Research: Epidemiology

Risk of future microvascular and macrovascular disease in people with Type 1 diabetes of very long duration: a national study with 10-year follow-up

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Abstract

Aims To describe factors associated with prevalence or absence of microvascular and macrovascular complications in people with Type 1 diabetes of very long duration and to investigate the risk factors associated with the incidence of such complications.

Methods We included individuals with Type 1 diabetes who had been entered in the Swedish National Diabetes Register between 2002 and 2004 (n = 18,450). First, risk factor distribution in people with diabetes duration of ≥ 50 years was compared between people with and without complications. Second, the incidence of complications during a 10-year follow-up period was studied in all individuals who had no complications at baseline.

Results Among people with a diabetes duration of ≥ 50 years (n = 12,235), 453 (44%) had macrovascular disease, 534 (52%) had microvascular disease and 319 (31%) did not have either of the diagnoses. Factors that differed significantly between people with and without macrovascular disease were gender, age, HbA1c, BMI, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, albuminuria, antihypertensive medication and lipid-lowering medication. The same factors differed significantly between people with and without microvascular disease, with the exception of gender and HDL cholesterol. During the follow-up period, 6.1% of the study cohort were diagnosed with macrovascular disease and 19.6% with microvascular disease. Incidence of macrovascular disease was significantly associated with HbA1c levels. Hazard ratios decreased with longer diabetes duration.

Conclusions People with Type 1 diabetes who have survived ≥ 50 years without complications are significantly younger, and have significantly lower HbA1c levels, BMI and triglyceride levels than survivors with complications. HbA1c level is a predictor of macrovascular disease, independently of diabetes duration.

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Introduction

Type 1 diabetes is associated with an increased risk of microvascular and macrovascular disease. People with Type 1 diabetes have a two to three times higher risk of death and a life expectancy that is shorter by more than a decade [1,2]. A follow-up study in Swedish people with diabetes who were hospitalized between 1965 and 1983 found that the majority of deaths (62%) were attributed to circulatory disease [3]. Some people with diabetes, however, never develop complications despite long duration of the disease.

Glycaemic control has been shown to be one of the strongest predictors of diabetes complications [4–8]. Previous studies in people with very long duration of diabetes have suggested several possible protective factors against these complications [9,10]. The design of these studies has, however, been mainly cross-sectional, relying on self-reported data, and the results are inconsistent. The Golden Years Study reported relatively mediocre glycaemic control among long-term survivors, whereas the Joslin 50-year Medalist study found no association between HbA1c levels and diabetes complications [9,10].

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Study population and methods

The present study was based on information from linking the Swedish National Diabetes Register (NDR), Hospital Discharge Register, Cause of Death Register and Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). The Regional Ethical Review Board at the University of Gothenburg approved the study.

Databases

The NDR has been described previously [11]. Briefly, the register was launched in 1996 as a tool for quality assurance in diabetes care, and contains information about risk factors, complications and treatment among people with diabetes aged ≥ 18 years. Trained nurses and physicians report data at least once a year either online or by electronic transmission of patient charts. Data are collected during appointments at specialist clinics and primary healthcare centres nationwide. All participants give their informed consent before inclusion in the NDR. Data on an estimated 90% of all adults with Type 1 diabetes in Sweden have been entered into the NDR [12].

The Hospital Discharge Register and Cause of Death Register are administered by the Swedish National Board of Health and Welfare. Since 1987, the Hospital Discharge Register has included data for all inpatient care. As of 2001, data from outpatient appointments with both private and public care providers have also been included. The data concern diagnoses, procedures and length of hospital stay.

The Cause of Death Register contains data for all Swedes, regardless of whether they died in Sweden or abroad. Administered by Statistics Sweden, the LISA register contains information about marital status, educational level and disposable income for all Swedes.

Baseline examinations and definitions

The clinical characteristics reported to the NDR at baseline are age, gender, diabetes duration, HbA1c, weight, height, blood pressure, total cholesterol, HDL cholesterol, triglycerides, microalbuminuria, macroalbuminuria, smoking status and use of antihypertensive and lipid-lowering medication. Smoking status is recorded as either yes or no. Marital status is either single, married/registered partner, divorced or widowed.

All laboratory analyses were performed at local facilities. HbA1c values are expressed in mmol/mol as specified by the International Federation of Clinical Chemistry and converted to National Glycohemoglobin Standardization Program [Diabetes Control and Complications Trial (DCCT) standard] values (%) [14]. BMI was calculated as weight in kg/height in m². LDL cholesterol concentration was based on Friedewald’s formula [15]. Microalbuminuria was defined as two positive results for three samples obtained within 1 year. A positive result was defined as an albumin/creatinine ratio of 3–30 mg per millimole (~30–300 mg/g) or a urinary albumin clearance of 20–200 μg/min (20–300 mg/l). Macroalbuminuria was defined as an albumin/creatinine ratio > 30 mg/mmol (~300 mg/g) or a urinary albumin clearance > 200 μg/min (> 300 mg/l).

Follow-up and definition of endpoints

People who did not have a history of cardiovascular disease (CVD), microvascular disease or albuminuria (n = 12 334) were monitored from the date of registration until death, first diagnosis of CVD/microvascular disease or the end of the period (31 December 2012; Fig. 1). CVD was defined as a primary or contributory diagnosis of one of the following conditions or procedures: ischaemic heart disease; myocardial infarction; stroke; unstable angina; percutaneous coronary intervention; coronary artery bypass grafting; and...
peripheral vascular disease or amputation. Cases were retrieved by linking Swedish personal identity numbers with the Hospital Discharge Register and the Cause of Death Register. Detailed information about the International Classification of Diseases (ICD) codes used is presented in the Supporting Information (File S1).

Microvascular disease was defined as renal impairment and/or severe retinopathy. Renal impairment was defined as a primary or contributory diagnosis of one of the following diagnoses or conditions: acute renal failure; chronic renal failure; specified diabetic kidney disease; unspecified diabetic kidney disease; other kidney disease; dialysis; haemodialysis; peritoneal dialysis; kidney transplant; or renal dialysis and transplantation.

Severe retinopathy was defined as a primary or contributory diagnosis using ICD codes stated in the Supporting Information (File S1). In Sweden, diabetic retinopathy is always diagnosed by an ophthalmologist, which enables a high sensitivity and specificity.

Statistics

The sample was stratified into six diabetes duration groups: 0–19 years; 20–29 years; 30–39 years; 40–49 years; and ≥ 50 years. Between 6 and 37% of the people included in the study had missing values for at least one of the following variables: HbA1c; blood pressure; total cholesterol; lipoproteins; triglycerides; albuminuria; smoking status; marital status; educational level; or disposable income. Multiple imputation, generating 10 datasets, was used to avoid a reduction in sample size. Chi-squared tests were used to compare people with and without previous CVD or microvascular disease. Cox proportional hazards regression was used to estimate hazard ratios for the association between various baseline variables and incidence of CVD and microvascular disease across the diabetes duration groups. The proportional hazards assumption was confirmed by plotting the negative log of the estimated survivor functions vs time. The survival analysis included only people who did not have a history of CVD, microvascular disease and albuminuria. The following variables were included in the models: age; gender; systolic blood pressure; BMI; total cholesterol; HDL cholesterol; triglycerides; antihypertensive medication; lipid-lowering medication; educational level; marital status; and income. All analyses were performed in sas version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics for the diabetes duration groups

The risk factor distribution among the various groups of diabetes duration is shown in Table 1. Of those with a diabetes duration ≥ 50 years (n = 1023), 453 (44%) had a
The hazard ratios for HbA1c showed a similar inverse relationship with diabetes duration, as in the case of CVD, although HbA1c levels were not significantly associated with incidence of CVD in all duration groups. The hazard ratios were also the only factors significantly associated with incidence of CVD in people with diabetes duration ≥ 50 years. Age and HbA1c were also the only factors significantly associated with incidence of CVD in all duration groups. The hazard ratios for HbA1c showed an inverse relationship with diabetes duration (Fig. 2).

### Incidence of microvascular disease

During the mean follow-up period of 8.7 years, 2412 people (19.6%) were diagnosed with renal impairment or severe retinopathy (22.5 per 1000 person-years). The relationships between various risk factors and incidence of CVD in the different diabetes duration groups are shown in Table S2. After adjustment for potential confounders, age and HbA1c were the only factors significantly associated with incidence of CVD in people with diabetes duration ≥ 50 years. Age and HbA1c were also the only factors significantly associated with incidence of CVD in all duration groups. The hazard ratios for HbA1c showed an inverse relationship with diabetes duration (Fig. 2).

### Incidence of cardiovascular disease

The descriptive statistics of those included in the survival analysis are shown in Table S1. During the mean follow-up period of 9.4 years, 747 people (6.1%) were diagnosed with CVD (6.4 per 1000 person-years). The relationships between various risk factors and incidence of CVD in the different diabetes duration groups are shown in Table S3. Marital status was the only factor that was significantly associated with incidence of microvascular disease in people with a diabetes duration of ≥ 50 years. The hazard ratios for HbA1c showed a similar inverse relationship with diabetes duration, as in the case of CVD, although HbA1c levels were not significantly associated with incidence of microvascular disease in people with a diabetes duration of ≥ 50 years (Fig. 2).
Table 2 Descriptive statistics of individuals with diabetes duration ≥ 50 years with and without previous cardiovascular disease

| Variable                        | No        | Yes        | P        |
|---------------------------------|-----------|------------|----------|
| Diabetes duration               | 54.9 (4.8) | 56.0 (5.3) | <0.001   |
| Male sex, n (%)                 | 276 (48.4) | 248 (54.7) | 0.044    |
| Age, years                      | 65.0 (7.5) | 66.9 (7.4) | <0.001   |
| Age at diagnosis, years         | 10.1 (6.6) | 10.9 (6.6) | 0.059    |
| HbA1c, mmol/mol                 | 62 ± 12    | 64 ± 12    | <0.001   |
| %                               | 7.8 ± 3.3  | 8.0 ± 3.2  |          |
| BMI, kg/m²                      | 25.0 (3.7) | 25.6 (4.0) | <0.001   |
| LDL cholesterol, mmol/l         | 2.9 (0.8)  | 2.7 (0.8)  | 0.001    |
| HDL cholesterol, mmol/l         | 1.8 (0.5)  | 1.6 (0.5)  | <0.001   |
| Total cholesterol, mmol/l       | 5.2 (0.9)  | 4.9 (0.9)  | 0.567    |
| Triglycerides, mmol/l           | 1.1 (0.6)  | 1.4 (1.0)  | <0.001   |
| Systolic blood pressure, mm Hg  | 144.5 (18.4)| 143.0 (18.7)|<0.001    |
| Diastolic blood pressure, mm Hg | 79.9 (9.6) | 79.9 (9.5) | 0.055    |
| Previous kidney disease, n (%)  | 89 (15.6)  | 370 (81.7) | <0.001   |
| Previous severe retinopathy, n (%) | 73 (12.8%) | 100 (22.1%)| <0.001   |
| Smoker, n (%)                   | 43 (7.9)   | 29 (6.7)   | 0.489    |
| Antihypertensive medication, n (%) | 345 (61.5) | 375 (83.7) | <0.001   |
| Lipid lowering medication, n (%) | 192 (35.7) | 260 (60.2) | <0.001   |
| Albunumiria, n (%)              | 180 (16.6) | 213 (47.0) | <0.001   |
| Microalbuminuria, n (%)         | 100 (19.5) | 105 (26.5) | 0.012    |
| Macroalbuminuria, n (%)         | 80 (15.6)  | 108 (27.3) | <0.001   |
| Married, n (%)                  | 345 (61.4%)| 283 (64.8) | 0.274    |
| Divorced, n (%)                 | 88 (15.7)  | 70 (16.0)  | 0.877    |
| Widow/widower, n (%)            | 57 (10.1)  | 40 (9.2)   | 0.600    |
| High education level            | 91 (16.2)  | 38 (13.4)  | 0.210    |
| Income: top quintile, n (%)     | 80 (14.2)  | 45 (10.3)  | 0.062    |

Data are presented as means (±SD) unless otherwise indicated.

Discussion

In this register-based cohort study, we found that people who had survived ≥ 50 years with Type 1 diabetes without microvascular or macrovascular complications were significantly younger and had significantly lower HbA1c levels, BMI and triglyceride levels than those who did have a history of such complications. They were also found to have higher LDL cholesterol levels, less albuminuria and less use of antihypertensive or lipid-lowering medication. In addition, we found that HbA1c levels were significantly associated with incidence of macrovascular complications, independently of duration of Type 1 diabetes. The risk estimates were inversely associated with duration of Type 1 diabetes, suggesting that HbA1c is less of a risk factor among people who have survived a very long diabetes duration.

A previous cross-sectional study of 400 people with > 50 years duration of Type 1 diabetes (the Golden Years cohort in the UK) suggested that they were relatively well protected from microvascular and macrovascular disease, possibly as a result of elevated HDL cholesterol levels [9]. The present study showed significantly higher levels of HDL cholesterol in corresponding people who did not have a history of CVD at baseline. A similar trend was observed in people who did not have a history of microvascular disease at baseline, although these differences were not statistically significant. Another cross-sectional study of 351 people with > 50 years duration of Type 1 diabetes (the Joslin 50-year Medalist study conducted in the USA) found lower HDL cholesterol levels in people who reported a history of CVD [10]. The same study, however, did not report any differences in HDL cholesterol levels among people with a history of nephropathy, retinopathy or neuropathy. In addition, a survival analysis of the present cohort showed no independent association between HDL cholesterol and incidence of microvascular or macrovascular complications in any of the diabetes duration groups. People without previous CVD or microvascular disease were also found to have significantly higher LDL cholesterol levels in the present study. This might be attributable to the fact that lipid-lowering medication was less common in these people than in those with a history of such complications and who were therefore undergoing secondary prevention measures.

In addition to having higher HDL cholesterol levels, long-term diabetes survivors have also been reported to have normal body weight, normal blood pressure and low insulin dosages [16]. Information on insulin dosage was not available in the present study, but people with diabetes duration ≥ 50 years without previous CVD or microvascular disease were found to have a significantly lower BMI than those with a history of such complications. People with a diabetes duration of ≥ 50 years without previous CVD had significantly higher systolic blood pressure than those with previous CVD in the present study; however, ~84% of people with a history of such complications reported the use of antihypertensive medication. The corresponding proportion of those without previous CVD was ~62%, which is more than twice as high as the figures reported in the Golden Years cohort [9]. This is somewhat surprising given that the mean age among people without complications in the present cohort was only 64 years, as opposed to 69 years in the Golden Years study, and is probably attributable to recent changes in risk factor treatment practices. People without previous microvascular disease were found to have significantly lower systolic and diastolic blood pressure than those with a history of such disease. Systolic blood pressure was, however, not associated with incidence of microvascular or macrovascular complications in any of the diabetes duration subgroups after adjustment for potential confounding factors.

Studies have generated conflicting results about the importance of glycaemic control among long-term survivors. The
Joslin Medalist study reported a mean HbA1c of 53 mmol/mol (7%) at the time of examination, whereas the Golden Years study reported a non-DCCT mean HbA1c of 7.6% (equivalent to 60 mmol/mol). The present study indicated even higher levels of HbA1c among people both without [61–62 mmol/mol (7.7–7.8%)] and with [64–65 mmol/mol (8.0–8.1%)] a
HbA1c is highly correlated with long-term HbA1c [17,18]. Studies based on the NDR have also shown that glycaemic control concomitant with a diagnosis of Type 1 diabetes in childhood or adolescence can predict glycaemic control in early adulthood [19]. Individuals with a high mean HbA1c level 3–15 months after diagnosis have macroalbuminuria and retinopathy significantly more often in early adulthood [19]. The development of complications is likely to be caused by the level of glycaemia over a period of many years (i.e., metabolic memory) against the backdrop of genetic disposition and other risk factors [20–22]. The present study showed that HbA1c levels were associated with incidence of microvascular and macrovascular complications, but that predictability was inversely related to diabetes duration.

The relatively high baseline HbA1c in long-term, complication-free survivors indicates the presence of other protective factors. It has been suggested that circulating and endothelial progenitor cells are involved in protection from cardiovascular complications and nephropathy [23]. It was also shown that certain advanced glycation endproducts were inversely associated with proliferative diabetic retinopathy in long-term survivors, as opposed to previous studies that showed strong associations between advanced glycation endproducts and diabetes complications [18]. Thus, long-term survivors of diabetes appear to develop a compensatory mechanism against the hazardous effects of advanced glycation endproducts, but the exact dynamic has yet to be discovered [24]. Given that longevity has been shown to be high among parents of long-term survivors, genetic factors are hypothesized to play a significant role, and studies to find protective genetic factors are underway [9,10].

Being married, divorced or widowed was, compared to being single, associated with a significantly lower incidence of microvascular disease among those with diabetes of ≥50 years duration. Previous studies from the NDR have shown a general protective effect of being married/cohabiting [25]. One could speculate that this protective effect will also remain for a certain time after the marriage has ended, if the individual was married long enough (e.g., ~50 years); in other words, a legacy effect of being married.

The main strength of the present study is the large number of participants, including people from a nationwide diabetes register with a high participation rate and data from day-to-day clinical practice. Another strength is the prospective design with a mean follow-up period of almost 10 years, which reduces the risk of reverse causation. Most previous studies on long-term survivors of Type 1 diabetes have been cross-sectional and included significant percentages of self-reported data. The present study, by contrast, obtained events from the Hospital Discharge Register and Cause of Death Register. Validation studies of the Hospital Discharge Register have been shown to have high overall specificity [26]. Overall, the registry study design differs significantly from previous studies of long-term survivors, where people have generally been brought into a centre for evaluation specifically for the study. This makes comparisons with previous findings more complex; however, because the present study included data from daily clinical practice, the results are likely to have a high external validity.

The present study was limited to individuals who had survived long enough to be included in the NDR. The Hospital Discharge Register has been nationwide only since 1987, such that early diabetes complications may not have been entered for some people with very long diabetes duration. In addition, some cases may be treated only in primary care, which is not covered by the Hospital Discharge Register; however, almost all people with Type 1 diabetes receive treatment at specialist hospital clinics. Thus, the assumption is that most diabetes complications are reported. We did not have information on whether the myocardial infarctions were silent or not, but we do not believe that this lack of information would have resulted in any systematic bias of our findings. Because all diagnoses were settled during a hospital stay, most cases are assumed to be valid.

Cases with urinary tract infections or recent ketoacidosis were not excluded from albuminuria cases. The numbers of people with these two complications were assumed to be low and therefore unlikely to alter the results in this large sample. Residual confounding is probable despite the analysis having been adjusted for several biological, lifestyle and social/demographic factors.

In conclusion, the present nationwide study shows that among people who had survived ≥50 years with Type 1 diabetes, >30% did not have microvascular or macrovascular complications. These individuals were younger and had lower HbA1c, BMI and triglyceride levels than survivors with complications. They also had higher LDL cholesterol levels, less albuminuria and less antihypertensive/lipid-lowering medication. In addition, this study shows that HbA1c is a predictor of macrovascular disease, independently of duration of Type 1 diabetes. The results suggest that HbA1c is less of a risk factor in people with very long diabetes duration.

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Competing interests
None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Definition of endpoints including ICD-codes.

Table S1. Descriptive statistics of individuals included in survival analysis.

Table S2. Hazard ratios for cardiovascular disease during follow-up in relation to risk factors in various duration groups.

Table S3. Hazard ratios for microvascular disease during follow-up in relation to risk factors in various duration groups.

Table S4. Number of events during follow-up in men and women with different diabetes duration.

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