Scandinavian Journal of Primary Health Care

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/ipri20

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To cite this article: Kajsa Andersson, Anders Halling & Björn Agvall (22 Apr 2024): Factors associated with development of retinopathy in patients with type 2 diabetes mellitus at onset and within three years after diagnosis, Scandinavian Journal of Primary Health Care, DOI: 10.1080/02813432.2024.2329215

To link to this article: https://doi.org/10.1080/02813432.2024.2329215

SCANDINAVIAN JOURNAL OF PRIMARY HEALTH CARE
https://doi.org/10.1080/02813432.2024.2329215

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RESEARCH ARTICLE

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Factors associated with development of retinopathy in patients with type 2 diabetes mellitus at onset and within three years after diagnosis

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ABSTRACT

Objective: To investigate the prevalence of diabetes retinopathy and evaluate the factors influencing its occurrence both at the onset of type 2 diabetes (T2D) and three years into its duration.

Design: Retrospective population-based study.

Setting: Data was retrieved from Regional Healthcare Information Platform in Region Halland 2016–2020.

Subjects: Patients 35-75 years old in Region Halland receiving first-time diabetes diagnosis according to ICD-code E11-14 in 2016–17. The total cohort consisted of 1659 patients.

Main outcome measures: The main outcome measure of the study was the occurrence of diabetes retinopathy at onset and within three years from the diabetes diagnosis. Multivariate logistic regression analysis was conducted for diabetes retinopathy at onset and within three years, adjusted for age, gender, comorbidities, levels of HbA1c, cholesterol, kidney functional and blood pressure.

Results: At onset, there were 12% with diabetes retinopathy and after three years, 32% of the patients had developed diabetes retinopathy. In the study cohort, 71 of patients who were examined with fundus photography within three years after onset, and 8% had had dietary recommendation without pharmacotherapy. High HbA1c levels, blood pressure values and impaired renal function already at onset were associated with development of diabetes retinopathy at onset and this association persisted after three years. The odds ratio for diabetes retinopathy was increased adjusted for HbA1c elevations, renal impairment, and increased blood pressure at index and when adjusted for these variables three years from index.

Conclusion: These findings indicate that the risk of developing diabetes retinopathy is present early on at onset and within the first three years of diabetes diagnosis. This highlights the importance of promptly regulating glucose- and blood-pressure levels and follow up kidney dysfunction to mitigate the risk of diabetes retinopathy.

KEY POINTS

- Among patients with type 2 diabetes, 12% had developed diabetes retinopathy already at onset.
- Among patients with type 2 diabetes, one-third had developed diabetes retinopathy after three years from onset.
- The presence of diabetes retinopathy already at diabetes onset, was associated with elevated HbA1c levels, renal impairment and elevated blood pressure.
- Diabetes retinopathy three years after the onset of the disease, was associated with increased HbA1c levels, high blood pressure, and renal dysfunction.

ARTICLE HISTORY
Received 10 October 2023
Accepted 6 March 2024

KEYWORDS
Diabetes mellitus complication; Type 2 diabetes; diabetic retinopathy

Introduction

The world-wide prevalence of type 2 diabetes (T2D) has rapidly increased during the last decades, probably due to both environmental and lifestyle related factors [1]. It is estimated that among people 20–79 years old, 10% had diabetes in 2021 and in 2045 this number is expected to be to increase to 12%. The prevalence in Sweden is around 5% and the vast

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/02813432.2024.2329215.

majority of the patients with have T2D [2, 3]. T2D is a chronic, metabolic disease defined by high blood sugar and can cause multiple serious complications that affect the individual's life [4].

Unfortunately, it is known that many patients with T2D are undiagnosed for a long time before it is detected [5]. Known risk factors for developing T2D are old age, heredity, smoking, obesity, high alcohol consumption, unhealthy diet, and physical inactivity, which also disrupts glucose regulation. Individuals suffering from T2D are at risk of developing organ damage, which can be categorized into two main groups: micro- and macrovascular. Nephropathy, retinopathy, and neuropathy are microvascular, while stroke, cardiovascular complications, and peripheral arterial diseases are macrovascular [5, 6]. Lifestyle interventions, e.g. physical activity, weight loss and dietary advice are crucial to prevent development and worsening of complications to T2D. Inclusion of smoking cessation is particularly crucial in an intervention program [5].

In addition to the above-mentioned lifestyle interventions, the medication metformin constitutes the basic treatment for most patients and should be initiated already at onset. If there is an inadequate effect of metformin, there are several treatment options regarding drug supplements. In modern treatment of T2D, it is possible to adapt the treatment based on the individual's special needs. For example, medications such as sodium glucose co-transporter-2 inhibitors (SGLT-2) are more suitable in case of cardiovascular comorbidity and glucagon-like peptide-1 receptor agonist (GLP-1) entail weight loss which is beneficial in patients suffering from obesity. Addition of insulin in T2D is required when other medications are insufficient for achieving glucose regulation or when the pancreas doesn't produce enough insulin [7].

Diabetes retinopathy is caused by microvascular abnormalities in the retina and causes initially no symptoms [8]. This condition is considered as the most common complication of diabetes and the leading cause of developing blindness or vision-loss that could be prevented among people in working age [8, 9]. Swedish guidelines recommend eye screening with fundus photography at onset, unless no need of pharmacotherapy, and follow-up every third year for patients with T2D [10]. Factors associated with increased risk of diabetes retinopathy are duration of diabetes, poor glucose control, high blood pressure levels, hyperlipidemia, renal disease, overweight, smoking, high alcohol consumption and physical inactivity [9]. Almost 80% of the patients with T2D have diabetes related eye-disease ten years after diagnosis [11].

Among individuals with T2D, there is a risk of developing diabetes retinopathy which could be the first sign of diabetes complication. The objective of this study was to investigate the prevalence of diabetes retinopathy and to assess factors influencing diabetes retinopathy at the onset of T2D and compared to three years into its duration.

Method

Study design

A retrospective population-based study.

Data source

The study is conducted in Region Halland, located in southwestern Sweden. The area has an estimated population of 330,000 residents and health care is provided by three acute care hospitals, 40 inpatient wards, two emergency departments, 30 outpatient specialized clinics and 48 primary care facilities. Half of the primary care facilities are public, and the rest are private with agreements with Region Halland. Data has been collected from all primary care facilities.

Patient data was collected *via* the Regional Healthcare Information Platform (RHIP), that contains complete and comprehensive healthcare records from residents of Region Halland [12]. Full details of medications, clinical investigation results (i.e. radiological examinations, laboratory data) and care delivery resources are available for each patient on the platform. The RHIP platform was supplemented with pharmacotherapy data from the Swedish Prescribed Drugs Register and the pharmacy's dose dispensing system, Apodos.

Study population

The study comprised adult patients aged 35–75 years, who were listed as residents and received healthcare services in Region Halland. The patients were newly diagnosed with type 2 diabetes (T2D) as indicated by the ICD-code E11-14, within the time frame of 2016–2017. The criteria for selecting patients with T2D were that they had ICD-10 diagnosis E11-E14. Patients with an E10 diagnosis at any point were excluded from the study. The ICD diagnoses E12 and E13 were used to determine diabetes onset when these diagnose codes appeared first, but all patients who were included also had ICD E11 or E14 at some point. Initially, 1769 patients were detected but of these there were 110 individuals who had no recorded visits, treatment, or blood sampling data in

the database and these 110 individuals were excluded from the study from onset.

Study process and variables

Data was collected during three years from the time of diagnosis, with diabetes retinopathy as the primary outcome measure. The variables gender, age and comorbidity were registered. Comorbidities are displayed in Appendix Table **A**1. Chronic kidney disease was defined according to the KDIGO-criteria: estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 in two separated blood test taken with at least 90 days apart and/or ICD-code referring to the diagnosis [13]. Obesity was defined as the ICD-code E66 and/or BMI >30 at the point of diagnosis. Diabetes retinopathy was registered and classified based on diagnosis code H360 in accordance with ICD-10, which is specified in Appendix-Table **A**1. The diagnosis relies on a fundus photography with a pupil dilation conducted at an ophthalmology clinic in every case, all of which were integrated into the RHIP. The collected laboratory tests included measurements of total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, HBA1c, eGFR, and proteinuria. Proteinuria has been identified based on urine-albumin-creatinine ratio (UACR) and, for this purpose, the conventional urine dipstick has not been employed. Blood pressures and BMI (height and length) were registered. The laboratory samples pertaining to the onset of diabetes were evaluated over a period extending one month before and after the index. Follow-up tests cover a duration of 6 months both before and after the 3-year follow-up. Islet antibodies were not used because at this time it was not used continuously and thus the assessment was made that the reliability would be limited. The anti-diabetes pharmacotherapies, including metformin, GLP-1 receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT-2 inhibitors, sulfonylureas (SU), acarbose, glitazones, meglitinides, and insulin are displayed Appendix-Table **A**2. To be classified as receiving treatment, an individual needed to have obtained anti-diabetes pharmacotherapy at least once per year during the study period of three years from the onset. The study also retrieved the fundus photography of ophthalmologist.

Statistics

The study population was described using descriptive statistics. Categorical data, such as age, lab tests, and care contacts were reported as a number, percentage and analysed with Chi-2 tests. Continuous data was reported with standard deviation (SD) and analysed with Student t-tests. Kruskal-Wallis tests were applied to compare mean values between multiple groups. Data was collected at onset and after three years.

HbA1c values were divided in <52, 52–57, 58–70 and >70 mmol/mol. Total-cholesterol was grouped in ≥4.5 mmol/l and <4.5 mmol/l, and LDL-cholesterol ≥2.5 mmol/l and <2.5 mmol/l. The renal function was sorted into eGFR levels >60, 30–60 and <30 mL/min/1.73m^2 [13, 14]. UACR was separated into normal albuminuria (<3 mg/mmol), microalbuminuria (3–30 mg/mmol) and macroalbuminuria (> 30 mg/mmol). Systolic blood pressure was separated in three groups, those with systolic blood pressure ≤130 mm Hg, 131–139 mm Hg and ≥140 mm Hg.

A multivariate regression analysis for the outcome diabetes retinopathy was conducted, adjusted for age, gender, hypertension, atherosclerotic cardiovascular disease, HbA1c levels, lipid levels, kidney function, and blood pressure levels. As the mortality was low (2%) and causes of death were unknown, no mortality analyzes were performed.

A multivariate regression analysis for diabetes retinopathy adjusted for pharmacotherapies, was not conducted since intensified treatment reflects the severity of the patient's diabetes rather than the protective benefit of the treatment. An analysis was conducted to compare patients who had fundus photography and those without, and the results are presented in Appendix–Table **A**3. All statistical tests were 2-sided and $p < 0.05$ identified significant differences. The statistical program IBM SPSS Statistics 27 was used to analyze and compile the extracted data.

Ethical considerations

The study was approved by the Swedish Ethical Review Board, Gothenburg Department 1 Medicine, registration number 2020-05769. Informed consent was not mandatory in this retrospective observational cohort study, and the study procedure was granted approval by the Swedish Ethical Review Board. The methods and procedures in this study were conducted in accordance with applicable research guidelines and regulations.

Results

A total of 1659 patients were included in the study. At onset of the diabetes diagnosis, 191 (12%) patients had a diabetes retinopathy and 530 (32%) patients had developed diabetes retinopathy after three years from onset. Examination by an ophthalmologist was completed by 71% of the patients and the

characteristics of those who had an examination and those who did not are outlined in Table A3. There were 36 patients (2%) who died during the study period of three years.

The basic characteristics at when first time diagnosed with diabetes such as age, gender and comorbidity (hypertension, atherosclerotic cardiovascular disease or heart failure) are presented in Table 1. The mean age was 61.3 (9.7) years in the total cohort and there was no significant difference between patients with or without diabetes retinopathy after three years. There were more men than women in the study cohort, 1102 (62%) compared to 669 (38%) respectively. The patients' levels of HbA1c, total cholesterol, LDL cholesterol, renal function and blood pressure level at the diabetes onset for the total group and allocated into those with or without diabetes retinopathy are shown in Table 1.

The laboratory findings of HbA1c, cholesterol, LDL-cholesterol, renal function and blood pressure after three years form onset is presented in Table 2. After three years, there were 28% having a HbA1c level ≥58 mmol/mol, 46% had a total-cholesterol ≥4.5 and 42% had a blood pressure level >140 mm Hg.

The pharmacotherapies regarding blood sugar and blood pressure regulation, in total and allocated into diabetes retinopathy and those without are presented in Table 3. There were 139 (8%) patients without any diabetes treatment during the three-year follow up period. These individuals were recorded as having diet-controlled diabetes.

Two multivariate regression analysis models were conducted using diabetes retinopathy as the outcome variable adjusted for variables obtained from onset and an additional model adjusted for variables after three years from onset, which is displayed in Table 4. The risk of developing diabetes retinopathy had an odds ratio twice as high when HbA1c ≥58 mmol/mol or when systolic blood pressure >130 mm Hg at onset and after three years. Systolic blood pressure ≥140 mm Hg was associated with a nearly four times as high risk

Table 1. Basic of characteristics at index.

	No DR, *n* (%)	DR, *n* (%)	Total, *n* (%)	*p*-value
Total cohort	1129 (69)	530 (32)	1659 (100)	
Age, (years)				
≤ 60	477 (42)	222 (42)	699 (42)	0.89
> 60	652 (58)	308 (58)	960 (58)	
Gender				
Men	691 (61)	340 (64)	1031 (62)	0.25
Women	438 (39)	190 (36)	628 (38)	
Comorbidities				
Hypertension	576 (51)	275 (52)	851 (51)	0.74
ASCVD	164 (14)	70 (13)	239 (14)	0.47
IHD	125 (11)	50 (9)	175 (10)	0.31
Ischemic CVI	30 (3)	14 (3)	44 (3)	0.98
TIA	18 (2)	10 (2)	28 (2)	0.67
PAD	0 (0)	2 (0)	2 (0)	0.04
Heart Failure	41 (4)	24 (4)	65 (4)	0.38
HbA1c (mmol/mol)				
<52	442 (40)	123 (23)	565 (34)	<0.001
52–57	215 (19)	80 (15)	295 (18)	
58–70	178 (16)	119 (22)	297 (18)	
>70	294 (26)	208 (39)	502 (30)	
Cholesterol (mmol/l)				
<4.5	328 (29)	147 (28)	475 (29)	0.10
≥4.5	748 (66)	369 (70)	1117 (67)	
Missing value	53 (5)	14 (3)	67 (4)	
LDL (mmol/l)				
<2.5	253 (22)	129 (24)	382 (23)	0.04
≥2.5	816 (72)	387 (73)	1203 (72)	
Missing value	60 (5)	14 (3)	74 (4)	
Kidney function (eGFR)				
≥60 mL/min/1.73^2	915 (81)	395 (74)	1310 (79)	0.003
31-59 mL/min/1.73^2	111 (10)	85 (16)	196 (12)	
<30 mL/min/1.73^2	14 (1)	8 (2)	22 (1)	
Missing value	89 (8)	42 (8)	131 (8)	
Proteinuria (UACR), n (%)				
<3	344 (30)	156 (29)	500 (30)	0.04
3–29	126 (11)	86 (16)	212 (13)	
≥30	37 (3)	14 (3)	51 (3)	
Missing value	622 (55)	274 (52)	896 (54)	
Blood pressure (systolic)				
<130 mmHg	424 (38)	120 (23)	544 (33)	<0.001
130–140 mmHg	157 (14)	95 (18)	252 (15)	
>140 mmHg	536 (48)	315 (59)	851 (51)	
Missing value	12 (1)	0 (0)	12 (1)	

Note; DR: diabetes retinopathy; ASCVD: atherosclerotic cardiovascular disease; eGFR: estimated glomerular filtration rate; UACR: urine albumin creatinine ratio.

Table 2. The characteristics after three years from index.

	No DR, *n* (%)	DR, *n* (%)	Total, *n* (%)	*p*-value
HbA1c (mmol/mol)				
<52	511 (45)	199 (38)	710 (43)	<0.001
52-57	225 (20)	113 (21)	338 (20)	
58-70	163 (14)	111 (21)	274 (17)	
>70	95 (8)	92 (17)	187 (11)	
Missing value	135 (12)	15 (3)	150 (9)	
Cholesterol (mmol/l)				
<4.5	439 (39)	210 (40)	649 (39)	<0.001
≥4.5	480 (43)	279 (53)	759 (46)	
Missing value	210 (19)	41 (8)	251 (15)	
LDL-cholesterol (mmol/l)				
<2.5	398 (35)	197 (37)	595 (36)	<0.001
≥2.5	561 (50)	311 (59)	872 (53)	
Missing value	170 (15)	22 (4)	192 (12)	
Kidney function (eGFR)				
≥60 mL/min/1.73^2	539 (48)	245 (46)	784 (47)	0.007
31–59 mL/min/1.73^2	132 (12)	92 (17)	224 (14)	
<30 mL/min/1.73^2	23 (2)	19 (4)	42 (2)	
Missing value	435 (38)	174 (33)	609 (37)	
Blood pressure (systolic)				
<130 mm Hg	474 (42)	121 (23)	595 (36)	<0.001
130–140 mm Hg	203 (18)	104 (20)	307 (19)	
>140 mm Hg	396 (35)	299 (56)	695 (42)	
Missing value	56 (5)	6 (1)	62 (4)	
Visiting an ophthalmologist, *n* (%)	776 (68)	411 (78)	1177 (71)	<0.001

Note; DR: diabetes retinopathy; HbA1c:hemoglobin A1c; LDL-cholesterol: low-density lipoprotein; eGFR: estimated glomerular filtration rate.

for getting diabetes retinopathy. Regarding the kidney function, the risk of having diabetes retinopathy was increased when eGFR levels were decreased. When reaching stage IV of kidney disease (eGFR <30 mL/min/1.73m^2), the risk was over twice as a high after three years. Age, gender, hypertension, atherosclerotic cardiovascular disease, or cholesterol were not significantly associated with increased risk of developing diabetes retinopathy either at onset or within three years from onset.

Table 3. Shows the pharmacotherapeutic treatment during the study period in total and divided between the patients with diabetes retinopathy and those without.

	No DR	DR	Total	p-value
Diabetes pharmacotherapy				
Dietary treatment, n (%)	114 (10)	25 (5)	139 (8)	<0.001
Metformin, n (%)	946 (84)	463 (87)	1409 (85)	0.06
SU, n (%)	13 (1)	15 (3)	28 (2)	0.01
GLP-1, n (%)	141 (12)	94 (18)	235 (14)	0.003
Insulin, n (%)	153 (14)	112 (21)	265 (16)	<0.001
DPP4, n (%)	181 (16)	112 (21)	293 (18)	0.01
SGLT-2, n (%)	85 (8)	74 (14)	159 (10)	<0.001
Lipid-lowering pharmacotherapy				
Statins, n (%)	682 (60)	346 (65)	1028 (62)	0.06
Ezetimibe, n (%)	34 (3)	23 (4)	57 (3)	0.17
Cardiovascular pharmacotherapy				
Betablockers, n (%)	434 (38)	206 (39)	640 (39)	0.87
RAASi, n (%)	668 (59)	357 (67)	1025 (62)	0.001
Calcium-blockers, n (%)	362 (32)	199 (38)	561 (34)	0.03

Note; DR = diabetes retinopathy, SU = Sulphonylureas, GLP-1= Glucagon-like peptide-1 receptor agonist, Insulin = includes fast-acting, intermediate-acting, intermediate-acting combined with fast acting or long-acting insulin, DPP4= Dipeptidyl peptidase 4 inhibitors, SGLT-2 = Sodium glucose co-transporter-2 inhibitors, RAASi = renin angiotensin aldosterone system inhibitors (including angiotensin converting enzyme inhibitors, angiotensin receptor blockers and angiotensin receptor neprilysin inhibitors).

Discussion

This study finds that 12% already had diabetes retinopathy at onset and one third had developed diabetes retinopathy within three years. Ophthalmological examination had not been performed in 29% of the patients. Almost than one third of the patients displayed insufficient glucose control, indicated by an HbA1c level ≥58 mmol/mol within three years. Approximately 42% exhibited inadequate blood pressure control, with a blood pressure ≥130 mm Hg. Increased risk of diabetes retinopathy was associated with elevated HbA1c, impaired renal function, and elevated blood pressure both at onset and after three years. Age, gender, hypertension, and atherosclerotic cardiovascular disease was not associated with increased risk of diabetes retinopathy.

It is widely known that diabetes retinopathy is a common cause of visual impairment and one of the most common causes of preventable vision-loss among people in working age [8, 9, 15]. A review article from 2003, establish that over 60% of patients with T2D had retinopathy within twenty years and up to 21% had it when diagnosed with diabetes [16]. In a worldwide review article including 20 000 patients, the overall prevalence of any diabetes retinopathy was 35% and estimated to 25% in patients with T2D [17]. In a Swedish study, the prevalence for diabetes retinopathy was 30-40% [15]. These results coincide with the results in our study having almost one third within three years form diabetes onset al.though patients with type 1 diabetes were not included. Prevalence of diabetes retinopathy seems to differ

Table 4. Presents the risk of developing diabetes retinopathy adjusted for glucose, cholesterol and blood pressure control as well as kidney function at index and at three years from onset.

	At onset (n = 1459)				Within three years from diagnosis (n = 940)			
		95% CI for odds ratio				95% CI for odds ratio		
	Odds ratio	Lower	Upper	p-value	Odds ratio	Lower	Upper	p-value
Age	0.99	0.98	1.01	0.39	0.99	0.97	1.00	0.17
Women	0.90	0.71	1.14	0.39	0.98	0.72	1.32	0.88
Hypertension	0.96	0.75	1.24	0.76	0.92	0.68	1.24	0.59
ASCVD	0.94	0.63	1.27	0.71	0.94	0.62	1.43	0.78
HbA1c				<0.001				<0.001
<52 mmol/mol		Reference				Reference		
52-57 mmol/mol	1.31	0.92	1.87		1.39	0.95	2.02	
58-70 mmol/mol	2.23	1.58	3.15		2.01	1.37	2.95	
>70 mmol/mol	2.60	1.92	3.50		2.17	1.41	3.34	
Lipids								
Cholesterol ≥4,5	0.94	0.73	1.73	0.71	0,98	0,64	1,50	0.91
Kidney function				<0.001				0.003
≥60 ml/min		Reference				Reference		
30-59 ml/min	2.02	1.43	2.84		1.75	1.22	2.51	
<30 ml/min	1.98	0.75	5.21		2.17	1.03	4.56	
Blood pressures				<0.001				<0.001
≤130 mm Hg		Reference				Reference		
131-139 mm Hg	2.34	1.63	3.36		2.23	1.48	3.37	
≥140 mm Hg	2.12	1.62	2.85		3.93	2.80	5.51	

Note: CI: confidence interval; ASCVD: atherosclerotic cardiovascular disease, HbA1c: hemoglobin A1c; LDL-cholesterol: low density lipoprotein cholesterol.

depending on population-characteristics, study methodologies and differences in diagnosis criteria of diabetes retinopathy [18]. The present study revealed a screening rate of 71% for retinopathy, suggesting that the actual prevalence of diabetes retinopathy may be even higher. In present study, diabetes retinopathy appeared early in the T2D disease and there were patients having diabetes retinopathy already at onset. It is known that many patients with T2D can be undiagnosed for a long time before it is detected [5].

Previous studies suggest that duration of diabetes, poor glycemic control as well as blood pressure were in other studies associated with a higher risk of diabetes retinopathy [15, 17].

A study from 2018 suggests that good glycemic control was associated with reduced risk of developing retinopathy, while gender and age were not associated [18]. Another study proposed that difference in gender had no association with development of diabetes retinopathy which was consistent with the findings in our study [15, 17, 19].

Conclusion

The present study revealed that diabetes retinopathy appeared in 12% already at onset and in almost one third within three-year duration of T2D. There were almost one third lacking ophthalmologist fundus photography during the study period. Poor regulation of glucose control and blood pressure as well as kidney dysfunction were associated with developing diabetes retinopathy within three years. This advocates thorough glucose and blood pressure regulation and follow-up of kidney dysfunction is crucial early from the diabetes onset as well as fundus photography to detect diabetes retinopathy.

Strengths and limitations

There was no observed improvement among individuals who received treatment for diabetes, hypercholesterolemia, and hypertension. The utilization of anti-diabetes pharmacotherapy, as well as treatment for hyperlipidemia and hypertension, were not associated with a decreased risk of diabetes retinopathy. The interpretation of these findings was that those individuals receiving intensified pharmacotherapy were actually those with severe disease and in the greatest need. Therefore, this study was not suitable for drawing conclusions about the effects of treatment.

There were a number of patients with no recorded examination of an ophthalmologist. It is likely that those without examinations were individuals with less severe diseases. However, it is possible that some individuals were examined and registered at other locations, although this is believed to be a small number. Consequently, the number of patients with retinopathy could be even higher than reported in the present study since some patients are not examined.

Factors such as physical activity, alcohol consumption and smoking would be of obvious interest, but this information has not been reliably reported and therefore not included in the study.

Acknowledgements

We are grateful to Awais Ashfaq for facilitating the retrieval of the dataset from RHIP.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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