Risk of Diabetic Retinopathy According to Subtype of Type 2 Diabetes

Pedersen, Frederik N.; Stokholm, Lonny; Andersen, Nis; Andresen, Jens; Bek, Toke; Hajari, Javad; Heegaard, Steffen; Højlund, Kurt; Kawasaki, Ryo; Laugesen, Caroline S.; Möller, Sören; Schielke, Katja; Nielsen, Jens Steen; Stidsen, Jacob V.; Thomsen, Reimar W.; Thinggaard, Benjamin; Grauslund, Jakob

Published in:
Diabetes

DOI:
10.2337/db24-0016

Publication date:
2024

Document version:
Accepted manuscript

Title:

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Running title:

Diabetic retinopathy in subtypes of type 2 diabetes

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Keywords: Type 2 diabetes, hyperinsulinemia, insulinopenic, insulin resistance, beta-cell function, diabetic retinopathy, incidence, progression, registry-based, HOMA.

Word count: 1999

Tables and Figures: 3 Tables and 1 Figure

Abstract

Type 2 diabetes is a heterogeneous disease that can be subdivided based on beta-cell function and insulin sensitivity. We aimed to investigate the presence, incidence and progression of diabetic retinopathy (DR) according to subtypes of type 2 diabetes. In a national cohort, we identified three subtypes of type 2 diabetes which included classical, hyperinsulinemic and insulinopenic type 2 diabetes based on HOMA2 measurements. From the Danish Registry of Diabetic Retinopathy (DiaBase) we extracted information on level of DR. We used several national health registries to link information on comorbidity, medications and laboratory tests. We found individuals with hyperinsulinemic type 2 diabetes were less likely to have DR at entry date compared to classical type 2 diabetes, whereas individuals with insulinopenic type 2 diabetes were more likely to have DR. In multivariable Cox regression analysis, individuals with hyperinsulinemic type 2 diabetes had a decreased risk of both incidence and progression of DR compared to classical type 2 diabetes. We did not find any clear difference in risk of incident or progression of DR in individuals with insulinopenic compared to classical type 2 diabetes. These findings indicate that subcategorization of type 2 diabetes is important in evaluating the future risk of DR.

- Type 2 diabetes can be subcategorized based on beta-cell function and insulin sensitivity, but little is known about the association of subtypes of type 2 diabetes with risk of DR.
- Do individuals with hyperinsulinemic or insulinopenic type 2 diabetes have an increased risk of DR, compared to individuals with classical type 2 diabetes?
- Individuals with hyperinsulinemic type 2 diabetes had almost halved risk of both prevalent, incident, and progression of DR compared to individuals with classical type 2 diabetes.
- These results suggest that more individualized screening intervals for DR may be possible within subgroups of type 2 diabetes.

Diabetic retinopathy (DR) is a common complication in type 2 diabetes affecting 25% globally [1]. Early detection is crucial to optimize treatment and prevent progression to sight threatening DR. Important risk factors of DR include type of diabetes, diabetes duration, and glycemic control [1]. Type 2 diabetes is a heterogeneous disease, which can be further categorized into subtypes based on the relative contribution of the two main pathophysiological defects namely deterioration in beta-cell function and insulin sensitivity, respectively: e.g. in classical, hyperinsulinemic, and insulinopenic type 2 diabetes [2]. Studies suggest that impaired beta-cell function measured by reduced fasting or stimulated C-peptide in patients with type 2 diabetes is associated with higher presence and elevated risk of incident and progression of DR, which implies that the hyperinsulinemic phenotype may be less prone to develop DR [3-7]. However the role of insulin resistance in DR development remains poorly understood, with limited data available [8]. Although the existing data within this area indicate that preserved beta-cell function is a protective factor of DR, earlier studies have been limited primarily by cross-sectional design or small samples. Thus, this study aims to investigate the risk of presence, incidence and progression of DR according to pathophysiological subtypes of type 2 diabetes.

Research Design and Methods

Main data sources, design & study population

In general, the Danish healthcare system is tax-funded providing free access to general practitioners and hospitals, and partial reimbursement for the cost of prescribed medication. The Danish Centre for Strategic Research in Type 2 Diabetes (DD2) has since 2010 enrolled individuals with newly diagnosed type 2 diabetes [9]. The median time of diabetes diagnosis to enrollment in the DD2 cohort is 1.3 [IQR

0.3-2.9] years [10]. The Danish Registry for Diabetic Retinopathy (DiaBase) has been collecting information for individuals aged 18 years and above who participate in Denmark's DR screening program since 2013 [11]. The screening examination is performed by practicing ophthalmologists or at designated hospitals, and it is mandatory for the reporting physician to report findings to DiaBase. The screening procedure primarily relies on retinal fundus images in accordance with national guidelines [12]. The severity of DR is categorized using the International Clinical Diabetic Retinopathy Disease Severity Scale, consisting of five stages: level 0 (no DR), levels 1-3 (mild, moderate, and severe DR), and level 4 (proliferative DR) [13]. DiaBase has recently been validated with high agreement between graders according to the severity of DR [14].

We performed a nationwide cohort study of individuals included in the DD2 cohort, who had at least one screening episode for DR registered in DiaBase. Entry date was defined as the first registered screening episode in DiaBase between 1st of January 2013 and 1st of June 2022. Level of DR was defined according to level of DR at the worse eye. The HOMA-2 computational model (University of Oxford, U.K.) was used to estimate beta-cell function (HOMA2-B) and insulin sensitivity (HOMA2-S) [2, 15]. Measurements were based on fasting serum C-peptide and plasma glucose values measured at DD2 enrollment. We classified individuals into three subtypes, where high/low HOMA2-B was defined as ≥115.3/<115.3% and high/low HOMA2-S as ≥63.5/<63.5%, based on median HOMA2-B and HOMA2-S values for a healthy control group with normal fasting plasma glucose [2]. Individuals categorized as hyperinsulinemic type 2 diabetes had high HOMA2-B and low HOMA2-S, those with insulinopenic type 2 diabetes had low HOMA2-B and high HOMA2-S, and individuals with classical type 2 diabetes had low HOMA2-B and low HOMA2-S.

Outcome

We estimated odds ratios (ORs) of DR presence at entry date by type 2 diabetes subtype and calculated risk of incident DR during follow-up. Incident DR was defined as absence of DR at entry date, followed by its registration at a later examination. Time of risk was from entry to outcome, or last registered screening episode in DiaBase. Lastly, we estimated progression risk by comparing the last registered screening episode for DR to baseline severity, with progression defined as at least one step worsening.

Covariates

The Danish National Patient Registry, which includes ICD-10 codes for diseases, was used to evaluate comorbidities using a modified Charlson comorbidity index (CCI) score excl. diabetes. CCI was calculated following the methodology described by Quan et al [16]. Medication usage was assessed using ATC-codes provided from the Danish National Prescription Registry, specifically for insulin (A10A*), non-insulin glucose-lowering medications (A10B*), antihypertensive treatments (C03*, C07*, C08*, C09*), or lipid-lowering therapy (C10*), provided that they were prescribed at least twice within one year of the entry date. Diabetes duration was calculated as the time elapsed between the diagnosis date of diabetes registered in DD2 and the entry date. BMI was calculated at the date of DD2 enrollment. Date of birth, sex, marital and vital status was obtained from the Danish Civil Registration System. From the Register of Laboratory Results for Research, we extracted information on mean laboratory values for measurements of HbA_{1c}, estimated glomerular filtration rate, LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides (TG) based on the measurement within one year before and after entry date.

Statistics

Continuous variables are presented as median with interquartile range and categorical variables as counts and proportions. We applied Pearson chi-squared test (χ^2) to test differences between groups. We estimated ORs with 95% confidence intervals (CI) for presence of DR at entry date (yes/no), using logistic regression. We applied a crude model, an age- and sex-adjusted model, and multivariable models that were first adjusted for age, sex marital status, glucose-, lipid- or blood pressure lowering medication, HbA_{1c}, and a modified CCI, and finally also adjusted for BMI.

We estimated hazard ratios (HR) for risk of incidence and progression of DR in a crude, age- and sex-adjusted and a multivariable Cox regression model which met the proportional hazard assumption (using the same stepwise adjustment models as for the multivariable logistic regression model). We performed a sensitivity analysis excluding individuals using insulin therapy (Supplementary Table 1). We also examined the dose–response association between beta-cell function, insulin sensitivity and incidence and progression of DR. We stratified the HOMA2-B model according to levels of HOMA-S values (HOMA-S<63.5%) in that analysis. When investigating the HOMA2-S model we stratified according to levels of HOMA-B<115.3%. Both models were adjusted for the same covariates as the fully adjusted multivariable model and adjusted for HOMA2-B when investigating HOMA2-S and vice versa. The use of medication and CCI were handled as time-varying covariates. Confidence intervals that did not include 1.0 and p-values below 0.05 were considered statistically significant. All statistics were performed using Stata version 18.0 (StataCorp LLC, College Station, TX, USA).

Ethics statement

The study was performed according to the tenets of the Helsinki Declaration, and permissions were obtained from relevant health authorities [17, 18].

Data and Resource Availability

Data are available from the Danish Health Data Authority, but restrictions apply to these data.

Results

Among 10 209 individuals enrolled in the DD2, 4373 individuals were subcategorized with 3672 individuals having at least one screening episode in DiaBase (Figure 1). In short, individuals with hyperinsulinemic type 2 diabetes had higher CCI, BMI, and TG, but lower level of HDL cholesterol and HbA_{1c} compared to the other subtypes (Table 1).

Individuals with hyperinsulinemic type 2 diabetes were less likely to have DR at entry date compared to classical type 2 diabetes (age and sex adjusted OR 0.46 [95% CI 0.30-0.72]) although the association weakened in the fully multivariable adjusted model (OR 0.69 [95% CI 0.42-1.14]) (Table 2). In contrast, individuals with insulinopenic type 2 diabetes were more likely to have prevalent DR (multivariable adjusted OR 1.52 [95% CI 1.23-1.89] before adjustment for BMI) with the risk estimate declining in the fully adjusted model (multivariable adjusted OR 1.30 [95% CI 1.02-1.65]) (Table 2).

Individuals with hyperinsulinemic type 2 diabetes exhibited a lower risk of incident and progression of DR compared to individuals with classical type 2 diabetes (incident: multivariable adjusted HR 0.60 [95% CI 0.45-0.80], progression: multivariable adjusted HR 0.53 [95% CI 0.37-0.77]) (Table 3). There was no clear difference between insulinopenic and classical type 2 diabetes (incident: multivariable adjusted HR 1.01 [95% CI 0.70-1.45], progression: multivariable adjusted HR 1.12 [95% CI 0.74-

1.68]). The results for both hyperinsulinemic and insulinopenic type 2 diabetes, did not change in sensitivity analysis in which we excluded individuals using insulin at cohort entry (Supplementary Table 1).

We found a linear relationship between HOMA levels and increased risk of DR incidence and progression. HOMA2-B levels below 100% correlated with higher risk while for HOMA2-S risk of DR incidence and progression started to rise at 50% (Supplementary Figure 1).

Discussion

In this Danish cohort study involving 3672 individuals with biochemically classified subtypes of type 2 diabetes, those with hyperinsulinemic type 2 diabetes had a lower risk of 31% for present DR, 40% for upcoming DR and 47% for worsening of DR. Individuals with insulinopenic type 2 diabetes had 30% higher risk of present DR at cohort entry but there were no clear differences in DR incidence or progression between insulinopenic and classical type 2 diabetes. We also found that lower HOMA2-B was associated linearly with an increasing incidence and progression of DR.

Duration of diabetes and degree of hyperglycemia are strong risk factors for developing DR in type 2 diabetes [1], but it is not fully understood how impaired beta-cell function and insulin sensitivity associate with DR. Most studies have investigated the association of beta-cell function and DR in persons with a long duration of diabetes [3-7, 19]. The current study confirms the association found in previous studies in persons with a short duration of type 2 diabetes. In addition, most studies have not taken the intricate correlation between beta-cell function and insulin sensitivity into consideration. Our results indicate that beta-cell function is associated with DR independently of insulin resistance. Suzuki et al. reported low pancreatic beta-cell insulin secretory capacity as a risk of proliferative DR, based on

10 year follow-up of 160 patients [19]. Another 5-year prospective study of 233 newly diagnosed individuals with type 2 diabetes, found that reduced beta-cell function at baseline was associated with incident DR, also after adjustment for insulin sensitivity [20], which is in line with our findings. Likewise, Ahlqvist et al. found that their severe insulin deficient (SIDD) subtype characterized by being GADA negative, low age at onset, relatively low BMI, low insulin secretion, and poor metabolic control had the highest risk of DR. On the contrary their severe insulin resistance diabetes (SIRD) subtype, characterized by high BMI and insulin resistance had the highest risk of kidney disease [21]. A previous analysis has demonstrated a 70% similarity between our hyperinsulinemic subtype and the SIRD identified by Ahlqvist et al. Conversely, the similarity between the SIDD subtype and our insulinopenic subtype was limited [10]. Studies outside Europe have shown the same results as Ahlqvist et al. [22, 23]. Of interest we found that BMI had a substantial effect on the DR risk estimate in our logistic regression model in the insulinopenic (and slimmer) subtype vs. classical type 2 diabetes, in which we saw a clear reduction in the elevated relative risk estimate when adjusting for BMI. This suggests that obesity may be an important confounder or mediator of the diabetes phenotype associations with DR.

This study benefits from a longitudinal design and a large well-defined cohort, and the utilization of national registries with valid, accurate and high completeness in combination with biochemical data. The limitations are also important to acknowledge. We were unable to investigate the risk of progression to proliferative DR due to few events. Furthermore, the study lacks information on socio-economic characteristics, smoking status and blood pressure. In addition, insulin use might have influenced HOMA values, however excluding insulin-users in a sensitivity analysis did not alter our

findings. Lastly, a subsample of individuals did not have a screening episode registered in DiaBase, which might cause a selection bias.

In summary, the results from this study indicates that subcategorization of type 2 diabetes may be important in order to tailor individualized diabetes treatment and screening of diabetic complications in individuals with type 2 diabetes.

Guarantors: FNP is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author Contributions: FP and JG designed the study. FP, LS and SM performed data analysis and statistical analysis. FP drafted the manuscript with input from all authors.

Funding: This work was supported by VELUX FONDEN (grant 00028744) and Synoptik Fonden. The DD2 study was supported by the Danish Agency for Science and Higher Education (grant nos. 09-067009 and 09-075724), the Danish Health and Medicines Authority, the Danish Diabetes Association, Region of Southern Denmark, and the Novo Nordisk Fonden (NNF17SA0030364).

Conflict of Interest Disclosures: None reported.

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Table 1 – Characteristics of type 2 diabetes stratified by subtype

	Overall	Classical	Hyperinsulinemic	Insulinopenic
Number of patients, n	3672	2334	966	372
Gender, n(%) male	2130(58.0)	1383(59.3)	534(55.3)	213(57.3)
Age, years (IQR)	64.3(55.7;70.8)	63.8(55.4;70.5)	64.7(56.0;71.7)	66.0(56.9;71.1)
Duration of diabetes, years(IQR)	3.7(2.3;5.5)	3.7(2.3;5.6)	3.5(2.2;5.5)	3.8(2.4;5.2)
Marital status, n(%)				
Never married	473(12.9)	305(13.1)	122(12.6)	46(12.4)
Married	2263(61.6)	1474(63.2)	556(57.6)	233(62.6)
Widowed or divorced	936(25.5)	555(23.8)	288(29.8)	93(25.0)
Charlson Comorbidity Index score, n(%)				
0 (low)	2699(73.5)	1741(74.6)	668(69.2)	290(78.0)
1 (moderate low)	452(12.3)	284(12.2)	128(13.3)	40(10.8)
2 (Moderate high)	337(9.2)	202(8.7)	106(11.0)	29(7.8)
>=3 (high)	184(5.0)	107(4.6)	64(6.6)	13(3.5)
Use of medication, n(%)				
Insulin	306(8.3)	201(8.6)	48(5.0)	57(15.3)
Glucose lowering treatment, excl. insulins	3190(86.9)	2054(88.0)	820(84.9)	316(84.9)
Antihypertensive drugs	2804(76.4)	1742(74.6)	815(84.4)	247(66.4)
Cholesterol lowering drugs	2845(77.5)	1794(76.9)	778(80.5)	273(73.4)
Level of DR, n(%)				
0 (No DR)	3484(94.9)	2208(94.6)	942(97.5)	334(89.8)
Level 1 (Mild DR)	144(3.9)	96(4.3)	19(2.0)	29(7.8)
Level 2 (Moderate DR)	33(0.9)	22(0.9)	<5	7(1.9)
Level 3 (Severe DR)	5(0.1)	<5	<5	<5
Level 4 (Proliferative DR)	6(0.2)	<5	<5	<5
Screening facility, n(%)				
Private practice	3177(86.5)	1995(85.5)	862(89.2)	320(86.0)
Hospital	495(13.5)	339(14.5)	104(10.8)	52(14.0)
Laboratory results				
HbA_{1c} mmol/mol, median(IQR)	48.5(44.0;55.3)	50.0(45.2;57.0)	46.0(42.5;51.1)	48.0(43.0;54.1)
HbA_{1c} %, median(IQR)	6.6(6.2;7.2)	6.7(6.3;7.4)	6.4(6.0;6.8)	6.5(6.1;7.1)

eGFR mmol/mol, median(IQR)	82.7(70.1;90.0)	83.9(71.6;90.0)	77.2(64.0;88.9)	86.0(77.0;90.0)
Cholesterol mmol/mol, median(IQR)	4.2(3.6;4.8)	4.2(3.7;4.8)	4.2(3.6;4.7)	4.2(3.7;4.7)
HDL mmol/mol, median(IQR)	1.2(1.0;1.5)	1.2(1.0;1.4)	1.1(0.9;1.4)	1.5(1.2;1.8)
LDL mmol/mol, median(IQR)	2.0(1.6;2.6)	2.1(1.6;2.6)	2.0(1.5;2.5)	2.1(1.6;2.5)
Triglycerides mmol/mol, median(IQR)	1.8(1.3;2.4)	1.8(1.3;2.5)	2.0(1.5;2.7)	1.2(0.9;1.5)
uACR, median(IQR)	12.0(6.0;28.0)	12.0(6.1;27.2)	12.1(6.5;36.0)	8.8(5.2;18.4)
HOMA2-B %, median(IQR)	90.0(68.5;117.4)	81.2(65.6;96.7)	137.2(124.8;159.9)	61.4(48.0;77.8)
HOMA2-S %, median(IQR)	35.7(26.9;48.5)	37.0(29.3;46.7)	27.2(21.9;34.7)	74.6(68.6;87.2)
BMI, median(IQR)	30.2(26.9;34.2)	29.9(26.9;33.6)	32.8(29.4;36.9)	25.7(23.4;28.7)

According to Danish legislation we are not permitted to present data below 5 cases. IQR: interquartile range. DR: diabetic retinopathy. uACR: urine albumin-creatinine ratio.

Table 2 - Odds ratio (OR) with 95% confidence interval (CI) for presence of prevalent diabetic retinopathy (DR) according to type 2 diabetes subtype.

Subtype	DR no	DR yes	OR (95% CI)			
			Crude	Age and sex adjusted	Multivariable model excl. BMI	Multivariable model
Classical	2208	126	Reference	Reference	Reference	Reference
Hyperinsulinemic	942	24	0.45 (0.29;0.70)	0.46 (0.30;0.72)	0.57 (0.36;0.92)	0.69 (0.42;1.14)
Insulinopenic	334	38	1.41 (1.17;1.71)	1.45 (1.20;1.76)	1.52 (1.23;1.89)	1.30 (1.02;1.65)

Multivariable logistic regression model adjusted for sex, age, civil, status, diabetes duration, glucose-, lipid- or blood pressure lowering medication, BMI, HbA1c, and a modified Charlson Comorbidity index.

Table 3 – Hazard ratio (HR) with 95% confidence interval (CI) for risk of incident and progression diabetic retinopathy according to subtype of type 2 diabetes.

Subtype	Event	Person-years at risk	HR (95% CI) Crude	Age and sex adjusted	Multivariable model excl. BMI	Multivariable model
Risk of incidence						
Classical	259	11136.4	Reference	Reference	Reference	Reference
Hyperinsulinemic	67	4378.9	0.75 (0.58;0.99)	0.76 (0.58;1.00)	0.62 (0.47;0.82)	0.60 (0.45;0.80)
Insulinopenic	38	1824.3	0.87 (0.62;1.23)	0.87 (0.62;1.22)	0.92 (0.65;1.30)	1.01 (0.70;1.45)
Risk of progression						
Classical	186	11383.1	Reference	Reference	Reference	Reference
Hyperinsulinemic	37	4396.0	0.63 (0.44;0.90)	0.63 (0.44;0.90)	0.53 (0.37;0.76)	0.53 (0.37;0.77)
Insulinopenic	32	1849.1	1.06 (0.73;1.55)	1.07 (0.74;1.56)	1.02 (0.69;1.51)	1.12 (0.74;1.68)

Multivariable logistic regression model adjusted for sex, age, civil status, diabetes duration, glucose-, lipid- or blood pressure lowering medication, BMI, HbA_{1c}, and a modified Charlson Comorbidity index (excluding diabetes).

Figure 1: Flowchart of study cohort.

LADA: Latent Autoimmune Diabetes in Adults. T2DM: Type 2 diabetes mellitus.