

Screening attendance, prevalence and severity of diabetic retinopathy (DR) in a cohort of patients with diabetes mellitus secondary to chronic pancreatitis (DMsCP) in Northern Ireland

Catherine Jamison ¹, Tunde Peto ¹, Nicola Quinn,¹ Rossella D'Aloisio,² Laura Nicole Cushley ¹, Philip C Johnston ^{3,4}

To cite: Jamison C, Peto T, Quinn N, *et al*. Screening attendance, prevalence and severity of diabetic retinopathy (DR) in a cohort of patients with diabetes mellitus secondary to chronic pancreatitis (DMsCP) in Northern Ireland. *BMJ Open Diab Res Care* 2021;**9**:e002267. doi:10.1136/bmjdr-2021-002267

Received 14 March 2021
Accepted 1 August 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Belfast Ophthalmic Reading Centre, Centre for Public Health, Queen's University Belfast, Belfast, UK

²Ophthalmology Clinic, Department of Medicine and Science of Ageing, University G d'Annunzio Chieti-Pescara, Chieti, Italy

³The Belfast Pancreatic Diabetes Clinic, Belfast City Hospital Health and Social Services Trust, Belfast, UK

⁴Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital Belfast, Belfast, UK

Correspondence to

Dr Philip C Johnston;
Pcjohnston@doctors.org.uk

ABSTRACT

Introduction This study investigated Northern Ireland Diabetic Eye Screening Programme (NIDESP) attendance and diabetic retinopathy (DR) prevalence/severity in patients with diabetes mellitus secondary to chronic pancreatitis (PwDMsCP).

Research design and methods Medical/NIDESP records for all PwDMsCP attending the pancreatic diabetes clinic were analyzed in 2017 (n=78) and 2019 (n=94).

Results Between 2017 and 2019, those without DR decreased (76% to 63%); mild non-proliferative DR (NPDR), severe NPDR and PDR were found in 30%, 2% and 5%, respectively (previously 18%, 4%, 2%); diabetic maculopathy (DMac) was present in 12% (previously 10%). There was no significant difference between worst-eye DR/DMac grade and HbA1c, gender, body mass index, pancreatitis etiology and screening attendance ($p>0.05$). Patients with proliferative DR had longer diabetes and pancreatitis duration than DR-free patients (both $p=0.001$). **Conclusions** DR prevalence was similar in PwDMsCP and patients with type 2 diabetes of similar disease duration. This work demonstrates the importance of reaching all patients for establishing DR severity reliably and to provide accessible, equitable care to PwDMsCP.

INTRODUCTION

Diabetic mellitus secondary to chronic pancreatitis (DMsCP) accounts for the majority of cases of pancreatogenic or type 3c diabetes.^{1,2} There is currently a scarcity of data on diabetic retinopathy (DR) rate and severity in patients with diabetes mellitus secondary to chronic pancreatitis (PwDMsCP); published studies are small in number and inhomogeneous in nature. Etiology of chronic pancreatitis includes alcohol, gallstones, and genetic and autoimmune diseases.³ DMsCP is characterized by both pancreatic endocrine and exocrine insufficiency, and can be associated

Significance of this study

What is already known about this subject?

- ▶ There is a paucity of information on diabetic retinopathy (DR) in patients with diabetes mellitus secondary to chronic pancreatitis (PwDMsCP).
- ▶ Vascular complications in patients with secondary diabetes are considered to be lower than in primary diabetes.

What are the new findings?

- ▶ DR prevalence is similar in PwDMsCP to those with type 2 diabetes with similar duration.
- ▶ Those with proliferative DR had a longer duration of diabetes and pancreatic disease when compared with those with no DR.
- ▶ This is the largest dataset of PwDMsCP and DR rates and enhances awareness and care provision to this hard-to-reach population.

How might these results change the focus of research or clinical practice?

- ▶ Combined healthcare efforts to improve patient engagement, including opportunistic screening at the time of diabetes appointments, and provision of multiple appointment offers prove beneficial for reaching these patients.

with an impaired quality of life, chronic pain, malabsorption and malnutrition.

This study assessed DR screening attendance, DR and diabetic maculopathy (DMac) prevalence and severity among PwDMsCP in Northern Ireland, UK.

RESEARCH DESIGN AND METHODS

All patients in the study had DMsCP with presence of pancreatic insufficiency, pathological

pancreatic imaging of chronic pancreatitis and absence of type 1 diabetes antibodies.

In 2017, 78 PwDMsCP living in Northern Ireland (NI) attending a specialised pancreatic diabetes clinic were reviewed for DR presence and severity using both the Northern Ireland Diabetic Eye Screening Programme (NIDESP) and hospital eye-services databases: over a third had never attended NIDESP and 4% were not known to NIDESP. Therefore, a combined effort was made to provide coordinated services for these patients. Subsequently in 2019, the original 78 plus 16 new patients were re-evaluated. DR/DMac severity from 2017/2019 were recorded, using the English National DR Screening Guidelines.⁴ Of the 94, 71 patients had a minimum of two DR grades for comparison. Progression was considered any increase in DR/DMac grading score; regression was any decrease. Clinical and laboratory data were obtained from electronic medical records (NIECR). Appropriate statistical analyses were carried out using SPSS V.26.

RESULTS

A total of 94 PwDMsCP were included. Mean age was 57±10.1 (range 29–87 years), 81% were male. Mean pancreatic disease duration was 13.6±6.9 (range 4–42 years), with mean diabetes duration at 10.3±5.9 (range 3–34 years). Etiology of chronic pancreatitis included alcohol abuse: 75% (n=70), gallstones: 9% (n=8), with hypertriglyceridemia, and medication-induced and portal vein thrombosis representing 4% in total (n=4). Idiopathic etiology was present in 12% (n=11); information was unavailable for one patient. Mean HbA1c was 8.9%±4.1% (74.3±20.9 mmol/mol), range 4.8%–14.8% (29–138 mmol/mol), and mean body mass index (BMI) was 25.3±6.0 kg/m² (range 13–37).

In 2017, 51 of 78 patients (65%) had attended NIDESP; of the 27 non-attenders, 3 (4%) were not registered with eye-screening. By 2019, 86 of 94 patients (91%) had attended screening; out of the remaining 8 (9%), 2 were unknown to NIDESP. Missed/re-scheduled appointments were high, 24% had missed at least one to two times, 21% had three to four missed appointments and 13% failed to attend five to eight times; categories were mutually exclusive.

In 2017, 39 patients (76%) had no DR, 9 (18%) had background DR, 2 (4%) had pre-proliferative DR and 1 (2%) had proliferative DR. Five (10%) had DMac in at least one eye. In 2019, 54 (63%) had no DR, 26 (30%) had background DR, 2 (2%) had pre-proliferative DR and 4 (5%) had proliferative DR. Ten (12%) had DMac in at least one eye.

There was no significant difference between worst-eye DR/DMac grade and HbA1c, gender, BMI, weight, pancreatitis etiology, screening attendance or number of missed appointments, all $p>0.05$ (table 1). Those with proliferative DR had a longer duration of diabetes (PDR: 18.5 years vs no DR: 7.5 years, $p=0.001$) and pancreatic

disease (PDR: 19 vs no DR: 11 years, $p=0.001$) when compared with those with no DR.

Altogether, 71 patients had first and second visit DR/DMac grades for comparison. The average duration between screening visits was 2.1 years. DR progressed in both eyes in five patients (7%), and in one eye only in 17 (24%), with three progressing to PDR. DR regression was noted in six patients (four in one eye; two in both). An additional two patients developed DMac, while two had regression. There was no statistically significant association between progression of DR/DMac and HbA1c, BMI, weight, gender, albumin-creatinine ratio (ACR), etiology of pancreatitis, duration of pancreatitis or diabetes, all $p>0.05$ (table 1).

DISCUSSION AND CONCLUSION

Diabetes mellitus attributed to pancreatic exocrine disease or type 3c diabetes is a unique form of diabetes and is often brittle in nature; this can be challenging to manage both for patients and their healthcare providers. Most cases arise from chronic pancreatitis, which can go undiagnosed as it is occasionally painless and is often not accompanied by clinical malabsorption until after hyperglycemia occurs.

There are limited data on DR rates and severity in PwDMsCP. Estimates range from 7.4% to 63%,^{5–11} with duration of diabetes, severity of pancreatitis and poor glycemic control being the main contributors. The only prospective study to date included 54 patients with chronic pancreatitis or pancreatectomy, and assessed DR presence and severity using fluorescein angiogram and ophthalmoscopic examination,⁹ with 31% having background DR, none PDR. Our study found that 37% had DR, with 5% of these having PDR.

PwDMsCP often have alcohol dependence, liver dysfunction, poor nutrition and malabsorption; these are frequently associated with impaired quality of life and reduced engagement with their own healthcare needs, including accessing hospital services.¹² A strength of the current study (which is the largest series to date) was that all 94 patients in this study had well-characterized chronic pancreatitis and were in a specialized clinic with well-organized care provision as soon as the patient engaged. We believe that our national data can be generalized to those with type 3c diabetes elsewhere.

Vascular complications in secondary diabetes are often considered to be lower than for type 1 and 2 diabetes; therefore, DR prevalence should also be expected to be lower. However, our 37% prevalence is within the range of similar duration in patients with type 2 diabetes. Voigt *et al* found that 25.8% (n=2272) of those with type 2 diabetes had DR (4.7% PDR).¹³ However, once diabetes duration was incorporated, their 39.9% for the diabetes duration of 11–15 years matches our 37% DR (5% PDR) prevalence. The relevant contribution from smoking, poor nutrition (including vitamin D deficiency) and the contribution of malabsorption (pancreatic insufficiency)

Table 1 Characteristics of study population and statistical analyses for the complete 2019 database (n=94) and follow-up screening grade comparisons (n=71)

Variable (n=94)		Value	vs worst-eye retinopathy (P)	vs worst-eye maculopathy (P)	
Mean age (range)		56.97 (29–87)	0.40	0.51	
Gender, n (%)	Female	18 (19.1)	0.64	0.42	
	Male	76 (80.9)			
Mean duration of chronic pancreatitis, years (IQR)		13.56 (8)	0.001	<0.001	
Mean duration of diabetes, years (IQR)		10.29 (7)	0.001	0.030	
Mean most recent HbA1c %/mmol/mol (SD)		8.9/74.33 (4.1/20.90)	0.94	0.30	
Mean BMI, kg/m ² (SD)		25.30 (5.99)	0.55	0.22	
Mean weight, kg (range)		74.90 (33–120)	0.82	0.24	
Mean ACR (IQR)		13.37 (9)	0.83	0.53	
Etiology of patients with pancreatitis (%)	Alcohol	70 (74.5)	0.76	0.64	
	Gallstones	8 (8.5)			
	High cholesterol	1 (1.1)			
	Unclear	11 (11.7)			
	Portal vein thrombosis	1 (1.1)			
	CF gene carrier	1 (1.1)			
	Medication induced	1 (1.1)			
No of screening DNAs (%)	0	39 (42)	0.09	0.13	
	1–2	23 (24)			
	3–4	20 (21)			
	5–8	12 (13)			
Worst-eye retinopathy/maculopathy grade no of patients (%)	R Visit 1	R Visit 2	M Visit 1	M Visit 2	
	R0/M0	39 (76)	54 (63)	46 (90)	76 (88)
	R1/M1	9 (18)	26 (30)	5 (10)	10 (12)
	R2	2 (4)	2 (2)	–	–
	R3	1 (2)	4 (5)	–	–
Change in retinopathy/maculopathy scores between visits compared with various parameters. RE=right eye, LE=left eye, RP=retinopathy progression, MP=maculopathy progression					
Follow-up (n=71)	vs RE RP	vs LE RP	vs RE MP	vs LE MP	
Gender	0.83	0.62	1.00	1.00	
BMI (kg/m ²)	0.54	0.27	0.72	0.32	
Weight (kg)	0.73	0.95	0.29	0.24	
Most recent HbA1c	0.21	0.76	0.87	0.88	
ACR	0.50	0.14	0.29	0.30	
Etiology of pancreatitis	0.71	0.32	1.00	1.00	
Duration of chronic pancreatitis (years)	0.08	0.50	0.18	0.57	
Duration of diabetes (years)	0.35	0.35	0.07	0.24	

ACR, albumin-creatinine ratio; BMI, body mass index.

were not assessed in this study but could form the basis of future research.

With enhanced coverage of this hard-to-reach patient population and improved NIDESP attendance, the profile of DR in PwDMsCP in NI shifted to a higher prevalence. Increased duration of pancreatic disease and diabetes were found to be associated with DR severity and was within the expected range.

The effort to reach these patients was considerable. This work demonstrates the importance of reaching all patients for establishing DR severity reliably and to provide accessible, equitable care to PwDMsCP.

Contributors CJ: manuscript draft, editing and completion. Data collection and analysis. TP: editing of the manuscript, conceptualization of the project and vital insight into diabetic retinopathy and eye screening. NQ: statistical analysis. RD/A:

data collection, cleaning and analysis. LNC: data collection and interim statistical analysis, editing of the manuscript. PCJ: supervision, data access and editing of the manuscript. Guarantor of this work and takes responsibility for the data integrity of this study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was a retrospective audit; therefore, patient consent was not obtainable. All data were anonymized and the study was approved by the Belfast Trust (QIPSD No.6440).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Catherine Jamison <http://orcid.org/0000-0003-0511-8000>

Tunde Peto <http://orcid.org/0000-0001-6265-0381>

Laura Nicole Cushley <http://orcid.org/0000-0003-0697-8854>

Philip C Johnston <http://orcid.org/0000-0003-1155-1863>

REFERENCES

- 1 Ewald N, Kaufmann C, Raspe A, *et al*. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3C). *Diabetes Metab Res Rev* 2012;28:338–42.
- 2 Makuc J. Management of pancreatogenic diabetes: challenges and solutions. *Diabetes Metab Syndr Obes* 2016;9:311–5.
- 3 Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol* 2013;19:7276–81.
- 4 Harding S, Greenwood R, Aldington S, *et al*. Grading and disease management in national screening for diabetic retinopathy in England and Wales. *Diabet Med* 2003;20:965–71.
- 5 Gullo L, Parenti M, Monti L, *et al*. Diabetic retinopathy in chronic pancreatitis. *Gastroenterology* 1990;98:1577–81.
- 6 Sevel D, Bristow JH, Bank S, *et al*. Diabetic retinopathy in chronic pancreatitis. *Arch Ophthalmol* 1971;86:245–50.
- 7 Maekawa N, Ohneda A, Kai Y, *et al*. Secondary diabetic retinopathy in chronic pancreatitis. *Am J Ophthalmol* 1978;85:835–40.
- 8 Couet C, Genton P, Pointel JP, *et al*. The prevalence of retinopathy is similar in diabetes mellitus secondary to chronic pancreatitis with or without pancreatectomy and in idiopathic diabetes mellitus. *Diabetes Care* 1985;8:323–8.
- 9 Tiengo A, Segato T, Briani G, *et al*. The presence of retinopathy in patients with secondary diabetes following pancreatectomy or chronic pancreatitis. *Diabetes Care* 1983;6:570–4.
- 10 Nakamura T, Imamura K, Takebe K, *et al*. Diabetic retinopathy in Japanese patients with long-standing pancreatic diabetes due to calcifying pancreatitis. *Tohoku J Exp Med* 1994;174:49–58.
- 11 Verdonk CA, Palumbo PJ, Gharib H, *et al*. Diabetic microangiopathy in patients with pancreatitic diabetes mellitus. *Diabetologia* 1975;11:395–400.
- 12 Hart PA, Bellin MD, Andersen DK, *et al*. Type 3C (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol* 2016;1:226–37.
- 13 Voigt M, Schmidt S, Lehmann T, *et al*. Prevalence and progression rate of diabetic retinopathy in type 2 diabetes patients in correlation with the duration of diabetes. *Exp Clin Endocrinol Diabetes* 2018;126:570–6.