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Risk factors for mortality and ischemic heart disease in patients with long-term type 1 diabetes

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Abstract

Aims: The purpose of this study is to evaluate the effect of glycemic regulation, dyslipidemia, and renal dysfunction on mortality (all-cause and cardiovascular) and ischemic heart disease (IHD) in a long-term follow-up of a population-based cohort of Danish type 1 diabetic patients with at least 20 years of diabetes. **Methods:** A population-based cohort of type 1 diabetic patients was identified as of July 1, 1973 (n=727). In 1993 to 1996, the cohort was reassessed and baseline data were collected from blood and urine samples in 389 patients. Mean (glycemic regulation and lipids) and highest values (creatinine and albuminuria) of the baseline period were used to predict mortality and IHD between baseline and 2006. Data of mortality and morbidity were provided by the Danish Civil Registration System, the Danish Causes of Death Registry, and the Danish National Patient Registry. **Results:** At the follow-up in 2006, 256 patients (65.8%) were still alive. In a statistical model adjusted for age, sex and duration of diabetes, the following parameters were related to all-cause mortality and cardiovascular mortality: glycemic regulation, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (inversely), total cholesterol, creatinine, and macroalbuminuria. Furthermore, all markers except macroalbuminuria were associated with IHD. Microalbuminuria at baseline was not related to any of the endpoints. **Conclusions:** Glycemic regulation, dyslipidemia, and renal dysfunction were all related to mortality and IHD in a 13-year follow-up of long-term Danish type 1 diabetic patients. These results underscore the better outcome for tightly regulated type 1 diabetic patients, even in long-term survivors.

Keywords: Type 1 diabetes; Mortality; Ischemic heart disease; Glycemic regulation; Lipids

1. Introduction

Type 1 diabetes is associated with a higher rate of all-cause (Dorman et al., 1984; Laing et al., 1999a; Laing et al., 1999b; Moss, Klein, & Klein, 1991; Soedamah-Muthu et al., 2006a) and cardiovascular mortality (Dorman et al., 1984; Laing et al., 1999b, 2003; Moss et al., 1991; Soedamah-Muthu et al., 2006a). Furthermore, type 1 diabetic patients have a 4.5-fold increased risk of major cardiovascular disease compared with nondiabetic subjects (Soedamah-Muthu et al., 2006b).

The Diabetes Control and Complications Trial (DCCT) recommended a tight glycemic control in type 1 diabetes to lower the risk of microvascular complications (DERI, 1993). However, despite a lower number of cardiovascular events in the DCCT intensive-treated group, a tight glycemic regulation was not significantly associated with a decreased risk of cardiovascular disease and mortality, probably due to the

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small number of events in the relatively healthy and young cohort of patients (DERI, 1993). This problem might be circumvented by studying the importance of glycemic regulation in an older aged type 1 diabetic population.

In most follow-up studies, long-term outcomes are evaluated based on data obtained at a single baseline examination. This might, however, lead to misleading conclusions since it is well known that a single measurement may not reflect long-term control due to intraindividual variations in regulation over time (Jorde & Sundsfjord, 2000; Klein, Klein, Moss, & Cruickshanks, 1996; Klein, Moss, & Klein, 1992).

In the present study, we identified a population-based cohort of Danish type 1 diabetic patients with at least 20 years of diabetes. Baseline values of glycemic regulation, various lipids and markers of renal function were obtained over a 4-year period and related to long-term all-cause mortality and cause-specific mortality and morbidity.

2. Patients and methods

2.1. Subjects

As of July 1, 1973, all insulin-dependent diabetic residents in Fyn County, Denmark, were identified based on insulin prescriptions (Grauslund, Green, & Sjolie, 2008; Green, Hauge, Holm, & Rasch, 1981; Sjolie, 1985). At that time, Fyn County had approximately 450,000 inhabitants and was considered to be a demographically representative 9% sample of the Danish population (Green et al., 1981).

In the present study, we included all patients alive as of January 1, 1993, and for whom blood analyses results for HbA_{1c}, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol, or creatinine and/or urine analysis of albumin were available between January 1, 1993, and December 31, 1996.

The study was approved by the Regional Committee on Biomedical Research Ethics of Southern Denmark and was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Blood and urine sampling

Glycated hemoglobin (HbA_{1c}) was measured by high-performance liquid chromatography as fraction of total hemoglobin A_0. High-density lipoprotein cholesterol and triglycerides were determined enzymatically from fasting blood samples and measured colorimetrically at 500 nm. Total cholesterol was measured by the same method, but not necessarily from fasting blood samples. Low-density lipoprotein cholesterol was calculated according to Friedewald formula. Albumin concentration was determined immunoturbidimetrically from overnight urine samples and measured spectrometrically at 340 nm. Serum creatinine was measured by the Jaffe method.

2.3. Follow-up

For the mortality analyses, patients were followed until death (all-cause or cardiovascular), loss to follow-up (due to emigration or refusal to provide data for scientific studies), or, if none of the above had happened, November 6, 2006.

Data on deaths were collected from The Danish Civil Registration System. In case of death or emigration during follow-up, the event date was retrieved. The Danish Causes of Death Registry provided data of the underlying cause of death for the period January 1, 1993, to December 31, 2001. According to death certificates, mortality was categorized by the Registry based on the *International Classification of Diseases*, 9th (World Health Organization, 1977) and 10th Revision (ICD-9/10) (World Health Organization, 1992). With respect to these categories, we classified cardiovascular death as being caused by ischemic heart disease (IHD) (ICD-9: 430.0–438.9; ICD-10: I20.0-I25.9) or stroke (ICD-9: 430.0–438.9; ICD-10: I60.0-I60.9). Causes of mortality were not available from The Danish Causes of Death Registry for patients who died after December 31, 2001 (n=49). For these patients, we collected death certificates, and deaths were classified as being caused by cardiovascular disease if IHD or stroke was mentioned as the underlying cause of death on the death certificate.

For the analysis of IHD, patients were censored at the time of the first registered ischemic cardiac event. For patients who did not develop IHD, the censoring date of the

Table 1
Baseline characteristics for patients included in analyses

	n	Median±SD (%) or interval
Age (years)	389	45.8±11.7
Duration of diabetes (years)	389	30.0±9.1
Sex (% male)	389	55.0
HbA_{1c} (%)	388	8.73±1.30
Quartile 1	97	5.47–8.03
Quartile 2	97	8.04–8.73
Quartile 3	97	8.74–9.72
Quartile 4	97	9.73–14.0
Triglyceride (mmol/L)	221	1.06±0.65
Quartile 1	54	0.40–0.80
Quartile 4	54	1.46–4.06
LDL cholesterol (mmol/L)	221	3.25±0.93
Quartile 1	53	1.70–2.68
Quartile 4	55	3.87–6.96
HDL cholesterol (mmol/L)	221	1.66±0.55
Quartile 1	55	0.43–1.31
Quartile 4	55	2.10–3.42
Cholesterol (mmol/L)	251	5.50±1.08
Quartile 1	64	3.20–4.94
Quartile 4	62	6.20–11.00
Creatinine (μmol/L)	262	97±188
Quartile 1	68	66–85
Quartile 4	65	120–1519
Albuminuria (mg/L)	250	17±1431
Normoalbuminuria (0–29)	151	10±7
Microalbuminuria (30–299)	59	87±68
Macroalbuminuria (>299)	40	1096±3115