to detect this difference. Sample size calculation did not consider the issue of multiple comparisons.

• **DATA COLLECTION:** An eye examination, clinical medical record review, and self-administered questionnaires provided data on possible risk factors for PVD. The main study questionnaire investigated a wide-range of potential risk factors including demographics, ocular history, medical history, and lifestyle factors (sunlight exposure, occupation, and education). Medical history information specifically pertaining to men (for example, history of prostate disease or related medication) and women (for example, number of children, menopause status, oral contraceptive use, and hormone replacement therapy) was also assessed. The food frequency questionnaire (FFQ) was a 108-item semiquantitative instrument that included portion size estimates as well as frequency, strength, brand, and type of supplements.[16] Subjects were asked to indicate the average frequency of consumption for each food item over the past year. Each food item was specified in a standardized portion size. This FFQ has been shown previously to be reliable amongst a population of patients with eye disease.[16]

• **STATISTICAL ANALYSIS:** Data analysis was performed using SPSS™ statistical program, Chicago, Illinois, USA (Version 10.0 for Windows). Demographic, medical, ocular, and lifestyle variables were reported as means or proportions for both cases and controls. Univariate analyses (Student *t* test and Chi-square test) were used to investigate the association between these variables and PVD. Dietary factors were recorded as continuous variables but were analyzed as categorical data (quartiles) to minimize the effect of possible outlying data points. For the analysis, ORs are presented for significant factors comparing the highest quartile of the nutrient to the lowest quartile of the nutrient. ORs were reported for associations that showed a trend towards statistical significance (defined in our analysis as $P < .05$) or statistical significance (defined in our analysis as $P < .01$). These cut-off values are liberal but were chosen in order to minimize the chance of missing a possible trend in this exploratory study.

In order to investigate possible associations with PVD simultaneously, a logistic regression analysis with backwards selection was employed with a cut-off value for exclusion of $P = .05$. Only variables that showed a trend towards significance or reached statistical significance in the univariate analysis ($P < .05$) were entered into the multivariate analysis. Age was forced into the model as it is known to be highly associated with PVD and is the strongest epidemiological predictor of visual health. Since the study was performed in patients from two different countries, we also controlled for site in the regression analyses. In addition, subgroup analyses for both men and women were analyzed separately using the gender specific variables that were collected. Dietary factors were entered into the multivariate analysis as dichotomous variables (high vs low, based on median levels). The regression analyses were performed initially using single variables only and then repeated including two-way interaction terms as possible variables in the analysis—one interaction term at a time.

RESULTS

IN TOTAL, 138 CASES AND 114 CONTROLS WERE ENROLLED in the study over the 18-month study period. The participation rate was 72.5% for cases and 46.9% for controls. Most patients cited the length of the questionnaire as the

TABLE 1. Demographic Data and Risk of Posterior Vitreous Detachment

Variable Continuous	Patients with PVD Mean	Controls Mean	Difference	*P* Value	Total Sample
Age	61.7	61.8	0.1 years	.999	252
Categorical	No. (%)	No. (%)	Odds Ratio (95% Confidence Interval)	*P* Value	Total Sample
Gender					252
Female	85 (61.6)	50 (43.9)	2.05 (1.24–3.40)	.005	
Ethnicity					242
Chinese	19 (14.3)	19 (17.4)	0.78 (0.37–1.67)	.922	
Caucasian	107 (80.5)	85 (78.0)	1.16 (0.59–2.27)	.781	
Other	7 (5.3)	5 (4.6)	0.86 (0.23–3.15)	.788	
Education					241
<Grade 12	16 (12.1)	23 (21.1)	N/A	baseline	
Grade 12	31 (23.5)	29 (26.6)	0.68 (0.27–1.59)	.301	
Technical school	18 (13.6)	14 (12.8)	0.82 (0.19–1.55)	.203	
Post-secondary degree	67 (50.8)	43 (39.4)	2.24 (0.99–5.05)	.034	

PVD = posterior vitreous detachment; N/A = not applicable.

reason for not wanting to be involved in the study. Two hundred and three participants [117 cases (57.6%) and 87 (42.4%) controls] were accrued from the Vancouver site and the remaining 49 [28 cases (57.1%) and 21 (42.9%) controls] were accrued from the United Kingdom site. Of the initial participants, 135 cases (98%) and 107 controls (94%) agreed to participate in the food questionnaire portion of the study. Not all participants answered every question in the study; however, for each individual question, the response rate was over 85%.

Participants from the Canadian and European study sites were generally similar other than a small difference in age, with the patients from the European site being slightly older (64.7 years vs 60.8 years; $P = .042$) than the patients from the Canadian site. Specifically, there was no significant difference between the sites with respect to gender, education level, or proportion of patients with myopia. Presenting medical diagnoses for controls were age-related macular degeneration (17.5%), diabetic retinopathy (13.4%), retinal vascular disease (14.4%), other retinopathies or maculopathies (21.1%), and other nonretinal problems (33.5%).

The average age of participants was 61.7 years and 135 (53.6%) were female. Although various ethnicities were present, most of the participants were (76.2%) Caucasian and (15.1%) were Chinese. Table 1 shows the demographic characteristics of both cases and controls along with univariate analyses. Female gender was associated with an increased risk of PVD (OR = 2.05; 95% confidence interval [CI] = 1.24 to 3.4; $P = .005$). Completion of a postsecondary degree showed a trend toward an association with PVD (OR = 2.24; 95% CI = 0.99 to 5.05, $P = .034$). We did not demonstrate an association between ethnicity and PVD.

Table 2 shows the medical and ophthalmic-specific characteristics of both cases and controls along with univariate analyses. Control subjects were more likely to have a history of stroke (OR = 0.11; 95% CI = 0.01 to 0.92, $P = .025$) and diabetes mellitus (OR = 0.10; 95% CI = 0.02 to 0.37, $P < .0005$). Myopic patients were over three times more likely to have PVD compared with controls (OR = 3.21; 95% CI = 1.93 to 5.7, $P < .0005$). PVD was not associated with a medical history significant for cataract surgery, glaucoma surgery, strabismus surgery, other ocular surgery, or past ocular trauma (not shown in the Tables).

Working outdoors was associated with a decreased risk of PVD (OR = 0.36; 95% CI = 0.13 to 1.06, $P = .002$). In addition, there was a trend towards an association between vigorous exercise of more than nine hours per week and less chance of PVD (OR = 0.33; 95% CI = 0.17 to 0.91, $P = .022$). There was no association found between PVD and estimated sunlight exposure, cigarette smoking, or alcohol consumption (not shown in the Tables). A subgroup analysis of factors pertaining to women only showed that 85% of cases were postmenopausal compared to only 54% of controls (total: n = 124). Thus, menopause was significantly associated with PVD among women participants (OR = 4.62; 95% CI = 2.0 to 13.81, $P < .0005$). In addition, the following factors were not found to be associated with PVD: number of total pregnancies, use of oral contraceptive pills, use of hormone replacement, age at menarche, age at first pregnancy, history of oophorectomy, history of hysterectomy, history of breast cancer, and the use of breast cancer drugs (tamoxifen, toremifene, anastrozole, letrozole, and aminoglutethimide). Subgroup analysis for men showed no

TABLE 2. General Medical and Ocular History and Risk of Posterior Vitreous Detachment-Univariate Analysis

Variable	Patients with PVD No. (%)	Controls No. (%)	Odds Ratio	*P* Value	Total Sample
Medical History					
Hypertension	44 (31.9)	46 (40.7)	0.68 (0.39–1.18)	.186	251
Hypercholesterolemia	34 (24.6)	27 (24.1)	1.02 (0.55–1.92)	1.00	250
Myocardial infarction	8 (5.8)	2 (1.8)	3.44 (1.07–23.9)	.119	250
Stroke	1 (0.7)	7 (6.2)	0.11 (0.01–0.92)	.025	250
Angina	8 (5.8)	5 (4.4)	1.45 (0.41–5.29)	.777	250
Diabetes mellitus	3 (2.3)	21 (18.8)	0.10 (0.02–0.37)	<.0005	245
Osteoporosis	8 (6.0)	5 (4.6)	1.32 (0.38–4.81)	.635	243
Rheumatoid arthritis	13 (9.8)	7 (6.4)	1.57 (0.56–4.57)	.282	242
Osteoarthritis	32 (24.1)	24 (22.0)	1.12 (0.59–2.14)	.761	242
Ophthalmic History					
Myopic prescription	90 (67.7)	43 (39.4)	3.21 (1.93–5.70)	<.0005	242
Family history of myopia	97 (77.6)	67 (63.8)	1.96 (1.03–3.03)	.028	230
History of cataract surgery	24 (18.6)	20 (18.2)	1.03 (0.54–1.94)	.999	239

PVD = posterior vitreous detachment.

TABLE 3. Association Between Micronutrients and Posterior Vitreous Detachment-Univariate Analysis

	Mean Nutrient Level				
Micronutrients	Cases PVD	Controls	Odds Ratio*	*P* Value†	Total Sample
Vitamin A	25,569 IU	21,028 IU	1.46 (0.64–3.07)	.653	242
Vitamin C	450 mg	415 mg	2.14 (0.95–4.67)	.154	242
Vitamin B6	7.4 mg	5.2 mg	1.94 (0.87–4.41)	.002	242
Vitamin D	384 IU	304 IU	1.52 (0.68–3.43	.035	242
Iron	28 mg	27 mg	0.81 (0.36–1.80)	.408	242
Calcium	1,034 mg	918 mg	1.72 (0.78–3.76)	.201	242
Vitamin B1	5.7 mg	4.1 mg	1.71 (0.76–3.86)	.005	242
Vitamin B2	6.1 mg	4.7 mg	1.81 (0.81–4.21)	.052	242
Niacin	33 mg	27 mg	2.28 (1.02–5.13)	.030	242
Vitamin B12	19 mcg	14 mcg	2.42 (1.09–5.44)	.074	242
Vitamin E	238 IU	211 IU	2.28 (1.02–5.13)	.155	242

PVD = posterior vitreous detachment; IU = international unit; mcg = microgram; mg = milligram.
*odds ratio of highest quartile of nutrient compared vs lowest quartile as baseline.
†based on Chi-squared statistical test using quartiles for trend.

significant associations with PVD. Specifically, history of benign prostate hypertrophy, prostate cancer, use of medication to treat these conditions, and use of testosterone replacement therapy were not associated with PVD.

Table 3 shows a comparison of the mean dietary factors for both cases and controls. There was no association between PVD and levels of macronutrients. Cases of PVD had higher absolute values for all micronutrients. Higher levels of intake of vitamin B6 ($P = .002$) and vitamin B1 ($P = .005$) were associated with a statistically significant higher risk of PVD in univariate analysis. Vitamin D ($P = .035$) and niacin ($P = .03$) showed a trend towards increased risk of PVD. Six percent of all subjects were taking glucosamine supplementation and 21% were taking beta-carotene supplementation. There was no significant association between supplementation with glucosamine ($P = .94$) or beta-carotene ($P = .14$) and the development of PVD.

Table 4 shows the results of the logistic regression analysis with backwards selection using all significant variables from the univariate analyses as potential variables in the model. Again, in each model, age and study site were controlled. After controlling gender, myopic refraction (OR = 4.43; 95% CI = 1.13 to 3.57, $P < .0005$) and high vitamin B6 intake (OR = 2.52; 95% CI = 1.40 to 4.53, $P = .002$) were associated with increased risk of PVD in all patients (model 1). No interaction terms were significant when all patients were analyzed together. Subgroup analysis of women only (model 2) showed menopause (OR = 18.9; 95% CI = 4.96 to 72.4, $P < .0002$),

TABLE 4. Risk Factors for Posterior Vitreous Detachment-Logistic Regression Analysis With Backwards Selection*

Variable	Odds Ratio (for PVD)	*P* value	Total Sample
No Interaction Terms			
Model 1: All Participants			232
Female gender	2.01 (1.13–3.57)	.017	
Myopic prescription	4.43 (2.37–8.28)	<.0005	
Vitamin B6 (high vs low)	2.52 (1.40–4.53)	.002	
Model 2: Women Only			115
Menopause	18.9 (4.96–72.4)	<.0005	
Myopic prescription	3.39 (1.3–8.7)	.012	
Vitamin B6 (high vs low)	3.60 (1.37–9.45)	.009	
Interaction Terms in Model			
Model 3: Women Only			
Menopause	3260 (16.2–344,000)	.002	115
Myopic prescription	3.44 (1.29–9.21)	.014	
Vitamin B6 (high vs low)	29.6 (2.72–322.6)	.005	
Vitamin B6 × menopause (interaction)	0.06 (0.004–0.84)	.037	

PVD = posterior vitreous detachment.
*controlling for age and study site.

and high levels of vitamin B6 intake (OR = 3.60; 95% CI = 1.37 to 9.45, P = .009) were associated with increased risk of PVD after controlling for age and myopia. When interaction terms were entered into the subgroup analysis for women (model 3), a significant inverse interaction between level of vitamin B6 intake and menopause was evident (OR = 0.06; 95% CI = 0.004 to 0.84, P = .037) in addition to the consistent association between PVD and menopause, myopic prescription, and high intake of vitamin B6.

DISCUSSION

IN THIS STUDY, WE FOUND A TWO-FOLD INCREASE IN RISK of PVD among women and three- to fourfold increase in risk of PVD amongst participants with myopic refraction. These results are consistent with previously published research.[10–13] We could not examine the previously reported relationship between age and PVD since our controls were age-matched to cases. We documented a strong and consistent association between PVD and a history of menopause and high intake of vitamin B6, independent of the influence of age and myopia. The association between PVD and menopause suggests that menopause may be driving the association between gender and PVD, a notion which was previously suggested by Sebag.[17] Interestingly, there is also evidence for the role of sudden hormonal changes in menopause in idiopathic macular holes,[18] a (female) gender-related[19–21] condition associated with perifoveal vitreous detachment and PVD.[4,22,23] It is possible that the vitreous collagen or the vitreoretinal interface may be influenced by perimenopausal hormonal changes. This hypothesis is supported by findings that the synthesis and metabolism of glycosaminoglycans can be affected by sex hormones.[24,25] In animal studies, glycosaminoglycan levels in the aorta were directly correlated with blood concentrations of estrogen.[26,27] Variation in the concentration of hyaluronic acid in rabbit vitreous was also observed following hormonal treatment.[28] The fact that we did not demonstrate an association between PVD and the length of exposure to sex hormones in our female subjects suggests that it may be the relative presence or absence of such hormones in the body at a given time, rather than the cumulative exposure in a lifetime, that affects the development of PVD. One may further hypothesize that there are hormone receptors in the vitreous that help modulate the vitreal integrity with hormonal stimulation. Although there is data suggesting that the decrease in estrogen after menopause is a risk for cataract formation and age-related macular degeneration,[29,30] the role of hormones in the maintenance of the vitreoretinal junction in humans has yet to be clarified.

The association between vitamin B6 and risk of PVD may also be explained by examining hormonal effects. Vitamin B6 is a water-soluble vitamin that is essential for normal growth and development.[31] It has long been known to serve as an obligatory cofactor for more than 100 enzymes involved in protein metabolism,[32] lipid metabolism,[33] neurotransmitter production,[34] and immune function.[35] There are six forms of vitamin B6, including pyridoxal 5′-phosphate (PLP). Steroid hormones, such as progestins, estrogens, and androgens, bind to nuclear steroid hormone receptors, forming DNA-binding hormone-receptor complexes that alter cell transcription to regulate physiologic functions in the body.[36] PLP is known to inhibit the association of progesterone,[37] estrogen,[38] and androgen[39] receptors with DNA through direct interaction

with steroid receptors. Furthermore, it has been shown that estrogen- and progesterone-induced cellular activity is suppressed under conditions that elevate intracellular PLP concentration.[40] Consequently, it has been proposed that vitamin B6 may play a role in disease processes affected by steroid hormones such as breast and prostate cancer.[41–43] We propose the possibility that high levels of vitamin B6 reduce the effect of estrogen on its cellular receptor; if estrogen were protective against PVD, then high levels of vitamin B6 would increase the risk of PVD through its hormonal effects.

This hypothesis can be further explained by examining model 3 in our multivariate analysis where interaction terms were used in the subgroup analysis of women. There was a significant inverse interaction between vitamin B6 and menopause. In other words, the association between vitamin B6 and PVD was different, depending on whether or not a patient was pre- or postmenopausal. To help clarify this issue, we analyzed the association between vitamin B6 and PVD separately for both premenopausal and postmenopausal women. Among premenopausal women, there was a significant association between vitamin B6 and PVD (OR = 20.2, $P = .011$) after controlling for age and refraction. However, vitamin B6 was not associated with increased risk of PVD ($P = .186$) among postmenopausal women. This may explain the possibility that high levels of vitamin B6 intake may decrease the protective actions of estrogen in premenopausal women, leading to a higher risk of PVD. However, vitamin B6 has no effect in postmenopausal women who have already lost the protective effect of higher estrogen levels.

Our results show an association between diabetes mellitus and decreased rate of PVD. This is likely attributable to a selection bias whereby controls were selected from patients who did not have PVD attending retinal practices and were, therefore, much more likely to be attending for a diabetic retinopathy check (13% of controls). The study demonstrated a trend between PVD and outdoor work, less vigorous physical exercise, no history of stroke, and increased dietary intake of vitamin D and niacin. However, the P values for these associations were not highly significant ($P > .01$) and each of these variables fell out of the multivariate analysis. Therefore, considering the number of multiple comparisons made in the univariate analyses, we believe that these associations are attributable to chance and not indicative of a true association. Our results also showed a univariate association between vitamin B1 and increased risk of PVD. However, vitamin B1 was not a significant predictor of PVD in any multivariate analysis. Consequently, we believe that this association was because of colinearity between the B vitamins.

There are a number of limitations to this study that must be addressed. First, it employs an observational case-control design and, as such, includes the potential for recall bias, although this should not be different for cases or controls. Secondly, some of the questions regarding lifestyle are based in the present tense (such as physical activity level) and, thus, the temporality of such associations with PVD cannot be assured. Third, we did not have specific hypotheses a priori, and we investigated many variables for their potential relationship to PVD. This has led to multiple comparisons and a higher likelihood of alpha-error (accepting an observed difference when there is truly no difference). Despite these downfalls, we believe that the main results from this study are valid. The association between PVD and menopause was highly significant ($P < .0005$), not subject to recall bias or temporality limitations, and was consistent throughout the various analyses performed. The association between PVD and high vitamin B6 was also highly significant ($P \leq .005$), of large magnitude (OR between 2.6 and 34.8), and consistent throughout the different multivariate models. Although these associations were highly significant, any definitive cause and effect cannot be concluded. Finally, our results confirmed associations between PVD and gender and myopia as previously shown in the literature.

In summary, we found that higher dietary intake of vitamin B6 was associated with an increased risk of PVD and that among women, menopause was a risk factor for development of PVD. In addition, there was an interaction between vitamin B6 intake and menopause whereby the association between high vitamin B6 levels and PVD was very high among premenopausal women and insignificant among postmenopausal women. These results may be explained through hormonal processes that are not completely understood. Further research including replicating these results with a prospective design and study into potential biological mechanisms is warranted.

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Biosketch

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