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Original article

Prevalence of comorbidities associated with type 2 diabetes and prediabetes and a case-control analysis of the emergence of new comorbidities in 2007 - 2019

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ABSTRACT

Aims: Diabetes and its comorbidities substantially contribute to morbidity. This study aimed to investigate the prevalence of cardiovascular diseases and diabetic kidney disease (CKD) among patients with type 2 diabetes (T2DM) and prediabetes, and the association of variables related to the treatment of T2DM with the risk of comorbidities.

Methods: We collected the data by extracting laboratory test results from real-world data of the catchment area of Turku University Hospital between 2005 and 2019 (fP-Gluk, 2-h glucose stress test, B-HbA1c). Cardiovascular diseases were ascertained using ICD10 codes from 1999 onward. CKD was diagnosed based on the measurement of estimated glomerular filtration rate (eGFR) and urine albumin creatinine ratio (U-AlbKre). The prevalence of comorbidities was studied in a cohort 1 in 2019 that included 37,209 patients with type 2 diabetes and 42,554 with prediabetes. The risk of comorbidities was studied in a cohort 2 of 41,664 T2DM patients during the years 2007–2019. We analyzed the emergence of type 2 diabetes comorbidities by logistic regression.

Results: Patients with T2DM exhibited a higher prevalence of all comorbidities compared with individuals with prediabetes. Hyperglycemia was associated with a higher risk of complications in all disease groups. Highest risk ratio in glycemic burden was in CKD (OR 1.006, 95% CI 1.005–1.006). Use of cholesterol-lowering drugs, GLP-1 receptor agonists and SGLT2 inhibitors was associated with a lower risk in comorbidities ($p < 0.0001$).

Conclusions: Early risk factor modification, optimal glycaemic control, and appropriate drug selection may substantially reduce the development of comorbidities.

Introduction

Diabetes mellitus is one of the fastest-growing diseases in the world. The International Diabetes Federation (IDF) estimates that in 2021, 537 million people (10.5% of the population) had diabetes, and an additional, approximately 541 million people have prediabetes [1]. According to the National Diabetes Registry, nearly half a million people in Finland were living with diabetes at the end of 2023, and approximately 80% had type 2 diabetes (T2DM) [2]. A global systematic review published in 2018 found that cardiovascular disease affected approximately 32.2% of all patients with T2DM between 2007 and 2017. Coronary artery disease is a major cause of mortality in patients with T2DM, accounting for approximately half of all deaths [3].

Diabetes and its associated comorbidities significantly contribute to morbidity and mortality and impose a substantial economic burden on both society and individuals [4–7]. Changes in cardiovascular risk factors have been studied with population surveys in Finland every five years for 30 years. The first studies to assess the impact of the North

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Karelia project were conducted in 1972 and 1977. A declining trend in key cardiovascular disease risk factors was observed in the Finnish population from 1992 to 2017, although this decline has slowed in recent years [8].

Intensive drug therapy in the early stages of diabetes has been shown to significantly reduce the risk of developing comorbidities and to improve life expectancy [9–13]. Diabetes treatment in Finland has been outlined in the Current Care Guidelines for Diabetes since 2007 [14,15]. SGLT2 inhibitors and GLP-1 receptor agonists have recently been shown to have a significant prognostic effect on cardiovascular and renal disease [16–20]. The incidence and prevalence of heart and cerebral artery complications have decreased in Finland from 2007 to 2017 [21].

Aims

This study aimed to investigate the prevalence of ischemic heart disease, heart failure, cerebrovascular disease, and diabetic kidney disease (CKD) among patients with type 2 diabetes (T2DM) and prediabetes in the catchment area of Turku University Hospital in 2019. The second objective was to assess the association of variables related to the treatment of T2DM with the risk of coronary heart disease, heart failure, cerebrovascular disease, or diabetes kidney disease between 2007 and 2019, by comparing patients with comorbidities to those without.

Materials and methods

We collected the data by extracting elevated blood glucose laboratory test results from studies fP-Gluk, 2-h glucose stress test, B-HbA1c. The Auria Information Service extracted values exceeding the reference value for 2005–2019 from the laboratory databases of Turku University Hospital and the health centers in municipalities. We supplemented the data with patients who had the right to special reimbursement for diabetes medicines granted by The Social Insurance Institution of Finland (Kela). The diagnostic data on diabetes and comorbidities, including their initial dates, were extracted from the patient registry of Turku University Hospital and Kela's benefit register of special reimbursement rights from 1999 onward. The municipality of residence information was checked each calendar year from the municipality of residence data in Kela's medicine purchase register at the end of the year.

We investigated Cohort 1 for the prevalence of named comorbidities in patients with T2DM and prediabetes who were alive and at the end of 2019. Type 2 diabetes was identified from the dataset's historical data based either on the diagnosis code beginning with E11 or, in its absence, based on laboratory results (fP-Gluk twice $\geq$7 mmol/ l /(twice) in the glucose tolerance test for a 2-hour value $\geq$11mmol/l or B-HbA1c $\geq$48 mmol/mol) when type 1 diabetes and other types of diabetes were excluded. Patients with elevated glucose levels were identified as having prediabetes, but laboratory test values never exceeded the diagnostic thresholds for diabetes. Comorbidities were identified based on specialized medical care and Kela's diagnostic data from the first entry onwards based on ICD10 diagnosis codes; laboratory tests were also considered for diabetes kidney disease, which were also available for primary health care. The prevalence of comorbidities was estimated in relation to the number of patients with type 2 diabetes or prediabetes at the end of the year. The comorbidities selected for study were diseases in which the diagnoses or laboratory test results indicating illness were sufficiently comprehensive. They involved being a customer of specialized medical care or of Kela's right to special reimbursement for whom diagnostic information was thus available. Primary care diagnostic data were not available. The subjects studied were ischaemic heart disease (I20–25), heart failure (I50), cerebrovascular diseases (I63-I66), and kidney diseases (N08.3*, N18, Z49, Z94, E11.2, or U-AlbKre >3 mg/mmol or cU-Alb-Mi >20 ug/min or eGFR <60 ml/min/1.73m^2).

We investigated Cohort 2 for the logistic regression-based associations with the occurrence of new comorbidities related to the treatment of T2DM. Four complication groups were studied in their own models. The index date for each patient was the date when a comorbidity was first recorded or death or 31.12.2019.

Individuals diagnosed with any comorbidity before 2007 were excluded from the cohort. This ensured that laboratory and medication data were available from 2005 onwards, i.e., at least two years before the onset of the comorbidity. The analyses compared patients with each comorbidity for first-time with individuals who were not previously diagnosed with the disease. In the disease group-specific analyses were excluded individuals, whose respective comorbidity occurred before the diabetes diagnosis, whose previous follow-up period was less than one year or whose municipality of residence was outside the catchment area of Turku University Hospital during the follow-up period.

In this case-control study, the study households were the same comorbidity groups and diagnoses as in the 2019 prevalence cross-sectional study. Kidney diseases were considered using the standard KDIGO threshold of eGFR <60 ml/min/1.73 m^2 combined with albuminuria (U-AlbKre >3 mg/mmol or cU-Alb-Mi >20 ug/min).The model classified age as a variable at the time of diabetes: persons under 65 and those 65 or over. Diabetes duration was defined as a complication (or death or until 31.12.2019). The treatment method considered was the situation in the previous calendar year (before the onset of the comorbidity/year of death/year 2019). The analysis compared the emergence of comorbidities among different diabetes treatment modalities (lifestyle therapy (L), tablet therapy (T), combination therapy (T + I), and insulin therapy (I)). Therapies were not evaluated as risk factors. The models included the following ATC-classified drug groups: C10 (cholesterol-lowering drugs), C09 (medicines that protect the kidneys, i.e., ACE inhibitors and ATR blockers), A10BJ (GLP-1 receptor agonists), and A10BK (SGLT2 inhibitors). The medication was included in the models so that the use of the medicine (medicine purchases) had to have started at least 1 year before the moment of compliment/ death/ 31.12.2019. As a measure of the effect of hyperglycaemia, the models were measured by the hyperglycemia test, the so-called glycemic burden that considers values of HbA1c deviating from the target value (HbA1c <53 mmol/mol). The glycemic burden was calculated by measuring the area between the curve of values above the target level for HbA1c, considering the duration of the exceedance. The LDL cholesterol burden was calculated correspondingly, considering the patient-specific LDL measurement values and their durations above the target value (<1.8 mmol/l). The variable 'Previous complication' consists of previously diagnosed comorbidities (diagnoses I20–25, I50, I63-I66, N08.3*, N18, Z49, E11.2 or laboratory tests U-AlbKre >3 mg/mmol or cU-Alb-Mi >20 ug/min or eGFR <60 ml/min/1.73m^2). The variable receives the value 1 if the individual has had any of these diagnoses before the response complication.

Questions of research integrity

This was a retrospective register study for which, according to Finnish law, a statement from an ethics committee is not required, and the processing of the data was based on scientific research, public interest and public interest related to public health as referred to in the EU General Data Protection Regulation (Articles 6.1 e and 9.2 I of the GDPR)

Research permits for the study were received from Turku University Hospital on 4.12.2019 (J47/2019), Kela on 26.3.2020 (extension permit 29.3.2021 33/522/2021), and from all health centers in the catchment area of Turku University Hospital.

Statistical analysis

We analyzed the prevalence of comorbidities between patients with type 2 diabetes and prediabetes and between men and women using the chi square test. We analyzed the emergence of type 2 diabetes comorbidities by logistic regression. The response variables in the analysis were ischaemic heart disease, heart failure, cerebrovascular diseases,

and diabetes kidney disease. Explanatory factors were gender, age, duration of diabetes, type of treatment, drug therapy (Lipid drugs, ACE inhibitors and ATR blockers, previous complication, GLP-1 analogues, SGLT2 inhibitors), glycemic burden [22,23] and cholesterol burden [24]) at the same model. The models used in the analysis were created separately for different comorbidity groups. Model assumptions were checked by assessing linearity in the logit for continuous variables, multicollinearity, and outliers. The threshold for statistical significance was a 95% confidence level in all analyses. We performed the analyses using SAS software version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

There were 37,209 people with type 2 diabetes (T2DM) and 42,554 with prediabetes in cohort 1 in 2019. There were 41,664 type 2 diabetes patients who did not yet have complications before 2007 in cohort 2 between 2007 and 2019. Table 1 presents the number of participants and age averages for men and women in both cohorts. Table 4 presents the final number of the people in the different analysis groups of comorbidities after a reduction implemented based on exclusion criteria.

Prevalence of comorbidities in 2019

Patients with T2DM exhibited a higher prevalence of all comorbidities compared with individuals with prediabetes. The prevalence of ischaemic heart disease was 18.8% in patients with T2DM and 14.0% in patients with prediabetes. The prevalence of chronic renal disease (reduced eGFR and/or albuminuria) was 18.8% in patients with T2DM and 5.3% in patients with prediabetes. (Table 2).

Among men, the most common comorbidity in both T2DM and prediabetes was ischemic heart disease. In patients with T2DM, kidney disease was equally prevalent as ischemic heart disease. However, kidney disease was more common than ischaemic heart disease in women with diabetes. The incidence of kidney disease was clearly lower than the incidence of ischaemic heart disease in both sexes in the prediabetes group. The prevalence of comorbidities according to disease group is presented in Table 3.

Analysis of the emergence of new comorbidities in 2007 - 2019.

In this study, we analyzed the association between T2DM treatment-related factors and the emergence of one of the four comorbidities. The control group in each analysis comprised individuals who did not develop the comorbidity in question during the follow-up period. Table 4 presents the analysis groups and proportions of the variables examined and the numbers and proportions of patients (Table 4). The most common new complication was kidney disease (22% of the study group). Men were more likely to develop ischaemic heart disease than women.

Table 5 presents the results of the analysis of variables affecting the emergence of comorbidities (Table 5). The duration of diabetes in each disease group was shorter in those who had complications than those in the control group ($p < 0.0001$). Ischaemic heart disease was more common in men and heart failure in women; gender did not affect disease risk in other groups. Complications were more common in people over 65 years of age than in those under 65 years of age. Previous complications were associated with kidney disease and heart failure ($p < 0.0001$).

Patients receiving insulin or combination therapy had a higher emergence of diabetic kidney disease and heart failure compared with those on lifestyle therapy alone. Patients receiving combination therapy also developed ischaemic heart disease significantly more often. The emergence of kidney disease was higher in all therapy groups with medication. No treatment group with medication had a statistically significant association with the emergence of cerebrovascular diseases.

Hyperglycaemia was associated with a higher risk of complications in all disease groups ($p < 0.0001$). The LDL cholesterol burden was lower in all disease groups than in the control groups in all comorbidities ($p < 0.0001$). Users of lipid therapy had a lower risk of developing renal disease, heart failure, and cerebrovascular disease ($p < 0.0001$), but no corresponding risk-reducing association was found with ischaemic heart disease. The use of ACE inhibitors and ATR blockers did not appear to reduce the risk of comorbidities, as expected. The association of GLP-1 receptor agonists and SGLT2 inhibitors with any of these complications was lower than in the control group ($p < 0.0001$).

Table 2
Prevalence of comorbidities in patients with type 2 diabetes and prediabetes in 2019 in the catchment area of Turku University hospital.

Year 2019		Type 2 diabetes	Prediabetes	
Total people		n = 37,209 (46.7%)	n = 42,554 (53.4%)	
	ICD 10 codes	n (%)	n (%)	p [1]
No comorbidities		19,687 (52.9)	28,152 (66.2)	<0.001
Ischemic heart disease	I20–I25	7,012 (18.8)	5,953 (14.0)	<0.001
Heart failure	I50	3,628 (9.8)	2,265 (5.3)	<0.001
Cerebrovascular disease	I63-I66	4,547 (12.2)	4,580 (10.8)	<0.001
Kidney disease	N08.3*, N18, Z94, Z49, E11.2, or U-AlbKre >3 mg/mmol or cU-Alb-Mi >20 ug/min) or eGFR <60 ml/min/1.73m2)	7,006 (18.8)	2,244 (5.3)	<0.001

[1] p describes whether there is a statistically significant difference in the relative proportions of comorbidities between type 2 diabetes and prediabetes (chi-square test).

Discussion

In the first part of the study, nearly half of individuals with type 2 diabetes (T2DM) and about one-third of those with prediabetes were found to have at least one comorbidity. We found that all comorbidities studied were more common in patients with T2DM, but macrovascular complications were also common in patients with prediabetes. All studied comorbidities were more common in men with diabetes than in women, except for heart failure. There was no statistically significant

Table 1
Basic information for research cohorts 1 and 2.

			Altogether	Males	Females	Age in years
			n	n (%)	n (%)	mean (SD)
Cohort 1	**2019**	**Prevalence of comorbidities**				
		Type 2 diabetes	37,209	19,273 (51.7)	17,936 (48.3)	71.4 (12.8)
		Prediabetes	42,554	19,733 (46.4)	22,821 (53.6)	69.9 (13.8)
Cohort 2	**2007–2019**	**Emergence of comorbidities**				
		Type 2 diabetes, No complications before 2007	41,664	20,807 (49.9)	20,857 (50.1)	63.8 (2.6)

Table 3
Prevalence of comorbidities in men and women with type 2 diabetes and prediabetes in the catchment area of Turku University hospital in 2019.

Year 2019	Type 2 diabetes			Prediabetes		
	males	females		males	females	
Total people	n = 19,273	n = 17,936		n = 19,733	n = 22,821	
	n (%)	n (%)	p[1]	n (%)	n (%)	p [1]
No comorbidities	9,400 (48.8)	10,287 (57.4)	<0.001	12,387 (62.8)	15,765 (69.1)	<0.001
Ischemic heart disease	4,376 (22.7)	2,636(14.7)	<0.001	3,420 (17.3)	2,533 (11.1)	<0.001
Heart failure	1,863 (9.7)	1,765 (9.8)	0.57	1,056 (5.4)	1,209 (5.3)	0.81
Cerebrovascular disease	2,443 (12.7)	2,104 (11.7)	0.005	2,169 (11.0)	2,411 (10.6)	0.16
Kidney disease	3,862 (20.0)	3,144 (17.5)	<0.001	1,006 (5.1)	1,238 (5.4)	0.13

[1] p describes whether there is a statistically significant difference in the relative proportions of comorbidities between males and females (chi-square test).

difference in the prevalence of comorbidities between men and women with prediabetes, except for ischaemic heart disease. The prevalence of diabetes kidney disease in patients with diabetes was equal to that of ischaemic heart disease.

In the second part of the study, we studied logistic regression-based associations with the occurrence of new comorbidities (Cohort 2). The risk of developing the disease was higher in older individuals, but the longer duration of the disease was surprisingly associated with a lower risk of developing the disease. The more severe form of the disease probably explains the association between a shorter duration of diabetes with the onset of comorbidities. An alternative explanation is survivorship bias: patients with longer diabetes duration who had not yet developed complications by 2007 were a selected, healthier subgroup. This may also be affected by the shorter observed duration, as individuals whose diabetes was diagnosed at the time of a complication (e.g., a heart attack) were excluded and thus not included in the analysis.

As expected, long-term hyperglycaemia increased the risk of the disease in all disease groups studied. HbA1c above the target value, glycemic burden of 10 mmol/mol for five years increased the risk of complications by 17–32%, depending on the complication group. The use of lipid drugs, GLP-1 analogs, and SGLT2 inhibitors reduced the risk of disease.

High LDL-C and use of ACE inhibitors and ATR blockers were not, surprisingly, associated with a higher risk of disease. The cholesterol burden was lower in patients who had developed complications. This could be explained by the fact that cholesterol-lowering drug therapy was started earlier in high-risk patients and therefore LDL levels were lower. Cholesterol-lowering drug therapy was used by nearly half of all patients in all disease groups of cohort 2. Use of ACE inhibitors and ATR blockers was even more common. Earlier initiation of these drugs,even before diabetes diagnosis for example, with a hypertonia or hypercholesterolemia indication, could explain why their use was common among patients in control groups, and no risk reduction was observed. Initiation of drug therapy before the diagnosis of a comorbidity in high-risk patients explains the apparent paradox. This is probably protopathic bias / reverse causation. We could try to deal with protopathic bias in 2 ways. a) By excluding the group of individuals who used these drugs before diabetes diagnosis. b) Considering whether the longer time-lag criterion (medication used 1 year before the event) would help to deal with this bias. Since hypertonia and other comorbidities are indications for initiation of these drugs before the occurrence of the complication and also in control groups, the current analytic structure may be inherently unable to detect a protective effect of these drugs in this dataset.

Insulin and combination therapy is used in patients with a more severe form of the disease and higher levels of HbA1c. Hyperglycaemia as a confounding factor partly explains the higher risk of comorbidities compared to those without antidiabetic drugs. Among the studied complication groups, as an exception, cerebrovascular events were not associated with diabetes medications. More effective treatment of hyperglycaemia can reduce the incidence of comorbidities, but it is important to address other risk factors early and select treatments that can reduce comorbidities. A Finnish population survey conducted between 1992 and 2017 revealed a downward trend in cardiovascular risk factors, although the decline has slowed down over this period [8]. A study based on register data from the FinDM project between 2000 and 2017 found that the incidence of heart and cerebral artery complications in diabetes had decreased, but kidney complications had increased [21]. In our prevalence study (cohort 1), the prevalence of kidney complications was higher than in that study, i.e., at the same level as the prevalence of ischaemic heart disease (18.8%). The number of new kidney disease patients in the cohort 2 between 2007 and 2019 was almost double that of the other disease groups. Kidney disease occurred in 8099 (22%) and ischaemic heart disease in 5904 (16%) T2DM patients in the analysis groups. The improved measurement coverage of albuminuria during the follow-up period partially explains this and thanks to the

Table 4
Comorbidity groups as response variables in the analyses and variables related to diabetes treatment in the catchment area of Turku University hospital in 2007–2019 as explanatory factors. The abbreviations of therapies in the table are lifestyle therapy (L), tablet therapy (T), combination therapy (T + I), and insulin therapy (I).

Analysis groups of comorbidities and percentages of variables		Ischemic heart disease	Heart failure	Cerebro-vascular disease	Kidney disease
Total people	N	35,962	36,802	36,538	36,702
Males	n	17,693	18,309	18,166	18,256
Females	n	18,269	18,493	18,372	18,446
Age <65 years / at least 65 years	%	57.1 / 42.9	56.8 / 43.2	57 / 43	56.7 / 43.3
Treatment: L / T / T + I / I	%	27/57/12/3	27/58/12/3	28/57/13/3	28/59/11/2
Established previous complication	%	10	40	38	32
Lipid drugs	%	45	47	46	47
ACE inhibitors and ATR blockers	%	44	55	54	55
GLP-1 analogues	%	3	3	3	3
SGLT2 inhibitors	%	9	9	9	8
Average duration of diabetes (years)	median (Q1, Q3)	8.3 (4.2, 12.3)	8.5 (4.4, 12.5)	8.4 (4.3, 12.5)	7.9 (4.1,11.9)
Glycemic burden (mmol/mol)	median (Q1, Q3)	0 (0, 9.5)	0 (0, 9.5)	0 (0, 2.0)	0 (0, 8.2)
LDL burden (mmol/l)	median (Q1, Q3)	5.7 (2.2, 10.8)	5.6 (2.2, 10.8)	5.6 (2.2, 10.8)	5.3 (2.0, 10.5)
The emergence of a new comorbidity in 2007 - 2019					
Males	n (%)	1,923 (10.9)	1,302 (7.1)	1,209 (6.7)	3,224 (17.7)
Females	n (%)	1,589 (8.9)	1,615 (8.7)	1,240 (6.7)	3,205 (17.4)
Altogether	n (%)	3,512 (9.7)	2,852 (7.7)	2,499 (6.8)	6,439 (17.5)

Table 5
The association between various explanatory factors with the appearance of type 2 diabetes comorbidities by logistic regression. We created the models used in the analysis separately for different comorbidity groups.(OR = odds ratio, CI = confidence interval). The abbreviations of therapies in the table are lifestyle therapy (L), tablet therapy (T), combination therapy (T + I), and insulin therapy (I).

	Ischemic heart disease		Heart failure		Cerebrovascular disease		Kidney disease	
Comorbidities that occurred between 2007 and 2019	n = 5,904		n = 4,434		n = 4,143		n = 8,099	
Variable	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Duration of diabetes (year)	0.95 (0.95–0.96)	<0.0001	0.97 (0.96–0.98)	<0.0001	0.96 (0.95–0.97)	<0.0001	0.96 (0.95–0.96)	<0.0001
Gender (male vs. female)	1.32 (1.22–1.42)	<0.0001	0.81 (0.74–0.88)	<0.0001	1.06 (0.97–1.16)	0.23	1.01 (0.95–1.07)	0.88
Age over 65 vs. under 65	1.63 (1.50–1.77)	<0.0001	2.13 (1.94–2.34)	<0.0001	1.71 (1.55–1.88)	<0.0001	1.48 (1.39–1.59)	<0.0001
Previous complication	0.97 (0.89–1.05)	0.46	2.41 (2.20–2.64)	<0.0001	0.95 (0.87–1.05)	0.32	1.16 (1.08–1.23)	<0.0001
Treatment								
I vs. L	1.13 (0.89–1.45)	0.32	1.53 (1.21–1.94)	0.0005	1.04 (0.79–1.36)	0.81	2.48 (2.04–3.02)	<0.0001
T vs. L	0.93 (0.84–1.02)	0.13	0.97 (0.87–1.07)	0.51	0.87 (0.78–0.98)	0.02	1.51 (1.39–1.64)	<0.0001
T + I vs. L	1.34 (1.15–1.57)	0.0003	1.36 (1.15–1.61)	0.0003	1.03 (0.85–1.23)	0.03	2.64 (2.33–3.00)	<0.0001
Glycemic burden (mmol/mol)	1.004 (1.003–1.005)	<0.0001	1.003 (1.002–1.004)	<0.0001	1.004 (1.003–1.005)	<0.0001	1.006 (1.005–1.006)	<0.0001
LDL cholesterol burden (mmol/l)	0.95 (0.95–0.96)	<0.0001	0.95 (0.94–0.95)	<0.0001	0.96 (0.95–0.97)	<0.0001	0.94 (0.93–0.94)	<0.0001
Lipid drugs	0.97 (0.89–1.05)	0.43	0.66 (0.60–0.72)	<0.0001	0.79 (0.72–0.87)	<0.0001	0.74 (0.69–0.78)	<0.0001
ACE inhibitors and ATR blockers	1.36 (1.25–1.48)	<0.0001	1.24 (1.12–1.36)	<0.0001	1.29 (1.17–1.43)	<0.0001	1.83 (1.71–1.96)	<0.0001
GLP-1 agonists	0.38 (0.28–0.52)	<0.0001	0.47 (0.33–0.66)	<0.0001	0.50 (0.35–0.72)	0.0002	0.65 (0.54–0.79)	<0.0001
SGLT2 inhibitors	0.19 (0.15–0.25)	<0.0001	0.21 (0.16–0.28)	<0.0001	0.19 (0.14–0.26)	<0.0001	0.21 (0.18–0.24)	<0.0001

laboratory studies, kidney complications were identified at an earlier stage than other comorbidities.

The prevalence of kidney disease in our study (cohort 1) corresponds to the results of the national Diabetes Register, which is based on the entire Finnish registry data (2).

The prevalence of diabetes kidney disease was significantly higher (41.9%) in the Finnish cross-sectional Stone HF study published in 2022 [25]). This difference is explained by the different methods of extracting the data. Our own dataset included all patients selected from the patient register in the catchment area of Turku University Hospital for 12 years, whereas the data for the Stone HF study included 1196 patients with T2DM who visited the doctors who participated in the study. 62% of them were high-risk patients. As only 60 of the 203 invited clinicians participated in study data collection, there may be a bias towards clinicians and centers that are particularly active in T2DM treatment. Our data also included diabetes patients with lifestyle treatment. Screening for albuminuria is still too poorly implemented in Finland [2,26], so there is underdiagnosis in identifying these high-risk patients. Nevertheless, kidney complications of diabetes were the most common new comorbidities in our study.

Those taking SGLT2 inhibitors had an almost five-fold lower risk of developing any comorbidity. The association between GLP-1 receptor agonists with comorbidities was also lower than those without the drug in this group. In Finland, these drugs have typically been started quite late, so patients have developed diabetes much earlier. The use of SGLT2 inhibitors started gradually in 2013 and gradually increased, so that only in 2019 the drug in this group was most common as the second drug after Metformin in the catchment area of Turku University Hospital [27]. The use of GLP-1 receptor agonists in Finland has increased even more slowly (due to Kela's reimbursement criteria) and this drug group is started only as the third or fourth diabetes drug despite research evidence and international treatment recommendations [18,19]. Among patients using GLP-1 RA and SGLT2 inhibitor medications, over 50% were at least 65 years old, and they had a longer duration of the disease than T2DM patients on average. The exposure of these medications was quite short-term. This can lead to an overestimation of the protective effect.

Strong evidence of a prognostic effect and effect on weight management would support the use of GLP-1 receptor agonists at an earlier stage, but Kela's reimbursement criteria seem to guide treatment choices more than treatment recommendations in Finland.

A strength of our study is the large, regionally comprehensive dataset, which, regarding pharmacotherapy, was based on actual medication purchases recorded by Kela. i.e., including all people who have used the studied medicines, regardless of the place of treatment. Public health care in Finland is responsible for patients with type 2 diabetes (over 90%). Extensive selection based on laboratory tests combined with diagnosis codes enabled a long-term follow-up study and the inclusion of patients with diabetes undergoing lifestyle care in the data. The data excluded primary health care records, except for laboratory tests, which may have led to the absence of milder forms of comorbidities. Data on important risk factors, such as obesity and blood pressure, were missing due to a lack of primary care data. The study design made it possible to assess the exposure impact of variables only indicatively.

Further studies are needed to assess how drug groups that improve prognosis will impact high-risk patients in real-world data across Finland, alongside more comprehensive analyses of risk factors.

Conclusions

Macrovascular complications are already common in patients with prediabetes. As the prevalence of prediabetes exceeds that of type 2 diabetes, the overall disease burden is expected to increase unless treatment intensity is enhanced at the prediabetes stage. Early intervention targeting modifiable risk factors, effective management of hyperglycaemia, and appropriate selection of pharmacological therapies can substantially influence the development of comorbidities.

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Data availability

Data not available / The data that has been used is confidential.

CRediT authorship contribution statement

Merja A Laine: Writing – original draft, Validation, Investigation. **Hannu Järveläinen:** Writing – review & editing, Supervision. **Markku Vielma:** Validation, Software, Methodology. **Helena Ollila:** Formal analysis. **Päivi Rautava:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial

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