Diabetes Epidemiology and Management 8 (2022) 100108

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Original article

Incidence and prevalence of diabetic retinopathy in the Greenlandic Inuit: A register-based study

Trine Jul Larsen[a,*], Marit Eika Jørgensen[a,b], Michael Lynge Pedersen[a,b], Henrik Lund-Andersen[c,d], Stine Byberg[c]

[a] Greenland Center of Health Research, Institute of Nursing and Health Science, University of Greenland, Ilisimatusarfik, Manutooq 1, Nuussuaq, Nuuk 3905, Greenland
[b] Steno Diabetes Center Greenland, Nuuk, Greenland
[c] Steno Diabetes Center Copenhagen, Copenhagen, Denmark
[d] Rigshospitalet-Glostrup University Hospital, Glostrup, Denmark

ARTICLE INFO

Article History:
Received 25 August 2022
Accepted 31 August 2022
Available online 1 September 2022

Keywords:
Diabetic retinopathy
Diabetes
HbA_1c
Epidemiology
ICDR-scale
Ultra wide-field fundus camera

ABSTRACT

Aims: Assess the incidence and prevalence of diabetic retinopathy (DR) among all persons registered with diabetes in the electronic medical records (EMR) from 2016 to 2020 and investigate factors associated with both incident and prevalent DR.
Methods: We calculated the five-year incidence rate of DR per 1000 person years, and calculated the prevalence of DR, using Poisson regression analysis. We calculated the incidence rate ratios (IRR) in univariate and multivariate Poisson regression analysis, to assess risk factors associated with incident DR. We calculated the Odds ratios (OR) to assess risk factors of prevalent DR in univariate and multivariate Logistic regression analyses.
Results: We found 10.4% persons developed incident DR during follow-up, equivalent to an incidence rate of DR of 29.2 pr. 1000 (95%CI: 22.9–37.3) person years. The total prevalence of DR was 13.6%. Higher HbA_1c levels and longer diabetes duration were significantly associated with incident and prevalent DR. Higher levels of LDL cholesterol were significantly associated with a lower risk of incident DR.
Conclusion: The incidence and prevalence of DR in Greenland is lower than in most other parts of the world. In agreement with previous studies on risk factors for DR, HbA_1c levels and diabetes duration were associated with incident/prevalent DR.

1. Introduction

In Greenland, the prevalence of type 2 diabetes mellitus (T2DM) has increased markedly during the last decades, especially in settlements and smaller towns [1,2]. According to results from population-based surveys, approximately 10% of the adult Greenlandic population have diabetes and 20% have prediabetes. Furthermore, until a few decades ago, most adults identified with diabetes were unaware of the condition [3,4].

Thus, the high prevalence of T2DM in Greenland poses a major public health challenge in a geographical dispersed population with a potentially high risk of developing long-term diabetes complications, as the awareness of diabetes and the knowledge of risk factors, symptoms and complications is low [5]. Adults with diabetes, unaware of their disease, are more prone to develop diabetic complications caused by prolonged hyperglycemia [6,7], such as diabetic retinopathy (DR) which initially is asymptomatic.

DR is one of the most frequent occurring complications of diabetes, causing blindness in working-age individuals, affecting many people with diabetes [8,9] and regular screening is recommended, in order to timely prevent permanent vision loss [10,11].

A previous study conducted in Nuuk, Greenland, estimated the prevalence of diabetes complications including neuropathy, microalbuminuria and DR, among Greenlanders and Danes registered with T2DM, based on electronic medical records (EMR). The study found neuropathy (51%) was the most frequent diabetes complication, followed by microalbuminuria (43%) and DR (14%) and further concluded that DR was more prevalent among persons with Danish ethnicity [12]. Latest, a study estimated and compared microvascular complications among Greenlanders and non-Greenlanders with T2DM in Nuuk, and found non-Greenlanders had a higher prevalence (21%) of DR compared to Greenlanders (7%) [13]. Additionally, in the 2018 population health survey covering all of Greenland, the overall

* Corresponding author.
E-mail address: tjul@uni.gl (T.J. Larsen).

https://doi.org/10.1016/j.deman.2022.100108

prevalence of DR among persons with screen detected and known diabetes and prediabetes was assessed, in which 9% with known diabetes had DR [14]. Nonetheless, both the studies by Pedersen et al and Larsen et al, are based on small population samples and comprise only prevalence data.

In this study, we aim to investigate the incidence and prevalence of DR among the entire Greenlandic population registered with diabetes using the national EMR data and investigate factors associated with both incident and prevalent DR, in order to identify subgroups at risk and target preventive initiatives.

2. Methods

This study is a nationwide retrospective observational study based on extraction of data from the national EMR system, comprising persons registered with type 1 diabetes mellitus (T1DM) and T2DM, attending the public lifestyle clinics in Greenland, over a five-year period, from 2016 to 2020.

The lifestyle clinics in Greenland were established in 2011, replacing a previously three year national diabetes project, aiming to implement primary care for patients with diabetes.

In accordance with the national diabetes project, special diabetes profiles were integrated in the EMR, making it possible to continually assess, monitor and evaluate diabetes treatment and care. The lifestyle clinics records contain general information on lifestyle factors including smoking, weight, blood pressure (BP), diabetes duration, HbA_1c, urine albumin-creatinine ratio (U-ACR), lipids and results of screening for neuropathy, DR and other parameters [15].

Lifestyle clinics in Nuuk and other bigger towns provides diabetes care. In addition, there is a general focus on prevention and management of other lifestyle related diseases, including hypertension and chronic obstructive lung disease. However, smaller towns and settlements are not able to carry out the same level of care, and several diabetes patients depend on visiting health care professionals for care or must travel to nearest hospital, in order to receive diabetes care and treatment [15,16].

2.1. Screening and grading

Since 2015, Optos® ultra wide-field fundus cameras have been placed in nine cities in Greenland, and comprise the backbone of the DR screening in Greenland. All persons registered with diabetes are invited for regular DR screenings in the city closest to their home. However, due to the wide distances, travelling to the nearest eye screening station can take days.

All images are uploaded to a server and graded by specialist ophthalmologist nurses at Steno Diabetes Center Copenhagen/Rigshospitalet-Glostrup University Hospital in Denmark, according to the International Clinical Diabetes Retinopathy disease severity scale (ICDR) [17].

Patients in need of treatment for DR are referred to an ophthalmologist and further treatment in Nuuk or Denmark.

2.2. EMR

This study is based on data from two different medical record systems, Æskulap and Cosmic, used in Greenland during the study period, in which all information from the lifestyle clinics and other medical information is registered. In 2007, Æskulap, was implemented in all health care sites in Greenland. In 2013, a new medical record system, Cosmic, was introduced, and fully replaced Æskulap in Nuuk, during 2015. Later during 2016 and the first half of 2017, Cosmic, was fully implemented in the rest of Greenland, and is now the only EMR system in the country, except in East Greenland, where limited internet capacity, limited its use and continued to use Æskulap [15].

2.3. Subjects

Based on pseudo-anonymized data extracted from Cosmic and Æskulap for East Greenland, we assessed the incidence and prevalence of DR over a five-year period among all residents of Greenland, who as of January 2016, were registered with either T1DM or T2DM and followed them until 31.12.2020. Persons with one or more screenings for DR were included in the study. To increase the number of persons with more than one screening, all persons with diabetes registered in Cosmic, were manually looked up in the previously used EMR system, Æskulap, to assess whether any of the persons previously were registered with DR. If they had no DR in Æskulap, the last DR screening registered in Cosmic counted as the first screening episode. The prevalence of DR was assessed among all persons registered with diabetes in Cosmic with at least one DR screening.

2.4. Ethics

Ethical approval was granted by the ethical review committee for Greenland (KVUG 2017-12) and by the Greenland Health Authorities.

2.5. Statistical analysis

We summarized clinical and demographic baseline characteristics available in the EMR records, using descriptive statistics and tested for differences using Chi2 test for categorical variables and T-test for continuous variables. Diabetes duration, weight, age, HbA_1c, and U-ACR, were not normally distributed, thus we reported the median and interquartile range (IQR). Systolic- and diastolic BP, LDL-, HDL- and total cholesterol were normally distributed and the mean and standard deviation (SD) was reported.

Baseline characteristics were reported both among persons included in the incidence and prevalence analyses.

For the incidence analyses, we excluded all persons with prevalent DR at first visit in Cosmic or last visit in Æskulap (if any record in Æskulap was available). We followed persons for incident DR from date of first eye screening in Cosmic or last eye screening in Æskulap (if no DR at last visit), until DR or their last recorded eye screening in Cosmic. Only persons with more than one screening were included in the incidence analysis.

We calculated the five-year incidence rate of DR per 1000 person years, using Poisson regression analysis with age as the underlying time scale and calculated the prevalence of DR, among all persons with one or more records in Cosmic.

To assess risk factors associated with incident DR, we calculated the incidence rate ratios (IRR) for data available in the EMR records; T1DM/T2DM, diabetes duration, sex, place of residence, age, smoking, weight, BP, HDL-, LDL-, and total cholesterol, HbA_1c and U-ACR at first entry in EMR. The effect of the risk factors were assessed in both univariate and multivariate Poisson regression analysis.

To assess risk factors associated with prevalent DR, we calculated the Odds ratios (OR) and assessed the effect of the risk factors in both univariate and multivariate Logistic regression analyses.

Due to intercorrelation with LDL- and HDL cholesterol, total cholesterol was not included in the multivariate analyses.

All statistical analyses were performed using Stata 17.

3. Results

A total of 1175 persons registered with T1DM or T2DM, with one or more screenings for DR, were identified. Of those a total of 623 had more than one screening and were included in the incidence analysis.

3.1. Baseline characteristics

All baseline characteristics were stratified by DR status during follow-up (Table 1).

No significant differences of DR were observed according to sex and according to place of residence.

The median diabetes duration was significantly higher among persons with incident DR (6.8 years) compared to persons with no DR during follow-up (3.8 years). This was similar for prevalent DR, however persons with prevalent DR had longer diabetes duration (8.8 years) compared to persons with incident DR.

The median age among persons with incident and prevalent DR was 61 years.

HbA_1c levels were significantly higher among persons with incident DR (8.7% (72 mmol/mol)) compared to persons with no DR during follow-up (7.2% (55 mmol/mol)) and higher among persons with prevalent DR (8.4% (68 mmol/mol)) compared to persons with no DR at first visit (7.0% (53 mmol/mol)). Also persons with prevalent DR, had a significantly higher level of U-ACR (3.6 mg/mmol) compared to persons with no DR at first visit (2.5 mg/mmol).

For persons with both incident and prevalent DR, the level of LDL cholesterol was significantly lower (2.7−3.0 mmol/l) compared to persons with no DR (3.3 mmol/l). The same trend was seen for total cholesterol, in which persons with no DR during follow-up significantly had a higher level of total cholesterol (4.9 mmol/l) compared to persons with incident DR during follow-up (4.1 mmol/l). The level of total cholesterol among persons with prevalent DR was higher (4.5 mmol/l) compared to persons with incident DR, however the level was still significantly lower compared to persons with no DR at first visit in Cosmic (4.8 mmol/l).

The majority of persons with DR in Greenland have T2DM, reflecting the much higher prevalence of T2DM compared with T1DM.

3.2. Incidence

We assessed the incidence of DR among persons with a first record in either Æskulap or Cosmic, without DR. We found 65 out of 623 (10.4%) persons developed incident DR during follow-up, equivalent to an incidence rate of DR of 29.2 pr. 1000 (95%CI: 22.9 −37.3) person years.

According to the ICDR severity scale, 558 persons (89.6%) had no apparent retinopathy (severity level 0), 46 persons (7.4%) had mild non-proliferative DR (severity level 1), 9 persons (1.4%) had moderate non-proliferative DR (severity level 2), 4 persons (0.6%) had severe non-proliferative DR (severity level 3) and finally 6 persons (1%) had proliferative DR (severity level 4).

We assessed the risk factors for incident DR in both univariate and multivariate analysis (Table 2).

In the univariate analysis, we found diabetes duration (per five year increase) to be significantly associated with incident DR. Further, HbA_1c (per 2.6% increase (5 mmol/mol)) and U-ACR (per 1 unit increase) significantly increased the risk of incident DR. Finally, we found higher levels of LDL cholesterol (per 1 mmol/l increase) significantly was associated with a lower risk of incident DR. The same trend was seen for total cholesterol, in which higher levels of total cholesterol (per 1 mmol/l increase) significantly was associated with a lower risk of incident DR in univariate analysis.

In the multivariate analysis, diabetes duration, and HbA_1c significantly increased the risk of incident DR, while higher levels of LDL cholesterol were significantly associated with a lower risk of incident DR.

3.3. Prevalence

During the five-year study period from 2016 to 2020, we found 160 out of 1175 persons had prevalent DR, equivalent to a prevalence of 13.6%.

According to the ICDR scale, 1015 persons (86.3%) had a DR severity level of 0, 102 persons (8.7%) had severity level 1, 29 persons (2.5%) had severity level 2, 5 persons (0.4%) had severity level 3 and finally 24 persons (2%) had severity level 4.

We assessed the risk factors for prevalent DR in both univariate and multi variate analysis (Table 3).

In the univariate analysis, females had a significantly higher risk of prevalent DR compared with males. Further, diabetes duration, HbA_1c and U-ACR were also significantly associated with prevalent DR.

Table 1
Baseline characteristics (* denotes a significant difference between the groups).

Baseline characteristic	No DR during follow-up	Incident DR during follow-up	No DR at first visit in Cosmic	Prevalent DR at first visit in Cosmic
Sex 1 missng				
-Male	48% (268)	37% (24)	47% (474)	38% (60)
-Female	52% (289)	63% (41)	53% (540)	63% (100)
Smoking status 32 missing, 81 missing				
-Yes	36% (199)	28% (18)	35% (356)	37% (59)
-No	59% (331)	66% (43)	58% (588)	57% (91)
Place of residence 1 missing, 5 missing				
-Town	89% (496)	88% (57)	87% (884)	89% (142)
-Settlement	8% (46)	6% (4)	7% (70)	6% (9)
-outside Greenland	3% (15)	6% (4)	6% (57)	5% (8)
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Diabetes duration (years)* 27 missing, 21 missng	**3.8 (1.9-6.8)***	**6.8 (3.5-13.1)***	**4.2 (1.8-8.0)***	**8.8 (3.4-16.6)***
Weight (kg) 15 missing, 56 missing	83 (71-96)	88 (78-99)	86 (73-100)	85 (72-97)
Age at entry (years) 1 missing, 1 missing	61 (53-68)	61 (52-68)	61 (54-69)	61 (52-69)
Systolic blood pressure (mmHg) (mean (SD)) 40 missing, 148 missing	138 (17)	136 (17)	136 (16)	137 (18)
Diastolic blood pressure (mmHg) (mean (SD)) 40 missing, 148 missing	81 (10)	82 (11)	82 (10)	81 (11)
HbA1c (%) (mmol/mol)* 6 missing, 18 missing	**7.2% (6.6-7.5%)* 55 (49-58)**	**8.7% (7.1-10.6%)* 72 (54-92)**	**7% (6.5-8.2%)* 53 (48-66)**	**8.4% (7.2-10%)* 68 (55-86)**
U-ACR (per 1 unit increase) 93 missing, 192 missing	**2.5 (2.4-6.8)**	**3.3 (2.4-12.6)**	**2.5 (2.5-7.7)***	**3.6 (2.5-16.1)***
LDL cholesterol (mmol/l) (mean(SD)) 40 missing, 83 missing	**3.3 (1.3)***	**2.7 (1.3)***	**3.3 (1.3)***	**3.0 (1.2)***
HDL cholesterol (mmol/l) (mean(SD)) 38 missing, 79 missing	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	1.3 (0.4)
Total cholesterol (mmol/l) (mean(SD)) 39 missing, 80 missing	**4.9 (1.3)***	**4.1 (1.1)***	**4.8 (1.2)***	**4.5 (1.2)***
Diabetes type				
-T1DM	3% (16)	6% (4)	3% (25)	13% (20)
-T2DM	97% (541)	94% (61)	97% (989)	88% (140)

Table 2
Risk factors for incident DR (* denotes a significant risk factor).

	Univariate analyses	Multivariate analyses
	Incidence rate ratio (95%CI)	Incidence rate ratio (95%CI)
Sex		
-Male	1.00 (ref)	1.00 (ref)
-Female	1.36 (0.82-2.25)	0.76 (0.40-1.43)
Smoking status		
-Yes	1.00 (ref)	1.00 (ref)
-No	1.34 (0.77-2.31)	1.21 (0.61-2.41)
Place of screening		
-Town	1.00 (ref)	1.00 (ref)
-Settlement	0.95 (0.34-2.61)	0.86 (0.26-2.88)
-outside Greenland	1.44 (0.52-3.96)	1.51 (0.51-4.44)
Diabetes duration (per 5 year increase)	**1.05 (1.02-1.08)***	**1.04 (1.00-1.08)***
Weight (per 5 kg increase)	1.04 (0.98-1.01)	1.07 (0.99-1.15)
Age at entry (per 5 year increase)	1.04 (0.93-1.15)	1.13 (0.95-1.36)
Systolic blood pressure (per 5 mmHg increase)	0.99 (0.92-1.06)	0.96 (0.92-1.08)
Diastolic blood pressure (per 5 mmHg increase)	1.04 (0.93-1.17)	1.11 (0.91-1.36)
HbA1c (per 2.6% (5 mmol/mol) increase)	**1.09 (1.04-1.15)***	**1.13 (1.06-1.22)***
U-ACR (per 1 unit increase)	**1.01 (1.00-1.03)***	1.00 (0.98-1.02)
LDL (per 1 mmol/l increase)	**0.77 (0.62-0.96)***	**0.67 (0.52-0.87)***
HDL (per 1 mmol/l increase)	0.85 (0.49-1.51)	1.48 (0.74-2.95)
Total cholesterol (per 1 mmol/l increase)	**0.62 (0.49-0.79)***	
Diabetes type		
-T1DM	1.58 (0.58-4.35)	1.31 (0.34-5.05)
-T2DM	1.00 (ref)	1.00 (ref)

Persons registered with T1DM had also a significantly higher risk of prevalent DR, while higher levels of LDL cholesterol and higher levels of total cholesterol significantly were associated with a lower risk of prevalent DR.

In the multivariate analyses, longer diabetes duration was significantly associated with an increased risk of prevalent DR the same was seen for HbA_1c and U-ACR. Finally higher levels of LDL cholesterol were significantly associated with a lower risk of prevalent DR. The association seen with T1DM in the univariate analyses were attenuated after adjustments and no longer significant.

4. Discussion

In this study we aimed to investigate the incidence, prevalence and risk factors associated with DR among all persons registered with diabetes in the Greenlandic EMR system.

We found a cumulative incidence of DR of 10.4%, during a five-year period in Greenland equivalent to an incidence rate of 29.2 cases per 1000 person years, and a total prevalence of DR of 13.6%.

We found higher levels of HbA1c significantly was associated with the risk of both incident and prevalent DR, in accordance with the previous studies, “The Diabetes Control and Complications Trial” and “The UK Prospective Diabetes Study”, which have demonstrated a strong linkage between blood glucose levels and the offset and advancement of DR, and showed that well controlled blood glucose levels, reduced DR by 25% compared to conventional treatment [18,19]. The mechanism behind DR is complex, but studies have found DR is caused by hyperglycemia-induced oxidative stress. The prolonged hyperglycemia causes blood vessels in the retina to leak fluid or hemorrhage, distorting vision and in its most advanced stage, new abnormal blood vessels can proliferate on the surface of the retina, leading to scarring and cell loss in the retina [20].

Table 3
. Risk factors for prevalent DR (* denotes a significant risk factor).

	Univariate analyses	Multivariate analyses
	Odd ratio (95%CI)	Odds ratio (95%CI)
Sex		
-Male	1.00 (ref)	1.00 (ref)
-Female	**1.46 (1.04-2.06)***	1.48 (0.90-2.45)
Smoking status		
-Yes	1.00 (ref)	1.00 (ref)
-No	0.93 (0.66-1.33)	0.78 (0.49-1.24)
Place of screening		
-Town	1.00 (ref)	1.00 (ref)
-Settlement	0.80 (0.39-1.64)	0.66 (0.24-1.72)
-outside Greenland	0.87 (0.41-1.87)	0.87 (0.31-2.39)
Diabetes duration (per 5 year increase)	**1.59 (1.31-1.93)***	**1.27 (1.02-1.58)***
Weight (per 5 kg increase)	0.98 (0.95-1.02)	1.00 (0.95-1.06)
Age at entry (per 5 year increase)	0.98 (0.91-1.05)	0.93 (0.82-1.05)
Systolic blood pressure (per 5 mmHg increase)	1.03 (0.97-1.09)	1.08 (0.99-1.18)
Diastolic blood pressure (per 5 mmHg increase)	0.97 (0.89-1.06)	0.88 (0.75-1.03)
HbA1c (per 2.6% (5 mmol/mol) increase)	**1.15 (1.11-1.19)***	**1.14 (1.08-1.20)***
Urine albumin-creatinine ratio (per 1 unit increase)	**1.01 (1.00-1.01)***	**1.01 (1.00-1.01)***
LDL (per 1 mmol/l increase)	**0.85 (0.74-0.98)***	**0.82 (0.68-0.98)***
HDL (per 1 mmol/l increase)	0.94 (0.63-1.40)	1.31 (0.75-2.28)
Total cholesterol (per 1 mmol/l increase)	**0.80 (0.68-0.93)***	
Diabetes type		
-T1DM	**5.65 (3.06-10.4)***	1.94 (0.73-5.12)
-T2DM	1.00 (ref)	1.00 (ref)

In addition, we found diabetes duration significantly was associated with the risk of both incident and prevalent DR, which also can be explained by a prolonged exposure to hyperglycemia, which increases the risk of vascular injury leading to DR [21].

In the univariate analysis, we found that a higher in U-ACR significantly increased the risk of incident DR, correspondent to a study conducted in Indonesia, in which high U-ACR have shown to cause endothelial dysfunction, influencing the vasculature in the kidneys and retina, and is closely associated to progression of DR [22].

For prevalent DR, we found females significantly had a higher risk of DR in univariate analysis, corresponding to a study conducted in China [23]. However, controversial results are to be found regarding DR and gender differences in the literature [24], as another study conducted in Germany, which assessed risk factors associated with DR in T2DM, found men had a higher risk of prevalent DR [25].

Surprisingly, we found higher levels of LDL cholesterol and higher levels of total cholesterol, were associated with a significantly lower risk of both incident and prevalent DR.

According to a meta-analysis, statins have shown to have a protective against DR. The protective effect is derived from the reduction of oxidative stress, endothelial dysfunction, inflammation and angiogenesis along with the improvement of the endothelial cells [26].

However, our findings may be a result of confounding by statin-indication, reflecting a higher use of statins in high risk groups of micro- and macrovascular complications. Unfortunately, information on medication was not available in the study at hand.

An alternative explanation could be confounding by genetic factors. A LDL receptor missense variant causing high LDL cholesterol is frequent in the Greenlandic population [27]. Thus, high LDL cholesterol may be a marker of Inuit genetic heritage rather than directly associated with DR, thus confounding the observed association.

In our study, we found a low incidence and prevalence of DR among the Greenlandic Inuit, compared with studies from other similar populations. In Canada, in which the prevalence of diabetes has increased steadily, studies have found Canadian Indigenous people have higher rates of DR compared to non-Indigenous populations [28]. Further, a study conducted on the population of Manitoba, Canada, found the average prevalence of any DR in each year during 2007−2013, was 25%, with a cumulative incidence of DR at 17% (95% CI: 15.4−18.7%) over a six-year period. The study was based on medical records with data from 49 communities from 2007 to 2013 [29].

In Denmark, the prevalence of T2DM has gradually increased, and is expected to increase, as a results of a decrease in mortality, improved treatments and longer life expectancy [30].

Based on data from The Danish Registry of Diabetic Retinopathy and Maculopathy (DiaBase), the latest annual report from 2014-2015, showed the nationwide prevalence of DR was 22% among all patients diagnosed with diabetes in Denmark [31].

In Funen, Denmark, a study conducted in 2014, estimated the prevalence of DR, and assessed the risk factors of DR among 22 098 persons registered with T1DM and T2DM, based on data from Funen Diabetes Database.

The study found the overall prevalence of DR was 23.8%, with a prevalence of 54.3% among persons with T1DM and prevalence of 21.2% among persons with T2DM [32]. The overall prevalence of DR and the prevalence of DR among persons with T2DM, were both higher compared to our results. Comparing the overall baseline characteristics with our study, the diabetes duration in both studies were quite similar, with a median diabetes duration at 9 years (IQR: 5−16) from the study of Funen and a median diabetes duration at 8.8 years (IQR: 3.4−16.6) in our study.

However, the median level of HbA_1c in the study of Funen, was lower with a level of 6.8% (51 mmol/mol) (IQR: 6.3%-7.7% (45 −61 mmol/mol)) compared to our study, where the level of HbA_1c was 8.4% (68 mmol/mol) (IQR: 7.2−10.0% (55−86 mmol/mol)), indicating Greenland Inuit may have a lower risk of prevalent DR, despite similar diabetes duration and higher HbA_1c levels. However, the difference in the sample size must be noticed.

Corresponding to our study, the study of Funen, found diabetes duration (OR: 1.39 (95%CI: 1.33−1.45), per five-year increase) and HbA_1c (OR: 1.15 (95%CI: 1.09−1.21), per 3.1% (10 mmol/mol) increase) significantly was associated with increased risk of prevalent DR.

In Gloucestershire, England, the prevalence and incidence of DR was assessed based on EMR during the period of 2012-2016, among 35 873 persons registered with diabetes, with at least one assessment for DR [33]. The study found the overall prevalence of DR in 2016, was 36.9% (95%CI: 35.9-37.3), while the four-year incidence of any DR in the study was 40.3% (95%CI: 39.1-41.5) per 100 people registered with diabetes. Their findings were both higher compared to our results. Comparing the baseline characteristics to our study, the duration of diabetes were similar, with a median diabetes duration of 9 years (IQR: 4-17) in the Gloucestershire study, but a lower level of HbA_1c with a median level of 7.5% (59 mmol/mol) (IQR: 6.7−9.0% (50-75 mmol/mol)) compared to our study, indicating potentially less severe effects of diabetes duration and HbA1c among Greenland Inuit.

Consistent with our study, diabetes duration (per five-year increase) and higher levels of HbA_1c (per 3.1% (10 mmol/mol) increase) were significantly associated with an increased risk of both prevalent and incident DR.

Considering the high prevalence of T2DM during the last decades in Greenland [4], and taking the modifiable risk factors of DR such as obesity, hypertension and poor glycemic control and unmodifiable risk factors as long diabetes duration into account [34], we assumed the absolute numbers and the incidence and prevalence of DR in the entire Greenlandic population registered with diabetes, would have been higher, nonetheless the results of our study, show DR is low in both incident and prevalent DR, and only very few persons have severe DR.

Studies of diabetes in Greenland have shown a higher prevalence of diabetes in settlements [2], thus a higher occurrence of DR in settlements in our study would have been expected however, this was not the case. Despite the vast distances in Greenland, with limited access to health care service, in which two-six days can be expected in order to receive an eye examination in smaller towns and settlements, a recent study only found minor differences in the quality of diabetes care in settlements compared to towns [35].

Further, based on recent data, a study found approximately 80% of diabetes patients in all regions of Greenland, had had an eye screening for DR within a two-year period while, 38.2% patients received an eye screening within the previous year.

Looking closer at the distribution of the screenings, approximately 40% of diabetes patients living in settlements received an eye screening within the previous year, while 78% received a screening within the two-year period [36]. Despite, the level of quality of care in Greenland has been maintain since 2014, the screening attendance still does not live up to the Danish standards, where the prevalence goal for eye examinations among patients registered with diabetes is 90% [37].

Globally, great variations in the prevalence of DR have been found, with a high prevalence of DR among South Asians (17.5%) and Latinos (30−50%) compared to Europeans (7.9%) [38]. Further, ethnicity is considered a complex and independent risk factor for DR, in which genetic polymorphism may cause predispositions to the development and progression of DR.

According to a meta-analysis, several studies demonstrated a relationship between the gene *TCF7L2* and the development of T2DM, as increased expression of this gene, was associated with poor serum glucose control. It was further found, that patients registered with the rs12255372 or rs7903146 variants of the *TCF7L2* gene, had a higher risk of developing DR.

However, Chinese population registered with the rs12255372 or rs7903146 variants of the *TCF7L2* gene, had a weakly, but not significant association with the development of DR, in which the variant rs7903146 of the *TCF7L2* gene, significantly associated with increased risk of developing DR, especially among the Caucasian population [19].

Finally, another meta-analysis, found the Ala allele of the *PPARy2* gene, which plays a key role in multiple pathways including glucose metabolism angiogenesis and inflammation, yielded a protective effect against DR in patients with T2DM, the study found a stronger association in Caucasian subgroups [39].

Thus, it is possible that Greenland Inuit may be less prone to DR compared with e.g. Danish people, based on ethnicity and genetic differences.

Genetically, the Greenlandic population, is differentiated from other populations such as Europeans, because of its isolated and generally small population size for a long period of time, where genetic adaptation to extreme environments is believed to have been essential for survival in the Arctic region [40]. Close to 20% of cases of diabetes in Greenland has a monogenic diabetes etiology, primarily explained by the recessive *TBC1D4* variant and *MODY* diabetes including a novel *HNF1A* variant with an allele frequency of 1·9% in the Greenlandic Inuit and absent elsewhere. Similar numbers for monogenic diabetes are 1−3% in large admixed populations [41].

A recent follow up study showed no increase in macrovascular risk or nephropathy with the *TBC1D4* variant [42].

However, during recent centuries, the Greenlandic population have intermixed with Europeans, leading to a relatively high proportion of genetic European ancestry in modern Greenlanders, where the average estimated degree of European ancestry admixture in present day Inuit in Greenland is 25%, varying with the degree of geographical isolation [43]. Thus, the unique genetic characteristics of the Greenlandic population may play an important role, in our findings, were we found both a low incidence and prevalence of DR.

Understanding the genetics of DR is a unique challenge because of the etiological mechanisms involved, influenced by ethnic differences, in which genetic and environmental factors is estimated to explain approximately 89% of the variation in the risk of DR. Further, familial factors have shown to influence the severity of DR, in which a study have found heritability of DR to explain around 27% of the cases [44,45].

4.1. Strengths and limitations

This is the first study to assess the overall prevalence and incidence of DR in Greenland over a five-year period. A major strength of the study, is that the study comprises all persons diagnosed with diabetes, registered in the national EMR.

A limitation in our study could be an under detection of DR, as a high proportion of persons in Greenland have unknown diabetes, and thus do not appear in the national EMR.

Finally, information on genetics as well as information on medication are needed, which could have had an explanatory impact on our results.

5. Conclusion

The incidence and prevalence of DR in our study, was low compared with other studies, with a highest proportion of mild non-proliferative DR. This may be explained by ethnicity or protective genetic factors, nonetheless continued focus on DR is recommended and further research on epigenetics traits is suggested.

Finally, in agreement with previous studies on risk factors for DR, higher HbA_1c levels and diabetes duration were significantly associated with prevalent/incident DR, while higher levels of both LDL and total cholesterol was associated with a lower risk of both incident and prevalent DR.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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