Received: 7 October 2022 | Accepted: 22 January 2023

DOI: 10.1111/aos.15643

Acta Ophthalmologica

ORIGINAL ARTICLE

Retinal microvascular markers in type 2 diabetes subphenotypes and latent autoimmune diabetes of adults

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Abstract

Purpose: To estimate if newly diagnosed patients with different subphenotypes of type 2 diabetes (T2DM) or latent autoimmune diabetes of adults (LADA) differ with respect to subclinical retinal microvascular structure or diabetic retinopathy (DR).

Methods: This population-based, cross-sectional study of 340 patients (675 eyes) classified patients with recently diagnosed T2DM in different subphenotypes according to beta cell function and insulin sensitivity in to; classical (n = 218), hyperinsulinaemic (n = 86), insulinopenic (n = 20), or LADA (n = 16). Retinal 6-field images were graded according to the International Clinical DR Severity Scale by a retinal expert. Retinal microvascular structures were analysed in eyes by a semi-automatic software.

Results: Median age and duration of diabetes were 58.1 (49.9; 65.5) and 0.9 (0.5; 2.4) years, respectively, and 56.8% were male. In a multivariate linear mixed model regression analysis of eyes without DR (n = 570), there was no statistically significant difference in retinal venular or arteriolar width between subtypes and patients with classical T2DM. In addition, eyes from different subphenotypes did not differ according to vessel density, tortuosity or fractal dimension. In a multivariate logistic regression model adjusted for age, sex, HbA1c, diabetes duration, body mass index, mean arterial blood pressure and history of cardiovascular disease, there was a tendency towards persons with hyperinsulinaemic T2DM to be more likely to have DR (OR 1.97, 95% CI 0.95; 4.09) compared to classical T2DM.

Conclusion: We found no difference in retinal microvascular structure in patients with newly diagnosed subtypes of T2DM. However, DR may be more prevalent in newly diagnosed patients with hyperinsulinaemic T2DM compared to individuals with classical T2DM.

KEYWORDS

diabetic retinopathy, microvascular complication, prevalence, retinal markers, type 2 diabetes

1 | INTRODUCTION

Worldwide one in ten is living with diabetes, of which type 2 diabetes (T2DM) accounts for 90% (Sun et al., 2022). It is evident that T2DM is overall a heterogeneous disease, which likely can be divided into different phenotypes. One approach suggests subphenotyping according to insulin sensitivity and insulin secretion (Stidsen et al., 2018). This clinical heterogeneity between subphenotypes may also be detectable in regards to the retinal microvasculature. Diabetic retinopathy (DR) is a common microvascular complication with a reported prevalence between 1.9% and 13.0% in patients newly diagnosed with T2DM (Ponto et al., 2016; Spijkerman et al., 2003). Incidence and progression of DR increases with the duration of diabetes

and varies between type 1 diabetes and T2DM (Yau et al., 2012). In addition, changes in retinal microvasculature markers have been associated with the development of DR (Bek, 2017). Wider venular calibre has been associated with risk of more severe stages of DR, while narrower arteriolar calibre, increased venular tortuosity and lower fractal dimension have been associated with increased risk of DR progression (Broe et al., 2014; Forster et al., 2021; Kifley et al., 2008; Klein et al., 2004, 2012).

In a clinical setting, it is important to establish whether certain subphenotypes of T2DM are at an increased risk of microvascular complications including DR in order to provide optimal prevention and medical treatment within different risk groups. Our aim of this study was to examine if early retinal microvascular damage was detectable in different subphenotypes of patients with newly diagnosed T2DM or LADA before the onset of DR. Secondly, we wanted to examine if the presence of DR varied between the T2DM subphenotypes or LADA.

2 | METHOD

2.1 | Research design and study population

This population-based cross-sectional study is nested in the "Individually tailored treatment in type 2 diabetes" (IDA) study (Stidsen et al., 2017), which is imbedded in the "Danish Centre for Strategic Research in Type 2 Diabetes" (DD2) cohort study (Nielsen et al., 2012). In brief, the IDA study aims to investigate the effect of individualized treatment in general practice for patients with newly diagnosed T2DM. Patients with newly, clinically diagnosed T2DM above 18 years of age were eligible for the DD2 cohort (Nielsen et al., 2012), while inclusion criteria for the IDA study were participation in the DD2 cohort, treatment at a DD2 participating general practitioner, life expectancy above 2 years and no type 1 diabetes. In short, 1172 patients were enrolled into the intervention arm of the IDA study and had a baseline clinical examination at central study sites. The 783 enrolled at Odense University Hospital were invited to participate in additional examinations of subclinical organ damage, including retinal fundus images, which were accepted by 375. Data were obtained between 11 December 2013 and 10 January 2019.

2.2 | Clinical examination and T2DM phenotypes

In total, 341 persons with newly diagnosed T2DM were screened with fundus images. One person was excluded because of secondary diabetes (Figure 1).

At inclusion, a clinical examination and interview was performed. History of cardiovascular disease was defined as atherosclerotic disease as well as heart failure obtained at patient interview and verified with medical journal audit. In addition, T2DM phenotype evaluation was performed. In summary, T2DM was

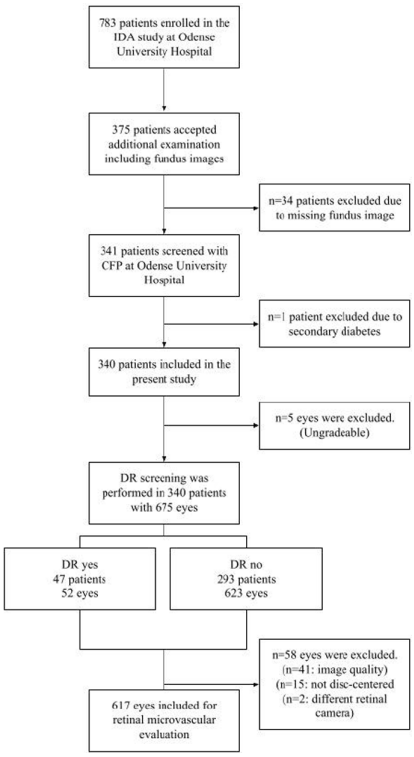

FIGURE 1 Flowchart of patient inclusion. CFP, Colour fundus photo; DR, Diabetic retinopathy; *n*, count.

categorized according to the estimated beta-cell function and insulin sensitivity using the version 2 of the revised homeostasis assessment model (HOMA2) (Hill et al., 2013; Levy et al., 1998; Turner et al., 1990), and median values of a healthy control population were used to define three subphenotypes (Stidsen et al., 2018). The subphenotypes were classical T2DM (low insulin sensitivity and low beta-cell function), hyperinsulinaemic T2DM (low insulin sensitivity and high beta-cell function) and insulinopenic T2DM (high insulin sensitivity and low beta-cell function). LADA were classified as positive for glutamic acid decarboxylase antibodies (GADA) titre ≥20 IE/mL and age > 30 years. The specific method for the classification into subphenotypes and LADA can be found elsewhere (Stidsen et al., 2018).

2.3 | Retinal imaging

Best-corrected visual acuity was measured in both eyes using Snellen chart by a trained optometrist. Afterwards, mydriatic 6-field 45° retinal fundus images were obtained using Topcon TRC-NW8, Tokyo, Japan (n = 339) or Topcon DRI OCT Triton, Tokyo, Japan (n = 1). DR grading was performed by a single ophthalmologist, specialized in DR screening. The grader was blinded from patient characteristics. The images were graded according to the International Clinical Retinopathy Disease Severity Scale which consist of five steps: level 0 (no DR), level 1–3 (mild, moderate and severe non-proliferative DR) and level 4 (proliferative diabetic retinopathy or prior panretinal photocoagulation) (Wilkinson et al., 2003).

2.4 | Retinal vascular analysis

Image analysis was performed in disc-centred retinal fundus photos using VAMPIRE® (Vessel Assessment and Measurement Platform for Images of the Retina, Universities of Dundee and Edinburgh, UK). A detailed description of the program can be found elsewhere (Perez-Rovira et al., 2011). In brief, an automated grid is placed around the optic disc and mark retinal area zones A, B and C between 0–0.5, 0.5–1.0 and 0.5–2.0 disc diameters from the optic disc margin, respectively. Retinal vessels are automatic colour labelled in red or blue, illustrating arterioles or venules, respectively. Misclassified arterioles or venules were manually relabelled by the grader. If the software erroneously labelled an artefact, haemorrhage or one vessel as two or the demarcation of one vessel was unacceptable, the vessel section was excluded. The following retinal structural markers were measured: vessel calibre, density, tortuosity and fractal dimension.

Vessel calibre is presented as the central retinal artery (CRAE) and vein (CRVE) equivalent, comprised of the six largest arterioles and venules in zone B (Knudtson et al., 2003). Vessel width was translated from pixel into μm using a conversion factor under the assumption of an average disc diameter of 1800 μm (Jonas et al., 1988).

Vessel density is the sum of pixels occupied by vessels in a given retinal area and provides a combined measure of vessel complexity and width. Tortuosity describes the degree of curvature of a vessel as compared to straight reference line of the same vessel. Total fractal dimension describes how the vascular pattern fills a space thereby summarizing the branching complexity of the retinal vasculature. Vessel density, tortuosity and total fractal dimension were measured in zone C (Figure 2).

Image quality and microvascular analysis were performed by a single grader, FP, blinded of participant's characteristics. A subsample (8%) of the retinal images was graded again by a second grader, SB, with high intergrader reliability of both CRAE and CRVE with interclass correlation coefficients >0.94.

2.5 | Ethics

The study has been approved by the Regional Committee on Medical Health Ethics (Region of Southern Denmark S-20120186) and performed according to the tenets of the Helsinki Declaration.

2.6 | Statistics

Continuous variables were presented with mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were presented with frequencies and percentages. Between groups, categorical data were compared using Pearson's chi-squared whereas continuous data were compared using Wilcoxon rank-sum test.

Since patients were allowed to participate with both eyes, linear mixed model with cluster robust standard error was applied to test for difference in retinal microvascular markers (Table 2). We performed two multivariable adjusted logistic regression models to test for difference in present DR on an individual

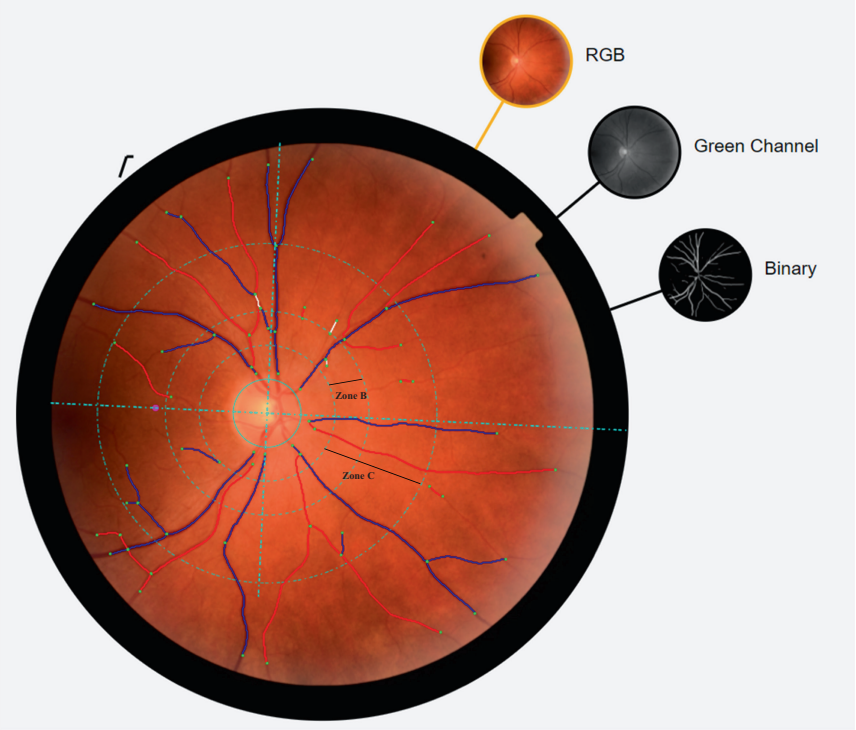

FIGURE 2 Example of the retinal vessel analysis programme Vampire (Vessel Assessment and Measurement Platform for Images of the Retina, Universities of Dundee and Edinburgh, UK). Vessel are colour labelled (arterioles red/venules blue) and vessel calibre is measured in zone B. Vessel tortuosity, vessel dimension and fractal dimension are measured in zone C. White lines indicate excluded vessel segments.

basis between subphenotypes. The first model adjusted for age and sex, whereas model two adjusted for age, sex, HbA1c, diabetes duration, body mass index, mean arterial blood pressure and history of cardiovascular disease. As a sensitivity analysis, we excluded patients with known cardiovascular disease (Appendix S1). Furthermore, we examined if there was a dose–response association between beta-cell function, insulin sensitivity and retinal vessel diameter as a sensitivity analysis (Appendix S1). As HOMA2-S and HOMA2-B are interdependent, the dose–response association analyses were stratified to intervals where the other variables were fairly constant, using the same cut-off values as used for the phenotype categorization. Though, for analysis of HOMA2-B, HOMA2-S were stratified according to HOMA2-S >63.5 and <63.5%, while analysis of HOMA2-S was stratified according to HOMA2-B >115 and <115%. Lastly, we divided the population in eyes with and without DR to investigate early retinal microvascular changes (Appendix S1). *p*-values below 0.05 were considered statistically significant. All statistics were performed using STATA version 17.0 (StataCorp LLC).

3 | RESULTS

In total, 340 patients were included of which 218, 86, 20 and 16 subjects were categorized into classical T2DM, hyperinsulinaemic T2DM, insulinopenic T2DM and LADA, respectively (Table 1). Median age and duration of diabetes (with IQR) were 58.1 (49.9–65.5) and 0.9 (0.5, 2.4) years, respectively, and 56.8% were male.

Compared to classical T2DM, patients with hyperinsulinaemic T2DM had a higher body mass index (median 31.2 vs. 33.4 kg/m^2, $p = 0.015$) but lower haemoglobin A1c (HbA1c) levels (median 49.0 vs. 46.0 mmoL/moL, $p < 0.001$) (Table 1). In contrast, patients with insulinopenic T2DM had a lower body mass index (median 31.2 kg/m^2 vs. 26.5 kg/m^2) compared to patients with classical T2DM. LDL-cholesterol, mean arterial blood pressure and prior history of cardiovascular disease did not differ significantly between classical T2DM and the other subphenotypes or LADA.

In a linear mixed regression model adjusted for age and sex of eyes without DR ($n = 570$), patients with hyperinsulinaemic T2DM and LADA had a tendency towards wider retinal venular calibre compared to patients with classical T2DM (276 µm vs. 270 µm $p = 0.075$ and 279 µm vs. 270 µm $p = 0.087$, respectively) (Table 2). Although not statistically significant, the association was comparable in the full-adjusted model (Table 2). Eyes across the subphenotypes did not differ according to retinal vessel density, tortuosity or fractal dimension compared to patients with classical T2DM (Table 2). In the full-adjusted logistic regression analysis, there was a tendency towards patients with hyperinsulinaemic T2DM to be more likely to have DR (OR 1.97, 95% CI 0.95; 4.09) compared to classical T2DM (Table 3). In a sensitivity analysis, we excluded patients with known prior cardiovascular disease and found patients with hyperinsulinaemic T2DM to be more likely to have DR compared to classical T2DM (OR 2.31 95% CI 1.04; 5.10) (Appendix S1). Likewise, our results are most compatible with an increased presence of DR in patients with LADA compared to patients with classical T2DM (full-adjusted OR 1.88 95% CI 0.49; 7.18). In contrary, our results are most compatible with no difference in DR prevalence between insulinopenic T2DM compared to classical T2DM (full-adjusted OR 1.14 95% CI 0.24; 5.41).

In a linear mixed model regression analyses, there were no significant association between beta-cell function or insulin sensitivity as continuous variables and retinal arteriolar or venular diameter (Appendix S1; Table 3).

When comparing those with ($n = 47$) and without ($n = 293$) DR, there were no differences in baseline characteristics such as age, gender, diabetes duration, HbA1c, LDL-cholesterol, HOMA2-S, HOMA2-B, body mass index or blood pressure (Appendix S1). In a linear mixed model regression analysis between eyes with ($n = 47$) and without DR ($n = 570$), we found those with DR to have more tortious venules (−8.44 vs. −7.48 $p = <0.001$) after adjustment of age, sex, HbA1c, diabetes duration, body mass index, mean arterial blood pressure and history of cardiovascular disease. There were no significant differences in any of the other retinal structural markers (Appendix S1).

4 | DISCUSSION

To our knowledge, this is the first study to investigate retinal microvascular markers in patients with newly diagnosed subphenotypes of T2DM or LADA without DR. We found that those with hyperinsulinaemic T2DM and LADA had a tendency towards wider retinal venular calibre compared to classical T2DM although not statistically significant. In addition, we found patients with hyperinsulinaemic T2DM to be twice as likely to have DR compared to patients with classical T2DM after exclusion of patients with known cardiovascular disease. Lastly, we found that those with newly diagnosed T2DM and DR to have more tortious venules compared to those without DR.

The tendency towards wider retinal venular calibre in patients with hyperinsulinaemic T2DM compared to classical T2DM may be associated with the higher presence of DR in those with hyperinsulinaemic T2DM. This is in line with earlier studies which have reported wider retinal venular calibre to be associated with DR (Klein et al., 2004). Previous studies have examined retinal microvascular markers in patients with T2DM without taking subphenotypes into account, which makes comparison between studies difficult. However, in a recent prospective study with 10-year follow-up, increased retinal venular tortuosity and decreased fractal dimension at baseline were associated with incident DR in patients with T2DM free from DR at baseline, whereas vessel widths were not (Forster et al., 2021). This is in line with the Wisconsin Epidemiologic Study of Diabetic Retinopathy, who did not find CRAE or CRVE to be associated with incidence or progression of DR in patients with T2DM (Klein et al., 2007). While our study focus on newly diagnosed T2DM subphenotypes and LADA, we

TABLE 1 Clinical characteristics of newly diagnosed type 2 diabetes subphenotypes and LADA.

	All	Classical type 2 diabetes	Hyperinsulinaemic type 2 diabetes	*p*-Value	Insulinopenic type 2 diabetes	*p*-Value	LADA	*p*-Value
Individuals, *n*	340	218	86		20		16	
Sex, *n* (%) male	193 (56.8%)	130 (59.6%)	43 (50.0%)	0.13	11 (55.0%)	0.69	9 (56.2%)	0.79
Age, years (IQR)	58.1 (49.9; 65.5)	57.7 (49.9; 65.2)	58.2 (47.8; 67.5)	0.95	58.5 (52.7; 62.4)	0.62	61.2 (50.7; 65.5)	0.68
Diabetes duration, years (IQR)	0.9 (0.5; 2.4	0.9 (0.5; 2.6)	0.9 (0.5; 1.7)	0.43	1.6 (0.5; 4.6)	0.31	0.6 (0.4; 2.1)	0.46
HOMA2-B, % (IQR)	87.4 (64.7; 116.0)	78.6 (60.0; 92.8)	139.1 (122.2; 170.0)	<0.001	58.4 (44.5; 78.8)	0.010	89.4 (54.3; 99.6)	0.38
HOMA2-S, % (IQR)	33.2 (24.1; 42.7)	34.6 (26.0; 42.6)	25.1 (17.9; 32.2)	<0.001	79.3 (70.6; 94.3)	<0.001	43.5 (30.9; 60.4)	0.030
Haemoglobin A1c, mmoL/moL (IQR)	49.0 (44.0; 54.0)	49.0 (45.0; 56.0)	46.0 (42.0; 51.0)	<0.001	47.5 (42.0; 53.0)	0.19	49.5 (46.0; 53.5)	0.85
LDL-C, mmoL/moL (IQR)	2.3 (1.85; 3.0)	2.3 (1.9; 3.0)	2.2 (1.8; 2.7)	0.17	2.5 (1.9; 2.8)	0.91	2.2 (1.5; 3.1)	0.56
Body mass index, kg/m^2 (IQR)	31.4 (28.3; 36.4)	31.2 (28.4; 35.3)	33.4 (28.6; 40.6)	0.015	26.5 (24.3; 31.5)	0.001	30.9 (29.0; 32.9)	0.59
Mean arterial pressure, mmHg, mean (SD)	99.0 (10.2)	99.9 (9.8)	97.4 (10.8)	0.054	96.9 (12.1)	0.20	99.0 (9.9)	0.75
History of prior cardiovascular disease, yes (%)	68 (20%)	39 (17.9)	22 (25.6)	0.13	4 (20.0)	0.81	3 (18.8)	0.93
Eyes, *n*	675	435	168		40		32	
Visual acuity (IQR)	1.0 (0.8; 1.0)	1.0 (0.9; 1.0)	1.0 (0.8; 1.0)	0.054	1.0 (0.8; 1.0)	0.33	1.0 (0.9; 1.0)	0.83
Diabetic retinopathy *n* (%)				0.33		0.14		0.22
Level 0	623 (92.3%)	404 (92.9)	152 (90.5)		38 (95.0)		29 (90.6)	
Level 1	38 (5.6%)	23 (5.3)	14 (8.3)		0 (0.0)		1 (3.1)	
Level 2	14 (2.1%)	8 (1.8)	2 (1.2)		2 (5.0)		2 (6.2)	
Level 3	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)	
Level 4	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)		0 (0.0)	

Note: All comparisons use classical type 2 diabetes as the reference group.

Abbreviations: HOMA, homeostasis model assessment; IQR, interquartile range; LADA, latent autoimmune diabetes in Adults; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

TABLE 2 Retinal microvascular markers of newly diagnosed type 2 diabetes subphenotypes and LADA.

	Classical type 2 diabetes	Hyperinsulinaemic type 2 diabetes	*p*-Value	Insulinopenic type 2 diabetes	*p*-Value	LADA	*p*-Value
Retinal arterial calibre, µm (SE) difference, *β* (95% CI)							
Model 1	181 (0.9) Ref.	181 (1.5) 0.2 (−3.2; 3.6)	0.90	178 (2.9) −2.8 (−8.9; 3.2)	0.36	186 (4.7) 5.1 (−4.3; 14.5)	0.29
Model 2	181 (0.9) Ref.	180 (1.5) −1.0 (−4.4; 2.5)	0.58	179 (3.0) −2.5 (−8.7; 3.7)	0.43	186 (4.7) 5.1 (−4.2; 14.4)	0.28
Retinal venular calibre, µm (SE) difference, *β* (95% CI)							
Model 1	270 (1.7) Ref.	276 (3.0) 6.0 (−0.61; 12.6)	0.075	264 (4.4) −5.9 (−15.1; 3.3)	0.21	279 (5.3) 9.5 (−1.4; 20.3)	0.087
Model 2	270 (1.7) Ref.	275 (2.9) 4.8 (−1.7; 11.3)	0.15	266 (4.3) −3.3 (−12.3; 5.6)	0.47	280 (5.0) 9.8 (−0.51; 20.1)	0.062
Arteriolar vessel density pixels (SE) difference, *β* (95% CI)							
Model 1	3413 (54.1) Ref.	3323 (89.8) −90 (−295; 115)	0.39	3261 (148.8) −152 (−462; 158)	0.34	3588 (172.5) 174 (−180; 529)	0.34
Model 2	3431 (53.5) Ref.	3270 (90.4) −161 (−368; 47)	0.13	3298 (151.2) −133 (−446; 181)	0.41	3599 (161.8) 168 (−167; 503)	0.33
Venular vessel density pixels (SE) difference, *β* (95% CI)							
Model 1	4832 (65.4) Ref.	4754 (114.8) −77 (−337; 182)	0.56	4526 (148.5) −305 (−622; 12)	0.059	5077 (147.6) 224 (−71; 561)	0.13
Model 2	4844 (64.8) Ref.	4707 (114.4) −136 (−396; 123)	0.30	4637 (152.0) −207 (−528; 114)	0.21	5090 (140.8) 246 (−59; 551)	0.12
Arteriolar vessel tortuosity (SE) Difference, *β* (95% CI)							
Model 1	−7.60 (0.14) Ref.	−7.21 (0.29) 0.39 (−0.23; 1.01)	0.22	−7.11 (0.67) 0.49 (−0.85; 1.83)	0.47	−7.65 (0.44) −0.05 (−0.95; 0.85)	0.91
Model 2	−7.61 (0.13) Ref.	−7.16 (0.30) 0.45 (−0.20; 1.09)	0.17	−7.14 (0.65) 0.47 (−0.84; 1.78)	0.48	−7.66 (0.43) −0.05 (−0.94; 0.84)	0.91
Venular vessel tortuosity difference, *β* (95% CI)							
Model 1	−7.99 (0.11) Ref.	−8.07 (0.16) −0.08 (−0.46; 0.30)	0.69	−7.35 (0.42) 0.63 (−0.23; 1.49)	0.15	−8.24 (0.29) −0.25 (−0.87; 0.37)	0.43
Model 2	−7.98 (0.11) Ref.	−8.08 (0.16) −0.10 (−0.50; 0.31)	0.64	−7.34 (0.41) 0.64 (−0.19; 1.47)	0.13	−8.27 (0.28) −0.29 (−0.89; 0.31)	0.34
Fractal dimension arterioles+venules (SE) difference, *β* (95% CI)							
Model 1	1.384 (0.002) Ref.	1.379 (0.003) −0.004 (−0.012; 0.032)	0.26	1.386 (0.006) 0.002 (−0.009; 0.014)	0.69	1.392 (0.005) 0.008 (−0.002; 0.018)	0.12
Model 2	1.384 (0.002) Ref.	1.378 (0.002) −0.006 (−0.013; 0.002)	0.13	1.387 (0.006) 0.003 (−0.009; 0.015)	0.64	1.392 (0.005) 0.008 (−0.002; 0.019)	0.13

Note: Cluster robust standard error linear mixed model analysis with predicted values. All comparisons use classical type 2 diabetes as the reference group. Model 1: Age and sex adjusted. Model 2: Age, sex, history of cardiovascular disease, body mass index, mean arterial blood pressure, diabetes duration and HbA1c.

Abbreviations: CI, confidence interval; LADA, latent autoimmune diabetes in adults; SE, standard error; *β*, coefficient of the linear mixed model regression.

TABLE 3 Odds ratio with 95% confidence interval for present diabetic retinopathy in persons with newly diagnosed type 2 diabetes subphenotypes and LADA.

	Crude	Model 1	Model 2
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Classical type 2 diabetes	Ref.	Ref.	Ref.
Hyperinsulinaemic type 2 diabetes	1.90 (0.97; 3.73)	1.90 (0.96; 3.74)	1.97 (0.95; 4.09)
Insulinopenic type 2 diabetes	0.86 (0.19; 3.92)	0.87 (0.19; 3.98)	1.14 (0.24; 5.41)
LADA	1.78 (0.47; 6.69)	1.79 (0.48; 6.73)	1.88 (0.49; 7.18)

Note: All comparisons use classical type 2 diabetes as the reference group. Model 1: Age and sex adjusted; Model 2: Age, sex, HbA1c, diabetes duration, body mass index, mean arterial blood pressure, history of cardiovascular disease.

Abbreviations: CI, confidence interval; LADA, latent autoimmune diabetes in adults; OR, odds ratio.

provide new and detailed information on vascular retinal markers.

From a European perspective, a study reported DR prevalence of 1.9% in newly diagnosed T2DM in general practice (Spijkerman et al., 2003). In contrast, the Gutenberg Health Study found a prevalence of 13.0% in a screening-detected T2DM population (Ponto et al., 2016), whereas the Danish population-based ADDITION study reported a DR prevalence of 6.8% in patients with screening detected T2DM (Bek et al., 2009). The reported overall DR prevalence of 13.8% in this study supports earlier findings but the varying prevalence of DR across studies may be due to differences in study design and study population including levels of HbA1c at baseline and time to DR screening after T2DM diagnoses. When evaluating the presence of DR according to subphenotypes, we found DR to be twice as prevalent in hyperinsulinaemic T2DM compared to classical T2DM. Although not statistically significant, we also found a high effect size in patients with LADA, which indicates that certain subphenotypes may be more prone to retinal changes. This also corresponds well to the tendency towards wider venules in those with hyperinsulinaemic T2DM and LADA. In comparison, a previous study by Martinell et al. did not find a difference in prevalence among 2451 patients with newly diagnosed T2DM and LADA (Martinell et al., 2016).

In a clinical setting, it is important to differentiate in risk of diabetic complications across different subphenotypes in order to provide optimal individual treatment and management including a differentiated DR screening interval between subphenotypes. This is also demonstrated by the higher venular tortuosity observed in those with DR compared to those without any overt DR, which is in line with a recent longitudinal study that reported higher venular tortuosity to be associated with increased risk of incident DR (Forster et al., 2021).

This study includes several strengths. First, the subphenotypes of T2DM were well defined. Second, a trained grader blinded for patient characteristics performed DR evaluation. However, limitations should also be acknowledged. The observation was cross-sectional and included few participants with insulinopenic T2DM and LADA which may have caused a power issue. We did not have information regarding refractive error, axial length or corneal curvature which have previously been described to have implications on dimensions measured within the eye. Furthermore, we did not adjust for multiple testing and therefore, the significant associations may be due to chance findings.

In conclusion, this population-based cross-sectional study reports no definite changes in retinal microvascular markers in patients with newly diagnosed type 2 diabetes subphenotypes compared to classical T2DM, but hyperinsulinaemic T2DM has higher presence of DR compared to classical T2DM. This cohort will be followed with annual retinal photos, which enable us to examine retinal microvascular markers over time in T2DM subphenotypes and LADA along incidence and progression of DR.

ACKNOWLEDGEMENTS

An abstract of the article has previously been presented at EuRetina congress Hamburg 1-4 September 2022.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pedersen, F.N., Stidsen, J.V., Rasmussen, M.N., Nielsen, H.-B., Henriksen, J.E., Olesen, T.B. et al. (2023) Retinal microvascular markers in type 2 diabetes subphenotypes and latent autoimmune diabetes of adults. *Acta Ophthalmologica*, 00, 1–8. Available from: https://doi.org/10.1111/aos.15643