

Mortality in childhood-onset type 1 diabetes: Nationwide population based data from Norway

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ABSTRACT

Type 1 diabetes with onset in childhood (0-14.9 years) represents one of the most frequent chronic diseases in children and young adults. Norway has one of the highest incidences of childhood onset type 1 diabetes in the world. Before introduction of insulin therapy in 1922, few children survived more than one to two years after clinical onset. When insulin came available, a major shift occurred in the distribution of causes of death in type 1 diabetic patients away from diabetic coma, which dominated the pre-insulin era, to renal and cardiac diseases. The disease is related to a significant burden to society and patients because most cases require lifelong treatment with insulin as well as day-to-day monitoring. Type 1 diabetes also confers increased risk of severe late complications such as renal failure, blindness, amputations, heart disease and stroke. Despite advances in diabetes treatment, type 1 diabetes is still associated with considerable premature mortality resulting from acute and chronic complications of diabetes and an increase in mortality at every age. Although the main cause of death in type 1 diabetes is long-term complications, an excess death rate has also been reported in subjects with short duration without signs of long-term complications.

INTRODUCTION

Third to Finland and Sweden, Norway has the highest incidence of childhood onset type 1 diabetes in the world (1). More than 300 children are diagnosed with type 1 diabetes in Norway each year, the annual incidence rate is 33-36/100 000 (2). Even in societies with well-organized health care systems and unrestricted access to treatment of diabetes and its complications, type 1 diabetes is associated with risk of premature death due to acute and late complications (3-8). Death after diabetes duration of 20 years has been related to renal complications and cardiovascular disease (4,6,9, 10). Early mortality has mainly been related to acute complications such as diabetic ketoacidosis (DKA) and severe hypoglycemia (5,6,11). It has also been reported that young and apparently healthy individuals seem to have a significant risk of sudden death during sleep (6,12-14).

This article concerns the epidemiological data on mortality in childhood-onset type 1 diabetes from Norway, set in relationship to data from other countries. Valid reports on mortality in children with type 1 diabetes are rare, even sparser from Norway (6,7).

One Norwegian study has documented a considerably increased risk of total and cardiovascular death in a young cohort of patients with childhood-onset type 1 diabetes, diagnosed in 1973-1982, after 24 years diabetes duration (6). The relative mortality was increased four times in this young cohort compared to the background population. The main cause of death in the total cohort was violent death (accidents, suicide and intoxication). When the cohort was divided in death before and after 30 years of age, the main death cause was acute complications in early years and cardiovascular events after the age of 30 years.

DEATHS IN CHILDHOOD

Deaths at onset

Globally. Children with type 1 diabetes in societies without access to insulin, blood-glucose monitoring, and health care services face a very high risk of dying in connection with the diagnosis of type 1 diabetes or soon after disease onset due to acute complications (mainly DKA). In many of these children it is likely that type 1 diabetes may have remained undiagnosed, being masked by a clinical picture of competing infectious diseases and malnutrition (12,15).

In Norway, the awareness for type 1 diabetes is high among health personnel, probably due to the high incidence. Data on mortality in children at the onset of type 1 diabetes is sparse, but it is no reason to believe this to be high. It is reported two cases of death in children at diabetes onset during the first 48 h because of DKA with cerebral edema, during the seventies (6). The first description of the worldwide variation in the frequency of DKA at presentation of type 1 diabetes was recently published, reporting large variations that may, at least in part, be explained by different levels of disease awareness and healthcare provision (16). EURODIAB indicated that the frequency of DKA in Europe at diagnosis varied from 11% to 67% (17). The first published data from Norway on DKA at presentation of type 1 diabetes reported that 18.0% of the children had DKA; 17.0% of the boys and 18.3% of the girls (18).

Risk factors for premature death

The age at onset of diabetes may influence the risk of late complications. Several studies (19-21) indicate that young age at onset of diabetes can prolong the time until development of microalbuminuria, nephropathy, end stage renal disease, and other vascular complica-

tions. It has been suggested that diagnosis during puberty could promote the development of chronic diabetes complications due to deterioration of glycemic control, rapid growth, and hormonal changes (22,23). Better long term survival could thus be expected in people diagnosed before puberty.

The prognosis of type 1 diabetes with onset in childhood and adolescence may be improving with lower risk of severe complications and premature death, but young people with diabetes are still at considerable high risk of diabetic retinopathy, diabetic nephropathy, peripheral diabetic neuropathy, cardiovascular disease and premature death (6,11,24,25). One recent study from Allegheny County, USA, reported a decline in total mortality rates for children diagnosed with type 1 diabetes at age < 18 years in the period 1965 to 1979 (26). They also report a decline in mortality rates for acute complications and renal disease. In this study women had a 30% higher rate than men from all diabetes related causes.

Causes of death in T1D; underreported and misclassified

Diabetes is a major global cause of premature mortality that is widely underestimated. Only a minority of patients with diabetes die from a cause uniquely related to the condition such as DKA or hypoglycemia. Diabetes is known to be under-reported on death certificates as an underlying or contributing cause of death (6,27-29). Cohort studies of subjects with a confirmed diabetes diagnosis, are the best way to assess the mortality risk among patients with diabetes.

When we classified causes of death in the Norwegian diabetes cohort, causes of death was registered and classified in two ways for different purposes (6): 1) Information on the cause of death was obtained from the death certificate and from the International Classification of Diseases (ICD) codes (30-32) for the underlying cause of death in the Cause of Death Registry. These data were used for comparing mortality rates with those of the background population. 2) Since the cause of death in patients with T1D is frequently misclassified (6,33,34), the cause of death was also ascertained by a clinical review committee, critically assessing all available information including hospital records, outpatient records, police reports, death certificates, post-mortem reports and necropsy reports. The clinical review committee included three diabetologists.

Violent death

Violent death including accidents, suicide and intoxications are common among young people with type 1 diabetes, especially in males, in whom it was the greatest single cause of death under 30 years of age. In the age group 30-40 years it was exceeded only by cardiovascular disease (CVD) as cause of death (6).

Acute metabolic complications

Acute metabolic complications were the largest single cause of death under the age of 30 years in the total

cohort (6). This is in keeping with a study from the UK (11). In the total Norwegian cohort, 15% died of DKA; two adolescents at diabetes onset, 13 had had diabetes for several years, 10% died of hypoglycemia (6).

Renal death

Renal disease has previous been identified as a major cause of death in patients with type 1 diabetes (35). In the Norwegian study, end-stage renal failure was responsible for 8% of all deaths (6). The standardized mortality ratio (SMR) was high for this cause, from which few deaths occur in patients without diabetes, especially at young age. At all ages the number of deaths certified to CVD exceeded those certified to renal disease.

Cardiovascular death

Several studies (36,37) have found diabetes to be a greater risk factor for morbidity and mortality from cardiovascular death in women than in men. In Norway, the mortality rates from ischemic heart disease (IHD) in women were not only greater than for women without diabetes, but were also considerably higher than for men without diabetes (6). In the general population mortality from IHD was much higher in men than in women. In the Norwegian diabetes cohort the mortality from IHD was also higher in men than in women, in contrast to data from UK reporting no differences between the sexes under the age of 40 years (37).

Dead-in-bed syndrome

The so-called dead-in-bed syndrome refers to sudden death in young diabetic patients without any history of long-term complications. It is a rare, but dramatic condition. Autopsy is typically negative. The causes of death are by definition unknown, but a plausible theory is a death in hypoglycemia, since a history of nocturnal hypoglycemia is noted in most cases (14). Another theory is that fatal cardiac dysrhythmias are considered the cause of dead-in-bed syndrome, which might be provoked by an episode of hypoglycemia (38). One study assessing UK and the Scandinavian countries found that such deaths occurred in 6% of all deaths in diabetic patients younger than 40 years. The frequency may also be expressed as 2-6 events per 10,000 patient years (14). A study of mortality in Norwegian patients with type 1 diabetes under the age of 40 years, during the period 1981-1990, reported that 6.7% of the cases were "dead in bed" (39). Another Norwegian study reported that 3.4% of all the patients fulfilled the criteria of "dead in bed". In this study severe episodes of hypoglycemia was reported in 75% of the cases (40). In the Norwegian study previously presented in this paper 3.9% met the criteria of "dead in bed", three males and one female aged 12-24 years (6). The Norwegian numbers are less than observed by others (12,41). A Swedish study reported dead-in-bed syndrome in 9% of the patients. Mean age at death in this group was 18.1 years (range 11.4-25.1) and mean diabetes duration 8.2 years (range 2.6-12.6) (12).

Increased relative mortality

In the Norwegian cohort, the standardized mortality ratio (SMR) was four times higher in patients with childhood-onset type 1 diabetes compared to the background population, similar for both genders (6). Mortality from childhood-onset diabetes differs markedly from country to country. In recent studies (3,12,42-44) from different countries, the SMR varies from 2.15 in Sweden to as high as 12.9 in Japan. Due to differences in methods, background populations and the populations studied, comparison should be done with caution.

Increased relative mortality in children 0-14 years

Studies from developed countries have consistently reported that the relative mortality (all causes considered) in type 1 diabetes is of the magnitude of about 3, corresponding to a mortality rate at about 1/1000 patient-years at risk in children 0-14 years (6,12,44). The excess death in children is predominantly caused by acute complications (mainly DKA), infections, external causes, and unexplained deaths (6,12,44,45). The literature indicate that mortality may be higher in countries

with lower incidence levels (42,45-47), suggesting that awareness and knowledge of treatment of type 1 diabetes in children may be an important factor (17). The literature is however not conclusive; EURODIAB reported that SMR varied between 0 to 4.7 between 12 different European countries, but found little relationship with the countries' incidence rate or gross domestic product (US\$ per capita) (5).

CONCLUSION

In conclusion, childhood-onset type 1 diabetes still carries an increased mortality risk when compared with the non-diabetic population in Norway. Violent deaths, acute metabolic complications and CVD are the main causes of deaths. This raises the importance of high awareness of psychological comorbidity in childhood-onset type 1 diabetes as well as to focus on late complications and premature death. In terms of preventable deaths, DKA among already diagnosed cases certainly belongs to this group.

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