ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

Marcus Lind, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mikhail Kosiborod, M.D.,
Soffia Gudbjörnsdottir, M.D., Ph.D., Aldina Pivodic, M.Sc., Hans Wedel, Ph.D.,
Sofia Dahlqvist, Mark Clements, M.D., Ph.D., and Annika Rosengren, M.D., Ph.D.

ABSTRACT

BACKGROUND

The excess risk of death from any cause and of death from cardiovascular causes is unknown among patients with type 1 diabetes and various levels of glycemic control. We conducted a registry-based observational study to determine the excess risk of death according to the level of glycemic control in a Swedish population of patients with diabetes.

METHODS

We included in our study patients with type 1 diabetes registered in the Swedish National Diabetes Register after January 1, 1998. For each patient, five controls were randomly selected from the general population and matched according to age, sex, and county. Patients and controls were followed until December 31, 2011, through the Swedish Register for Cause-Specific Mortality.

RESULTS

The mean age of the patients with diabetes and the controls at baseline was 35.8 and 35.7 years, respectively, and 45.1% of the participants in each group were women. The mean follow-up in the diabetes and control groups was 8.0 and 8.3 years, respectively. Overall, 2701 of 33,915 patients with diabetes (8.0%) died, as compared with 4835 of 169,249 controls (2.9%) (adjusted hazard ratio, 3.52; 95% confidence interval [CI], 3.06 to 4.04); the corresponding rates of death from cardiovascular causes were 2.7% and 0.9% (adjusted hazard ratio, 4.60; 95% CI, 3.47 to 6.10). The multivariable-adjusted hazard ratios for death from any cause according to the glycated hemoglobin level for patients with diabetes as compared with controls were 2.36 (95% CI, 1.97 to 2.83) for a glycated hemoglobin level of 6.9% or lower (≤52 mmol per mole), 2.38 (95% CI, 2.02 to 2.80) for a level of 7.0 to 7.8% (53 to 62 mmol per mole), 3.11 (95% CI, 2.66 to 3.62) for a level of 7.9 to 8.7% (63 to 72 mmol per mole), 3.65 (95% CI, 3.11 to 4.30) for a level of 8.8 to 9.6% (73 to 82 mmol per mole), and 8.51 (95% CI, 7.24 to 10.01) for a level of 9.7% or higher (≥83 mmol per mole). Corresponding hazard ratios for death from cardiovascular causes were 2.92 (95% CI, 2.07 to 4.13), 3.39 (95% CI, 2.49 to 4.61), 4.44 (95% CI, 3.32 to 5.96), 5.35 (95% CI, 3.94 to 7.26), and 10.46 (95% CI, 7.62 to 14.37).

CONCLUSIONS

In our registry-based observational study, patients with type 1 diabetes and a glycated hemoglobin level of 6.9% or lower had a risk of death from any cause or from cardiovascular causes that was twice as high as the risk for matched controls. (Funded by the Swedish Society of Medicine and others.)

Table 1. Baseline Characteristics of Patients with Type 1 Diabetes and Controls.

Characteristic	Controls (N=169,249)	Patients with Type 1 Diabetes (N=33,915)						
		Glycated Hemoglobin Level†						
		Total (N=33,915)	≤6.9% (N=6142)	7.0–7.8% (N=7759)	7.9–8.7% (N=8951)	8.8–9.6% (N=5442)	≥9.7% (N=4000)	Missing Data (N=1621)
Female sex — no. (%)	76,382 (45.1)	15,302 (45.1)	2711 (44.1)	3470 (44.7)	3984 (44.5)	2451 (45.0)	1942 (48.6)	744 (45.9)
Age — yr	35.7±14.6	35.8±14.6	33.9±14.2	37.2±15.1	37.5±14.8	36.1±14.2	32.8±14.5	32.6±14.5
Born in Sweden — no. (%)	146,353 (86.5)	31,838 (93.9)	5732 (93.3)	7333 (94.5)	8462 (94.5)	5110 (93.9)	3728 (93.2)	1473 (90.9)
Educational level — no. (%)								
Low	31,238 (18.7)	6503 (19.3)	859 (14.1)	1372 (17.8)	1704 (19.2)	1181 (21.9)	1028 (25.9)	359 (22.4)
Middle	80,436 (48.1)	16,890 (50.2)	2729 (44.8)	3688 (48.0)	4557 (51.2)	2926 (54.2)	2204 (55.6)	786 (49.1)
High	55,547 (33.2)	10,249 (30.5)	2507 (41.1)	2627 (34.2)	2631 (29.6)	1293 (23.9)	734 (18.5)	457 (28.5)
Information from National Diabetes Register								
Glycated hemoglobin — mmol/mol		65.8±15.8	45.6±5.5	57.3±2.6	67.2±2.8	76.9±2.8	94.9±11.3	
Diabetes duration — yr		20.4±14.8	16.4±15.9	22.0±15.0	22.8±14.3	21.5±13.6	18.3±12.9	16.8±14.8
BMI		25.1±4.0	24.6±4.0	25.0±3.8	25.3±3.8	25.4±4.1	25.0±4.7	24.7±5.0
LDL cholesterol — mmol/liter		2.66±0.83	2.53±0.76	2.60±0.79	2.68±0.83	2.74±0.86	2.87±0.95	2.59±0.81
Blood pressure — mm Hg								
Systolic		126.9±17.0	124.4±15.9	126.8±16.6	128.4±17.1	127.8±17.2	127.0±18.1	123.7±16.6
Diastolic		73.6±9.2	72.2±8.9	73.0±8.9	73.8±9.0	74.4±9.3	75.1±9.6	72.9±9.4
Smoking — no. (%)		4277 (13.6)	515 (8.9)	770 (10.5)	1121 (13.3)	859 (16.9)	855 (23.4)	157 (13.1)
Information from Inpatient Register before baseline — no. (%)‡								
Acute myocardial infarction, ICD code I21	967 (0.6)	745 (2.2)	78 (1.3)	181 (2.3)	221 (2.5)	140 (2.6)	95 (2.4)	30 (1.9)
Coronary heart disease, ICD codes I20–I25	1826 (1.1)	1459 (4.3)	173 (2.8)	349 (4.5)	433 (4.8)	262 (4.8)	180 (4.5)	62 (3.8)
Atrial fibrillation, ICD code I48	938 (0.6)	242 (0.7)	46 (0.7)	58 (0.7)	72 (0.8)	31 (0.6)	25 (0.6)	10 (0.6)
Heart failure, ICD code I50	515 (0.3)	513 (1.5)	62 (1.0)	100 (1.3)	159 (1.8)	82 (1.5)	76 (1.9)	34 (2.1)
Stroke, ICD codes I61–I64	728 (0.4)	501 (1.5)	67 (1.1)	117 (1.5)	140 (1.6)	82 (1.5)	68 (1.7)	27 (1.7)
Cancer, ICD codes C00–C97	2506 (1.5)	607 (1.8)	105 (1.7)	155 (2.0)	170 (1.9)	90 (1.7)	53 (1.3)	34 (2.1)

* Plus–minus values are means ±SD. Percentages for glycated hemoglobin level are based on values from the National Glycohemoglobin Standardization Program, and concentrations are based on values from the International Federation of Clinical Chemistry. International Classification of Diseases (ICD) codes from the 10th revision were used. BMI denotes body-mass index, the weight in kilograms divided by the square of the height in meters and LDL low-density lipoprotein.
† Molar equivalents for glycated hemoglobin level are as follows: 6.9% or lower, 52 mmol per mole; 7.0 to 7.8%, 53 to 62 mmol per mole; 7.9 to 8.7%, 63 to 72 mmol per mole; 8.8 to 9.6%, 73 to 82 mmol per mole; 9.7% or higher, 83 mmol per mole or higher.
‡ Diagnostic codes for the conditions listed are from the ICD, 10th Revision.

Table 2. Mortality among Patients with Type 1 Diabetes as Compared with Controls According to Baseline Level of Glycated Hemoglobin.*

Variable	Controls (N=169,249)	Patients with Type 1 Diabetes (N=33,915)					
		Glycated Hemoglobin Level					
		Total (N=33,915)	≤6.9% (N=6142)	7.0–7.8% (N=7759)	7.9–8.7% (N=8951)	8.8–9.6% (N=5442)	≥9.7% (N=4000)
Death from any cause — no. (%)	4835 (2.9)	2701 (8.0)	333 (5.4)	553 (7.1)	757 (8.5)	473 (8.7)	478 (12.0)
No./1000 patient-yr (95% CI)	3.45 (3.36–3.55)	9.97 (9.59–10.35)	7.01 (6.28–7.80)	8.73 (8.01–9.49)	10.14 (9.43–10.89)	10.54 (9.61–11.53)	16.25 (14.83–17.78)
Death from cardiovascular disease — no. (%)	1444 (0.9)	927 (2.7)	102 (1.7)	201 (2.6)	280 (3.1)	164 (3.0)	139 (3.5)
No./1000 patient-yr (95% CI)	1.03 (0.98–1.09)	3.42 (3.20–3.65)	2.15 (1.75–2.61)	3.17 (2.75–3.64)	3.75 (3.32–4.22)	3.65 (3.12–4.26)	4.73 (3.97–5.58)
Cancer-related death — no. (%)	1671 (1.0)	349 (1.0)	61 (1.0)	77 (1.0)	121 (1.4)	51 (0.9)	34 (0.9)
No./1000 patient-yr (95% CI)	1.19 (1.14–1.25)	1.29 (1.16–1.43)	1.28 (0.98–1.65)	1.22 (0.96–1.52)	1.62 (1.34–1.94)	1.14 (0.85–1.49)	1.16 (0.80–1.62)
Diabetes-related death — no. (%)	110 (0.1)	912 (2.7)	91 (1.5)	166 (2.1)	238 (2.7)	168 (3.1)	214 (5.4)
No./1000 patient-yr (95% CI)	0.08 (0.06–0.09)	3.37 (3.15–3.59)	1.92 (1.54–2.35)	2.62 (2.24–3.05)	3.19 (2.80–3.62)	3.74 (3.20–4.35)	7.28 (6.33–8.32)
External cause of death — no. (%)	558 (0.3)	163 (0.5)	20 (0.3)	42 (0.5)	37 (0.4)	22 (0.4)	33 (0.8)
No./1000 patient-yr (95% CI)	0.40 (0.37–0.43)	0.60 (0.51–0.70)	0.42 (0.26–0.65)	0.66 (0.48–0.90)	0.50 (0.35–0.68)	0.49 (0.31–0.74)	1.12 (0.77–1.58)
Other cause of death — no. (%)	1052 (0.6)	350 (1.0)	59 (1.0)	67 (0.9)	81 (0.9)	68 (1.2)	58 (1.5)
No./1000 patient-yr (95% CI)	0.75 (0.71–0.80)	1.29 (1.16–1.43)	1.24 (0.95–1.60)	1.06 (0.82–1.34)	1.09 (0.86–1.35)	1.51 (1.18–1.92)	1.97 (1.50–2.55)

* Mortality rates were calculated as events per 1000 patient-years; exact Poisson confidence intervals (CIs) of 95% were used.