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Retinal venular oxygen saturation is associated with non-proliferative diabetic retinopathy in young patients with type 1 diabetes

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ABSTRACT.

Purpose: **To determine the contribution of retinal vessel density (VD), central retinal vessel diameter and retinal oxygen (O_2) saturation independently of other known risk factors in the development of non-proliferative diabetic retinopathy (NPDR).**

Methods: **Macular optical coherence tomography angiography (OCTA), central retinal artery/vein equivalent diameter (CRAE/CRVE) measurements and retinal oximetry were performed in a cross-sectional study of 166 eyes from 166 individuals with type 1 diabetes (T1D) aged 14–30 years. Multiple logistic regression analysis was used to investigate whether O_2 saturation, retinal vessel diameters and vessel density in the deep capillary plexus (VD-DCP) were associated with NPDR, when adjusting for known risk factors. The individuals were allocated to one group without and one group with NPDR.**

Results: **Multiple logistic regression analysis showed that age (OR = 1.25, 95% CI: 1.04–1.49) and AV-difference in O_2 saturation (OR = 0.85, 95% CI 0.77–0.93) were significantly associated with NPDR.**

Conclusion: **Our findings suggest that age and lower AV-O_2 saturation difference contribute to explaining the grade of NPDR independently of other well-known risk factors. Reduced delivery of O_2 to the retinal tissue is associated with the development of NPDR in young patients with T1D and should be given appropriate weight in the risk stratification at early stages of the disease.**

Key words: retinal oximetry – retinal vessel oxygen saturation – diabetic retinopathy – type 1 diabetes – retinal vessel calibres – retinal microvasculature – OCT angiography

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Introduction

Diabetic retinopathy (DR) is a vision-threatening disease characterized by hypoxia, vascular alterations and oedema (Kohner, 1993). Oxygen (O_2) metabolism is involved in the development of DR (Hammer et al. 2009; Hardarson & Stefansson, 2012). New discoveries in retinal O_2 metabolism and vascular changes are essential to better understand the pathophysiology of DR. The O_2 saturation in larger retinal vessels is a marker of retinal metabolism and vascular function (Bek et al. 2019) and retinal O_2 saturation is controlled by autoregulation of the vessel diameters and blood flow (Pournaras et al. 2008). Vessel diameter has been shown in several studies to be associated with micro- and macrovascular complications in patients with diabetes mellitus (DM) (Klein et al. 2004; Grauslund et al. 2009; Miller et al. 2009; Ding et al. 2012; Broe et al. 2014; Drobnjak et al. 2017).

The Oslo Study (Dahl-Jørgensen et al. 1986) and the DCCT study (Nathan et al. 1993) demonstrated that intensive treatment of patients with type 1 diabetes (T1D) could prevent or at least delay retinopathy, nephropathy and neuropathy. The DCCT study also revealed that the total glycaemic exposure (the combined effect of diabetes duration and HbA1c)

only explained ~12% of the total variation in the risk of DR, which means that up to 88% must have been explained by other factors (1995; Lachin et al. 2008). Well-known risk factors such as DM duration, hyperglycaemia, obesity and hypertension do not sufficiently explain the risk of DR. Therefore, it is important to explore how much of the variation in DR can be explained by metabolic and vascular factors in the retina.

It has previously been shown that venular O_2 saturation increases and AV-O_2 saturation difference decreases with increasing severity of DR (Hammer et al. 2009; Jorgensen & Bek, 2014; Man et al. 2014; Man et al. 2015; Veiby, 2020) and vessel density in the deep capillary plexus (VD-DCP) as measured by macular Optical Coherence Tomography Angiography (OCTA) decreases with increasing level of non-proliferative diabetic retinopathy (NPDR) (Veiby et al. 2020).

Bek et al. found that venular O_2 saturation can explain the DR grade independently of other well-known risk factors, with proliferative DR (PDR) and clinically significant diabetic macular oedema (CSMO) as endpoints. The effect of venular O_2 saturation was of the same magnitude as that of the diabetes duration and HbA1c (Bek et al. 2019). We wanted to explore whether this is also valid in a younger population with type 1 diabetes with NPDR as endpoint, as well as include structural microvascular measures in the analysis.

This cross-sectional study aimed to determine if macular vessel density, retinal vessel diameters and retinal O_2 saturation is associated with the development of NPDR independently of known clinical risk factors. Furthermore, we aimed to determine how much each variable contributes, and to explore whether the ocular parameters covariate with the other clinical risk factors.

Materials and methods

Study design, population, eligibility criteria and ethics

This is a cross-sectional, case-control ophthalmological study performed in 2017–2019 as a part of the 10-year follow-up of the Norwegian Atherosclerosis and Childhood Diabetes (ACD) study, an ongoing prospective population-based study, initiated in 2006, with follow-up every fifth year. The ACD cohort consists of 329 individuals with childhood-onset T1D and 135 healthy controls of similar age and gender distribution. In this paper, we did not include the controls. At the baseline examination of the ACD study the T1D cohort was found to be representative of all children with T1D in Norway, as registered in the Norwegian Childhood Diabetes Registry (NCDR, www.oslodiabetes.no/ncdr). The details of the study inclusion process and examination have been described elsewhere (Margeirsdottir et al. 2010; Heier et al. 2015; Veiby, 2020). All the individuals enrolled in the ACD 10-year follow-up study were invited to participate in the present ophthalmological study at the Department of Ophthalmology, Oslo University Hospital, and 189 persons with T1D were willing and eligible to participate. The described research adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all individuals and their parents below the age of 18 years. Approval for all study-specific procedures was obtained by the appropriate Regional Committee for Medical and Health Research Ethics (Ref no. 2011/1818).

Clinical and ophthalmological examinations

All individuals were examined according to a study protocol (Margeirsdottir et al. 2010) that included diastolic (DBP) and systolic blood pressure (SBP), height, weight, waist circumference, fasting blood samples and urine samples. A questionnaire on medical history, family history of eye disease, iris colour and medication was conducted. Routine ophthalmological examination was undertaken including refraction and best corrected visual acuity (BCVA) (Early Treatment Diabetic Retinopathy Study, ETDRS, LogMAR) at 100 LUX (Hagner Model EC1), intraocular pressure (IOP) measured with Icare tonometer (ic100, Icare, Vantaa, Finland) followed by dilation of the pupils using Tropicamide 1% eye drops, only supplemented with Phenylephrine 10% when needed. Mean ocular perfusion pressure (MOPP) was calculated as 2/3(MABP – IOP) (Sehi et al. 2005). Slit-lamp examination with ophthalmoscopy, fundus photography including oximetry imaging (Topcon TRC-50DX, Japan) and OCTA (NIDEK RS-3000 Advance AngioScan, NIDEK CO., LTD., Japan) was performed after dilation. The grade of retinopathy was classified according to the International Clinical Diabetic Retinopathy classification system (ICDR) (Wilkinson et al. 2003), and the individuals with T1D were allocated into two groups, one group without and one group with NPDR. The study only comprised individuals with NPDR without CSMO. One eye was included in the analyses, primarily the right eye; however, if the image quality was poor or a vessel was ungradable, the left eye was measured instead.

Patient exclusion

Reasons for exclusion were poor OCTA image quality and poor fixation (n = 2), CSMO (n = 5), PDR (n = 2), spherical equivalent (SE) >6 Dioptres (n = 2) and 13 subjects could not have their OCT taken due to technical problems. Other: current or recent (<3 months) pregnancy, any other history of ocular disease, ocular-surgery or ocular-trauma (n = 0).

Clinical characteristics

Clinical characteristics have been presented in a previous publication: Mean age was 24.3 ± 3.3 years (±SD), 59% women and 41% men, mean duration of diabetes was 15.7 ± 3.8 years and mean age of onset was 8.6 ± 3.4 years. Longer duration of DM, higher waist circumference and sparser VD-DCP in the macula was significantly associated with increasing level of NPDR in the present population (Veiby et al. 2020).

We examined 189 subjects aged 14–30 years with T1D. After exclusion criteria were applied, 166 subjects were suitable for analysis. One hundred and twenty-one individuals had no retinopathy and 45 had retinopathy (33 had mild-, 10 had moderate- and 2 had severe NPDR).

OCTA image acquisition and analysis

Optical coherence tomography angiography (OCTA) images were obtained by RS-3000 Advance AngioScan (NIDEK CO., LTD., version 1.7.0.4, Gamagori, Japan) a spectral domain

OCTA using a custom 3 × 3 mm acquisition protocol centred in the fovea. The different OCTA parameters were automatically computed by the built-in Navis-EX 1.7 software. The vessel density (VD) was analysed in two vascular layers, the superficial capillary plexus (SCP) and the deep capillary plexus (DCP), between the inner limiting membrane (ILM) and the retinal pigment epithelium (RPE) from the enface OCTA. The DCP consists of capillaries in the inner nuclear layer between IPL/INL + 13 μm and IPL/INL + 88 μm. The Navis-EX software automatically computed VD and average central macular thickness (CMT) from the OCTA tomograms. The VD was expressed in mm^2 and converted to percentage of the surface, that is occupied by capillaries per area of the entire scan (9 mm^2). Clinically significant diabetic macular oedema (CSMO) was defined according to ETDRS (ETDRS study report number 1, No authors listed, 1985).

OCTA quality control

Two independent readers (NCBBV and NS) carefully evaluated each OCTA scan before the quantitative analysis. The readers were blinded to all patient characteristics. Optical coherence tomography angiography (OCTA) with poor image quality (SSI < 6/10) and significant image artefacts (motion lines, blurry images, poor centration) were excluded. We also excluded those eyes that did not have all OCTA parameters measured, to avoid missing parameters.

Oximetry

The retinal oximetry procedure, described by Hardarson, was used to determine the O_2 saturation in retinal vessels (Hardarson et al. 2006). The patient was positioned in front of the fundus camera of the oximeter (Oxymap T1, Oxymap ehf., Reykjavik, Iceland) and images were taken of both eyes. This has been described in more detail in previous publications on the same population (Veiby, 2020). All analyses were performed by an experienced ophthalmologist (NCBBV) using the Oxymap analysis software (Oxymap T1, software 2.2.1., version 5436) according to the standardized protocol (Version 21, November 2013; Oxymap Inc.) (Geirsdottir et al. 2012). The examiner was blinded to the presence of DM. O_2 saturation was measured in all arterioles and venules > 8 pixels (~74 μm) in vessel width and >50 pixels (~460 μm) in length in a peripapillary annulus within the standard grid of 1.5–3.0 disc diameters from the optic disc centre (Fig. 1). Arteriolar-venular (AV) O_2 difference was calculated from mean arteriolar- and mean venular O_2 saturation values based on measurements from all vessels around the optic disc. The influence of vessel diameter was automatically corrected for in the analysis software (Geirsdottir et al. 2012).

Retinal vessel diameters

Digital grey-scale fundus photographs (50°, 1024 × 1024 pixels) centred on the optic disc were recorded in red-free illumination using the oximeter (TRC-50X; Topcon Corp., Tokyo, Japan). Vessel calibres were assessed using a custom-developed semi-automated computer algorithm according to the international gold standard (Vessel Measurement System, IVAN protocol, version 2, University of Wisconsin) using the revised formulas (Knudtson et al. 2003). The method is described in more detail elsewhere (Gudmundsdottir et al. 2010) (Fig. 2).

When central retinal artery equivalent diameter (CRAE) narrows and central retinal venular equivalent

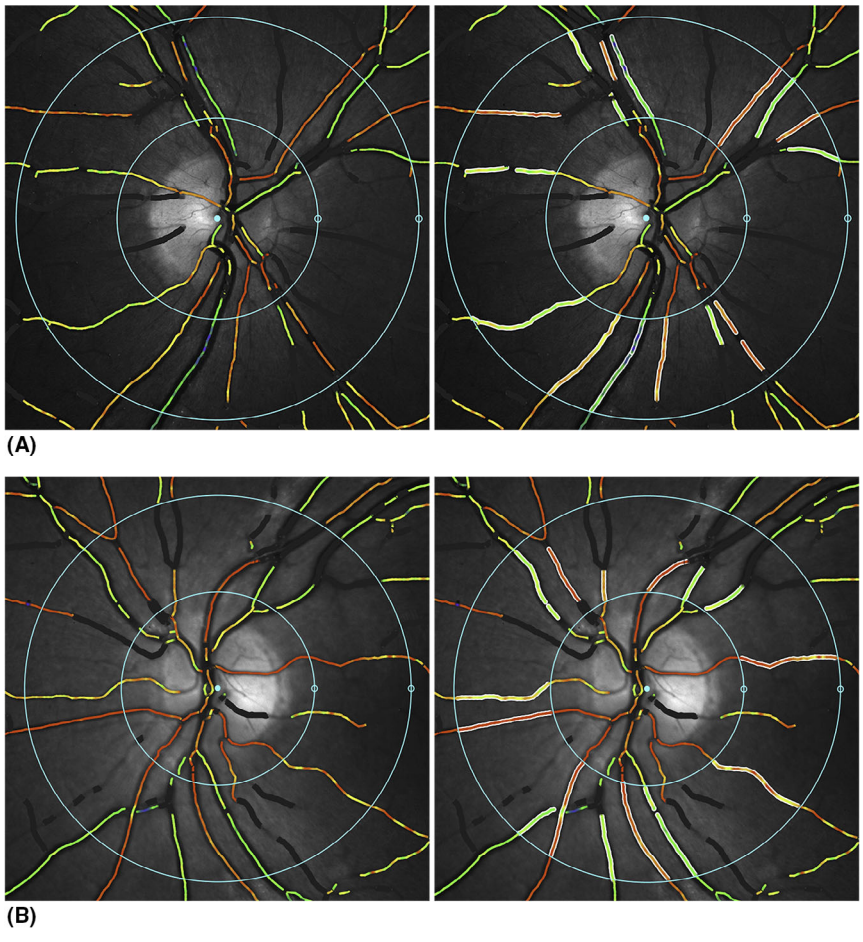

Fig. 1. Representative images of the Oxymap Analyzer showing the original image (left) and the image with measured arterioles and venules within the two circles 1.5–3.0 disc diameters from the optic disc centre (right) in a patient with mild NPDR with arteriolar O_2 saturation of 91.2% and venular O_2 saturation of 61.5% (A), and in a patient with severe DR with arteriolar O_2 saturation of 92.3% and venular O_2 saturation of 65.6% (B). The patient with severe DR has higher O_2 saturations. The colours indicate O_2 saturation in the retinal vessels where red is 100%, yellow is 75%, green is 50% and blue is 25%. The white lines indicate the delimitations of the vascular segments selected for analysis. All the vessels having >8 pixels in width and >50 pixels in length were chosen for analysis. The black vessels are <8 pixels wide and are not measured.

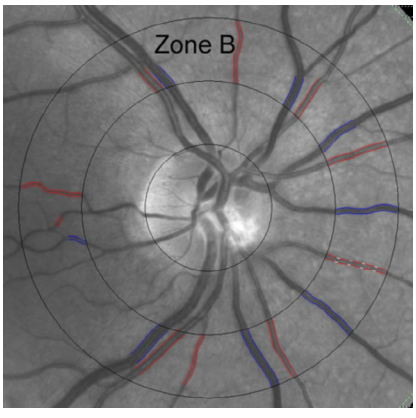

Fig. 2. Fundus image showing a standard grid with measured arterioles and venules delineated in red and blue, respectively. The inner circle demarcates an average optic disc, the middle circle demarcates 0.5 disc diameters (DD) from the outer rim of the optic disc and the outer circle demarcates 1.0 disc diameters from the outer rim of the optic disc. Zone B was defined as the region between the two outer circles.

diameter (CRVE) dilates, the arteriolar-to-venular ratio (AVR) decreases. Arteriolar-to-venular ratio (AVR) is a dimensionless measure and does not vary with ocular magnification and is also robust towards apparent increase in vessel broadening in blurred images (Taarnhoj et al. 2006), yet AVR is a more precise measure than CRAE and CRVE.

Statistics

A p-value of <0.05 was considered statistically significant. Clinical characteristics are presented as means with standard deviations (SD) and range. Quantile–quantile (Q–Q) plots were used to check all continuous variables for normality. We checked for multicollinearity amongst all the clinical variables with Pearson correlation coefficient (r) of 0.7 as a cut-off. To find out how the ocular parameters (VD-DCP, vessel diameters and O_2 saturations) covariate and how strongly they associate with each of the risk factors; BMI, waist circumference, MABP, HbA1c, age, gender, diabetes duration, and MOPP, scatterplots, linear regression and Pearson's correlations were performed accordingly.

The population consisted of two groups, one with and one without retinopathy. The association with retinopathy of each individual parameter was studied in a univariable logistic regression analysis. The following variables were included in the model: age, age onset of DM, gender, DM duration, HbA1c, systolic- and diastolic BP, waist circumference, BCVA, VD-DCP, CRAE, CRVE, AVR, arterial O_2 saturation, venular O_2 saturation, AV-O_2 saturation difference, MOPP, triglycerides, total cholesterol, HDL, LDL, BMI, IOP, vessel density in superficial capillary plexus (VD-SCP) and central retinal thickness and AVR pr. SD. The variables that were significantly associated with retinopathy were: age, DM duration, waist circumference, VD-DCP, CRVE and arterial-, venular O_2 saturation and AV- O_2 saturation difference. They were included in the multiple linear logistic regression analysis. We tested both the AV-O_2 saturation difference and the venular O_2 saturation. The regression results are presented as odds ratio (OR), 95% confidence intervals (CI), and p-values.

Waist circumference was a statistically stronger risk factor than BMI, for which the same results were obtained. Our study had no 'missing data' on waist circumference; therefore, this parameter was chosen instead of BMI.

Results

Ocular characteristics are presented in Table 1. Univariable logistic regression showed that age (OR = 1.3, 95% CI: 1.2–1.5, p < 0.001), DM duration (OR = 1.2, 95% CI: 1.1–1.3, p < 0.001), waist circumference (OR = 1.0, 95% CI: 1.0–1.1, p = 0.02), VD-DCP (OR = 0.1, 95% CI: 0.02–0.4, p = 0.001), CRVE (OR = 1.0, 95% CI: 1.00–1.03, p = 0.04), arterial oxygen saturation (OR = 1.1, 95% CI: 1.0–1.2, p = 0.02), venular oxygen saturation (OR = 1.2, 95% CI: 1.1–1.3, p < 0.001) and lower AV-O_2 saturation difference (OR = 0.9, 95% CI: 0.8–0.9, p < 0.001) were significantly associated with having diabetic retinopathy.

Multivariable logistic regression showed that for one year change in age the odds of getting retinopathy increased with 25% (OR:1.25, 95% CI 1.04–1.49, p = 0.015), for one unit change/increase in venular O_2 saturation the odds of getting retinopathy increased with 15% (OR: 1.15, 95% CI: 1.07–1.25, p < 0.001, Table 2A), whilst for one unit change/decrease in AV-O_2 saturation difference the odds of getting retinopathy decreased with 15% (OR:0.85, 95% CI: 0.77–0.93, p = 0.001, Table 2B).

Since vessel density, vessel diameter and oxygen saturation most likely correlate we did the multivariable logistic regression with all the different combinations with all three, two or one of the vascular parameters. In all the models, it was only the venular O_2 saturation and the AV-O_2 saturation difference that was significantly associated with diabetic retinopathy (data are not shown). We also checked for multicollinearity between the vascular parameters: VD-DCP and CRVE ($r = -0.28$, p < 0.001), VD-DCP and AV-O_2 saturation difference ($r = 0.14$, p = 0.086), and CRVE and AV-O_2 saturation difference ($r = 0.007$, p = 0.93).

The AV-O_2 saturation difference was associated with diastolic- and systolic blood pressure and gender (Pearson's correlation, data are not shown). The VD-DCP was significantly associated with all risk factors except for systolic and diastolic BP and MOPP, and the strongest associations were with HbA1c, age, gender and diabetes

Table 1. Ocular data from the included 166 eyes from 166 persons with type 1 diabetes

	Mean	SD	Range
Visual acuity (LogMAR)	−0.05	0.07	−0.3 to 0.8
Arteriolar O_2 saturation (%)	91.2	3.8	81.7 to 100.0
Venular O_2 saturation (%)	59.5	6.3	40.9 to 75.2
AV-O_2 saturation difference (%)	31.7	5.2	18.3 to 44.45
CRAE (μm)	179.5	16.1	126.2 to 221.9
CRVE (μm)	274.9	22.2	183.5 to 346.3
AVR	0.65	0.05	0.51 to 0.79
VD-DCP (%)	3.22	0.25	2.36 to 3.75

AVR = arteriolar-venular ratio, CRAE = central retinal artery equivalent, CRVE = central retinal venular equivalent, VD-DCP = Vessel density in the deep capillary plexus.

Table 2. Multiple logistic regression analysis of vascular and clinical risk parameters associated with diabetic retinopathy

	OR	95% CI	p Value
A with venular O_2 saturation			
Age	1.25	1.04–1.49	0.015*
Diabetes duration	1.11	0.97–1.26	0.129
Waist circumference	1.02	0.99–1.06	0.238
VD-DCP	0.32	0.05–2.13	0.236
CRVE	1.02	1.00–1.04	0.076
Venular O_2 saturation	1.15	1.07–1.25	<0.001*
B with AV-O_2 saturation difference			
Age	1.25	1.04–1.49	0.015**
Diabetes duration	1.11	0.97–1.26	0.129
Waist circumference	1.02	0.99–1.06	0.238
VD-DCP	0.32	0.05–2.13	0.236
CRVE	1.02	1.00–1.04	0.076
AV-O_2 saturation difference	0.85	0.77–0.93	0.001**

No DR (n = 121) and NPDR (n = 45).
* Significant variables $p < 0.05$. CRVE = central retinal venular equivalent, VD-DCP = Vessel density in the deep capillary plexus).
** Significant variables $p < 0.05$. AV = arteriolar-venular, CRVE = central retinal venular equivalent, VD-DCP = Vessel density in the deep capillary plexus.

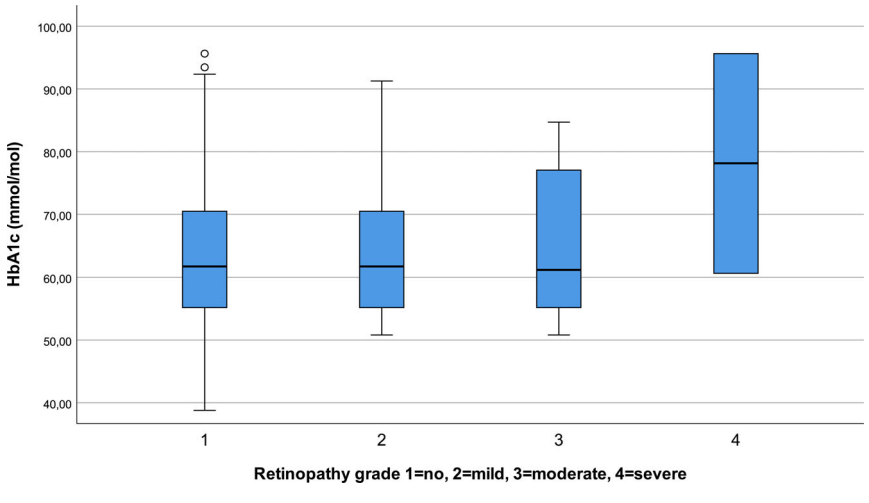

Fig. 3. The HbA1c is almost equal in no-, mild- and moderate NPDR, and it increases in the severe NPDR group. Only 2 individuals had severe NPDR, thus the association between HbA1c and NPDR does not appear statistically significant. (1) no NPDR, n = 121. (2) mild NDPR, n = 33. (3) moderate NPDR, n = 10. (4) severe NPDR, n = 2. NPDR = non-proliferative diabetic retinopathy.

duration. Central retinal venular equivalent diameter (CRVE) was only associated with HbA1c.

HbA1c was almost equal in no-, mild- and moderate NPDR, and it was higher in the group with severe NPDR (Fig. 3).

Discussion

In this population of young individuals with childhood-onset T1D, we found that age and lower AV-O_2 saturation difference (or higher venular O_2 saturation) were significantly associated with having diabetic retinopathy, independently of other known risk factors for developing DR.

AV-O_2 saturation difference does not vary with ocular magnification; that is difference in refraction, and is also robust towards apparent increase in saturation in blurred images yet is a more robust measure than arteriolar- and venular O_2 saturation. A recent study has shown that the O_2 saturation measured by dual wavelength oximetry is inversely correlated to the linear velocity of the blood in larger retinal arterioles and venules. Significant differences in O_2 saturation amongst the four quadrants was reduced when correcting for linear velocity in arterioles and venules, whereas the AV-O_2 saturation difference was not significantly different amongst the four quadrants, neither before nor after the correction. This finding implied that increased oxygen saturations in patients with diabetes may simply reflect decreased blood flow, but that the AV-O_2 saturation difference was more robust to this effect (Jeppesen & Bek, 2019). That is why we chose to focus on the AV-O_2 saturation difference in our study.

No indication of multicollinearity between CRVE, AV-O_2 saturation difference and VD-DCP was found statistically. However, theoretically vessel density, vessel diameter, and oxygen saturation can influence each other. AV-O_2 saturation difference was the only significant ocular parameter in the multivariable logistic regression analysis. Vessel density had an OR of 0.32, which is high, although it was not significant, probably because of the low number of individuals with moderate and severe diabetic retinopathy.

To put our findings in a proper context, we have only found one previous study that our results can be compared with. That study included patients with both type 1 and type 2 diabetes with an average age of 58.4 years and mean duration of DM being 16.1 years with profound DR changes and a more vision-threatening endpoint (PDR and CSMO) than ours. They also found venular O_2 saturation to be significantly associated with the grade of retinopathy independently of other risk factors and the effect was of the same magnitude as HbA1c and diabetes duration. This may imply that oxygen saturation level in the large retinal vessels is an important biomarker in both early and late stages of diabetic retinopathy and should be further explored in the future prospective studies. Blood pressure showed no significant associations with DR in either study, probably because the individuals were well-regulated (Bek et al. 2019).

HbA1c was not significantly associated with NPDR in the logistic regression analysis, probably due to the low

number of individuals with severe NPDR. Although CRVE and VD-DCP were associated with HbA1c.

We provide further evidence on how to prevent visual loss from diabetic retinopathy by increasing O_2 delivery to the retinal tissue. It is important to start preventive measures as early as possible. Therefore, our population of individuals aged 14–30 years with T1D with at least 10 years of DM duration is of special interest. More advanced insulin therapy is now evolving, using insulin pumps and subcutaneous tissue glucose sensors, either separate or combined in hybrid closed loop systems, making long-term near normal glucose values more feasible. At present HbA1c values continuously improve as reported from the NCDR, which will hopefully prevent more diabetic retinopathy in the future (www.kvalitetsregistre.no/registers/nasjonalt-medisinsk-kvalitetsregister-barne-og-ungdomsdiabetes) (Charalampopoulos et al. 2018).

The ACD study has several strengths. It has a well-planned protocol, and all the clinical and ophthalmological data were collected on the same day and within a few hours in each individual. According to the international standards, this is considered a large childhood-onset-T1D population. The individuals had no cataract and their pupils were dilated well, resulting in a high oximetry image quality (mean: 8.2 ± 0.5 on a scale from 0 to 10). The O_2 saturation results are considered very reliable due to the high image quality, and one experienced ophthalmologist performing all the analyses (NCBBV). An advantage of this study is that the individuals included are young and are not taking systemic medication, thus reducing the effect of confounders such as age and blood pressure that can influence the blood vessels (Wong et al. 2003). This isolate and clarifies the effect of DM. We measured all the vessels around the optic disc, which we believe gives the best representation of the oxygenation of the retina.

The lack of influence of HbA1c and blood pressure in our population might be related to patient selection, risk of volunteer bias and few patients with moderate- and severe NPDR. Modifiable risk factors are often well-regulated in high quality primary and secondary health care settings, such as in Norway. The imbalance between the groups with many patients with no or mild retinopathy is a limitation; however, this may also be considered as an asset since this makes a perfect baseline for following these patients prospectively. This cross-sectional study was carried out to investigate associations between a disease and possible risk factors and does not provide information about causality. Highly fluctuating variables are only represented with a single value, such as HbA1c and blood pressure, which may underestimate the effect of the cumulated exposure to these parameters over time. Prospective studies are more suitable to investigate what risk factors affect diabetic retinopathy. We did not correct for mean ocular perfusion pressure (MOPP) because it was not associated with NPDR, and it has been shown to not affect the oximetry values in healthy young adults (Man et al. 2014); furthermore, it did not affect the VD-DCP in our population (Veiby et al. 2020).

We analysed SBP and DBP because a recent study has shown that systolic- and diastolic blood pressures play particular roles for the risk of developing diabetic retinopathy and that the risk of Hba1c is related to fluctuations in this parameter more than to the level of HbA1c (Bek, 2020).

In conclusion, age and lower AV-O_2 saturation difference contribute to explaining the grade of NPDR in T1D patients independently of other well-known risk factors. Oximetry is a non-invasive measurement, it is reliable, easy to perform and comfortable for the patient. Reduced delivery of O_2 to the retinal tissue is associated with the development of NPDR in young patients with T1D, and should be given appropriate weight in the risk stratification at early stages of the disease. Maybe in the future, we should focus on medicine that can increase the oxygen delivery to the retina, dilate the vessels, increase the blood flow in addition to maintaining a low and stable blood sugar.

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