Vitamin D Deficiency Is Associated With Retinopathy in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE—To examine the hypothesis that vitamin D deficiency (VDD) is associated with an increased prevalence of microvascular complications in young people with type 1 diabetes.

RESEARCH DESIGN AND METHODS—In a cross-sectional study of 517 patients, 25-hydroxyvitamin D was measured. Retinopathy was assessed by 7-field stereoscopic retinal photography, peripheral neuropathy by thermal and vibration threshold testing, and microalbuminuria by albumin excretion rate or albumin-to-creatinine ratio.

RESULTS—Retinopathy prevalence was higher in cases with VDD versus sufficiency (18 vs. 9%, $P = 0.02$); deficiency was not associated with microalbuminuria or neuropathy. In logistic regression, retinopathy was associated with VDD (odds ratio 2.12 [95% CI 1.03–4.33]), diabetes duration (1.13, 1.05–1.23), and HbA_{1c} (1.24, 1.02–1.50).

CONCLUSIONS—VDD is associated with an increased prevalence of retinopathy in young people with type 1 diabetes. The inflammatory and angiogenic effects of VDD may contribute to early retinal vascular damage; however, further investigations are warranted.

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Vitamin D deficiency (VDD) has been implicated in the development of diabetes complications based on studies in mice, cell cultures, and adults with diabetes (1–6). Vitamin D may confer protection via inhibition of inflammation, downregulation of the renin-angiotensin system, improved insulin secretion, and an antiproliferative effect on endothelial cells (1). In a mouse model of ischemic retinopathy, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] inhibited retinal neovascularization (5), while in cell culture it inhibited endothelial cell proliferation (6). The severity of diabetic retinopathy was inversely related to serum $1,25(OH)_2D_3$ levels in adults with type 2 diabetes (2). However there are no studies examining vitamin D and complications in young people. We examined the hypothesis that vitamin D deficiency is associated with microvascular complications in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

—This was a cross-sectional study of 517 adolescents aged 8–20 years attending the Diabetes Complications Assessment Service (DCAS) at the Children's Hospital at Westmead, Westmead, Australia, from 2009 to 2010. The study received ethical approval from the Children's Hospital at Westmead.

Retinopathy was assessed using 7-field stereoscopic fundal photography and defined as at least one microaneurysm or hemorrhage (7). Neuropathy in the foot was assessed by thermal threshold and vibration threshold testing (NeuroSensory TSA-II and Vibratory Sensory Analyzer; Medoc Ltd., Ramat Yishai, Israel). Presence of peripheral neuropathy was determined using published data on thermal perception testing in children and adolescents using the same equipment (8). Microalbuminuria was assessed, as previously described (7). Elevated albumin excretion rate/albumin-to-creatinine ratio (AER/ACR) was defined as AER $\geq$7.5 μg/min in at least 2/3 overnight urines or a mean ACR $\geq$1.0 mg/mmol (males) and $\geq$1.4 mg/mmol (females). The AER/ACR equivalent thresholds were derived from data on 7,170 adolescents with diabetes (T. Jones, Perth, Australia, personal communication).

Total 25-hydroxyvitamin D (25-OHD) was measured using the LIAISON analyzer (DiaSorin Inc., Stillwater, MN). Levels were seasonally adjusted using correction factors obtained from multiple linear regression of 550 samples from healthy children from Sydney, Australia; summer (−7.71), autumn (5.14), winter (5.03), spring (−2.46). VDD was defined as $\leq$50 nmol/L (9). Hemoglobin A_{1c} (HbA_{1c}) was measured using the Bio-Rad Diamat analyzer (Bio-Rad, Hercules, CA).

Individuals were classified as Caucasian/non-Caucasian using the Australian Bureau of Statistics (ABS) standards for classifying the ethnic and cultural composition of the Australian population (10). Socioeconomic status was determined by postcodes using the ABS Socio-Economic Indexes for Areas (10). Logistic regression was used to examine factors associated with complications (PASW, V18, IBM, Chicago, IL).

RESULTS

—Vitamin D levels were performed on 495/517 (96%) patients, with mean ± SD age 14.9 ± 2.4 years, diabetes duration 7.2 ± 3.5 years, and median HbA_{1c} 8.6 ± 1.5%. Mean ± SD 25-OHD level was 70.1 ± 23 nmol/L and 80/495 (16%) were deficient. Retinopathy was more common in young people with VDD compared with their sufficient counterparts (18 vs. 9%, $P = 0.02$), but there were no between-group differences for elevated AER/ACR, microalbuminuria, or peripheral nerve function. Sex, age, diabetes duration, BMI standard

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deviation score (SDS), systolic blood pressure (SBP) SDS, diastolic blood pressure (DBP) SDS, HbA_{1c}, cholesterol, insulin dose/weight, C-reactive protein, prevalence of celiac disease, and socioeconomic status also did not differ between groups. Factors associated with retinopathy, abnormal peripheral nerve function, and elevated AER/ACR are in Table 1.

CONCLUSIONS—This is the first study to our knowledge of young people with type 1 diabetes to demonstrate an association between VDD and diabetic retinopathy, independent of diabetes duration and HbA_{1c}. However, VDD was not associated with abnormal peripheral nerve function or elevated AER/ACR. We speculate that the angiogenic effect of VDD contributes to retinal vascular damage, whereas renal vessels and peripheral nerves may be less susceptible.

This novel association is supported by studies of adults with type 2 diabetes and more advanced retinopathy; $1,25(OH)_2D_3$ levels were inversely correlated with a higher grade of retinopathy (2), and lower 25-OHD levels were associated with proliferative retinopathy (3). The current finding suggests that VDD may have a permissive role in earlier stages of retinopathy.

Biological models support a causal role for VDD in proliferative retinopathy, which is characterized by neovascularization and angiogenesis. Higher serum $1,25(OH)_2D_3$ was associated with reduced angiogenesis in both a transgenic retinoblastoma model and ischemic retinopathy in mice (5,11). This may be explained by an interaction between vitamin D and vascular endothelial growth factor (VEGF); the addition of $1,25(OH)_2D_3$ reduced VEGF-induced proliferation in aortic endothelial cell culture (6).

The vitamin D receptor (VDR) is present in the human retina, and polymorphisms of VDR are related to retinopathy risk in type 1 diabetes. The *Fok 1* single nucleotide polymorphism of the VDR gene was associated with increased transcriptional activity of the VDR and less severe diabetic retinopathy (12), and individuals with the *TT* genotype of the VDR *Taq 1* polymorphism were less likely to have retinopathy (13). We did not examine genetic risk factors in our population; in future studies it would be valuable to examine the relationship between genes involved in vitamin D metabolism and retinopathy.

We cannot exclude the possibility that VDD is a confounder for other factors contributing to retinopathy. For example, VDD may mask the effect of ethnicity on retinopathy, given that lower vitamin D is associated with darker skin pigmentation and higher retinopathy rates are found in Hispanic, African American, and South Asian people (14). However, we found no relationship between ethnicity and retinopathy.

Because of the cross-sectional nature of this study, we cannot assume a causal relationship between VDD and retinopathy. Indeed, it is possible that VDD is a consequence of retinopathy because individuals with complications may be less mobile and have lower sun exposure. This is unlikely, however, because the study population consisted of adolescents who were otherwise well, and only early complications were detected. Although, this study is clinic-based, the individuals attending DCAS comprise approximately one-third of cases in the state of New South Wales (15).

In conclusion, this study demonstrates a novel association between VDD and retinopathy in children and adolescents with type 1 diabetes. This is supported by clinical, biological, and genetic data; however, prospective studies are required to validate this relationship and elucidate the underlying mechanisms.

Table 1—*Univariate and multivariate analysis of retinopathy, abnormal peripheral nerve function, and elevated AER or ACR in children and adolescents with type 1 diabetes*

	Univariate analysis			Multivariate model*		
Outcome	OR	95% CI	*P*	OR	95% CI	*P*
Retinopathy†						
Vitamin D (deficient)	2.29	1.11–4.70	0.02	2.12	1.04–4.33	0.04
Age	1.23	1.06–1.41	0.01			
Diabetes duration	1.12	1.03–1.22	0.01	1.13	1.05–1.23	<0.01
HbA_{1c}	1.25	1.04–1.50	0.02	1.24	1.02–1.50	0.03
Ethnicity (Caucasian)	0.63	0.33–1.19	0.15	—	—	—
BMI SDS	1.26	0.83–1.92	0.28	—	—	—
SBP SDS	1.26	0.87–1.80	0.22	—	—	—
DBP SDS	0.94	0.67–1.31	0.71	—	—	—
Elevated AER/ACR	1.04	0.46–2.36	0.92	—	—	—
Abnormal peripheral nerve function†						
Age	1.15	1.06–1.25	<0.01	1.13	1.04–1.24	0.01
Sex (male)	1.53	1.03–2.28	0.04	1.60	1.06–2.41	0.03
BMI SDS	1.40	1.07–1.84	0.01	1.46	1.11–1.92	0.01
SBP SDS	1.33	1.05–1.69	0.02	—	—	—
DBP SDS	1.25	1.01–1.55	0.04	—	—	—
Elevated AER/ACR†						
SBP SDS	1.33	1.02–1.73	0.04	1.34	1.03–1.74	0.03
HbA_{1c} (≥7.5)	1.95	1.02–3.73	0.04	—	—	—
Ethnicity (Caucasian)	0.59	0.37–0.94	0.03	0.59	0.37–0.94	0.03

*Multivariate logistic regression models for retinopathy used the subset of 495 (96%) patients that had 25-OHD levels performed. Variables with $P < 0.05$ in univariate analysis were included in the multivariate model. Because of significant collinearity between age and duration ($P < 0.001$), both variables were not included in the same model. The model containing duration was chosen because of goodness-of-fit and clinical relevance. †The 495 individuals with vitamin D levels were used in retinopathy analysis. The entire population of 517 was used in peripheral nerve function and elevated AER/ACR analysis.

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