MORTALITY IN CHILDHOOD-ONSET TYPE 1 DIABETES

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ABSTRACT

It is well-recognized that diabetes-related complications are the leading cause of the still increased morbidity and mortality from diabetes and exert a heavy economic burden on society. The discovery of insulin led to a dramatic change in life expectancy of patients with type 1 diabetes (T1D). Furthermore, it caused a major shift in the distribution of causes of death - from diabetic coma in the pre-insulin era, to long-term complications being the predominant causes of death nowadays. The aim of the present review is to assess the trends in the absolute and the relative mortality rates as well as the leading causes of death among patients with childhood-onset (<18 years) T1D in populations from different latitudes. It is also observed how disease duration, age at diagnosis, and year of diagnosis affect these mortality trends. Eight population-based studies published in English in the last 14 years, as well as another one, published in 2001, with different duration of follow-up, are included in the review. However, it is hard to compare different populations due to the dissimilarities in the study methods and the characteristics of the examined cohorts.

Keywords: *childhood-onset type 1 diabetes, trends in mortality, causes of death*

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INTRODUCTION

Type 1 diabetes (T1D) is the most common endocrine disorder and represents one of the most frequent chronic diseases in children. Major studies have shown a significant decrease in mortality after the implementation of insulin therapy (1,2). In the Joslin Clinic in the United States, for example, mortality rates have declined substantially for patients aged between 10 and 30 years - from 360-824/1000

person-years in 1897-1914 to 1.0-14.4/1000 in 1950-1961 (1). However, T1D is still associated with considerable premature mortality (3-8).

The geographic differences in mortality among patients with childhood-onset T1D are well-recognized (8-11). The Diabetes Epidemiology Research International (DERI) mortality study shows the highest mortality rate in Japan despite the lowest incidence of T1D there (12). According to another large study, mortality rates are the highest in Japan, Russia, and Eastern Europe, while individuals in Bulgaria are 10 times more likely to die than those in Norway prior to the age of 25 years (13).

In contrast to earlier years, when the leading cause of death was diabetic ketoacidosis (DKA), long-term complications and particularly cardiovascular and renal disease, are the predominant causes of mortality in T1D nowadays (14). Nevertheless, high levels of excess mortality are also observed in subjects with short duration of the disease without signs of chronic complications (15-19). Early mortality is mainly associated with the development of DKA and severe hypoglycemia (7,8,20). On the other hand, the EURODIAB study reveals that only 35% of deaths in children diagnosed after 1989 and followed up for 7.6 years are due to acute diabetes complications, while another 53% of deaths are due to non-diabetes causes (accidents, suicide, etc.) (7). It is worth noting that, sudden death during sleep is among the frequent causes of early mortality in some countries (8,19,21,22).

The aim of the present review is to assess mortality trends in subjects with childhood-onset T1D and to make comparisons with the general population. Altogether, nine population-based studies are included. Five of them are long-term (≥14-year follow-up), respectively those from Finland (5), Norway (8), USA (9, 14), and Japan (10). The cohort from Israel (23) has a mean duration of follow-up of 14±8 years. The T1D subjects in Allegheny County (Pennsylvania) are used as representative of the T1D population in the USA (9, 14). The studies from Sweden (24), Wales (25), and Northern Ireland (26) are with a shorter mean duration of follow-up - between 8 and 12 years. The characteristics of the included studies are given in Table 1.

Absolute and Relative Mortality

Mortality is found to be similar in two of the countries with the highest incidence of T1D, Finland and Sweden (27) - 2.45/1000 and 2.2/1000 person-years for those diagnosed in 1970-1999 in Finland and in 1973-1982 in Norway, respectively (5,8). The duration of follow-up for both cohorts is more than 20 years. Kenet et al. report lower rates of mortality in their study from Israel (1.55/1000) including T1D subjects with a similar year of diagnosis to that of the cohorts from Finland and Norway (1965-1993) (23). Significantly higher mortality rates (more than

Table 1. Characteristics of the population-based studies

	Number of Diseased	Age at Diagnosis	Year of Diagnosis	Mean Duration of Follow-Up (Years)	Final Year of Survey
USA/Allegheny County	1075	<18 yrs	1965-1979	32±7.6	2008
Finland	10492	0-14 yrs	1970-1999	21.4	2007
Sweden	10200	0-14 yrs	1977-2000	8	not applicable
Norway	1906	0-14 yrs	1973-1982	24.2	2002
Japan	1385	<18 yrs	1965-1979	24.4±6.4	2005
Northern Ireland	3129	<15 yrs	1989-2012	12.1	2012
Wales	3642	<15 yrs	1981-2015	11.8	2015
Israel	1861	<17 yrs	1965-1993	14±8	1996

6/1000) are observed among the T1D patients diagnosed from 1965 through 1979 in Allegheny County and Japan, and followed up until 2008 in the USA and 2005 in Japan, respectively (9,10).

The absolute mortality is found to be higher among males in all of the long-term studies, except for that from the USA (5,8-10). On the other hand, the relative mortality, represented by the standardized mortality ratio (SMR), is female-dominated, only in Norway it is similar in both sexes (5,8-10). No difference in the mortality rate between sexes is observed in the cohort from Israel and no data exists regarding the relative mortality in the same population (23). Especially high is the overall SMR in Japan - 10.7, and that in Allegheny County is 6.9 (9,10). The relative mortality is found to be lower in Norway, Finland, and Israel - overall SMR 4, 3.6, and 2.98, respectively (8,5,23).

Lower all-cause mortality is observed in two short-term studies from Wales and Northern Ireland (subjects followed until 2015 and 2012, respectively) - 0.7/1000 in Wales and 1.5/1000 in Northern Ireland (25,26). It is found to exceed almost 3 times the mortality rate of the general population (overall SMR 2.91 and 2.96 in Wales and Northern Ireland, respectively). The SMR is again female-dominated, while the absolute mortality is shown to be higher in males in Wales and similar for both sexes in Northern Ireland. The mortality registered by Dahlquist et al. in Sweden (the country with the second highest incidence of T1D in the world) is 0.96/1000 for the subjects diagnosed between 1977 and 2000 and followed up for a mean time of 8 years (24). Similar to most of the other studies, the SMR of 2.15 is significantly higher in females (p=0.045), but it is lower compared with the SMR in the rest of the Scandinavian countries (24,5,8). However, the follow-up period of the T1D subjects in this study is substantially shorter.

It is noteworthy that the mortality is especially high in Japan, as mentioned above, a country with one of the lowest incidences of T1D in the world (more than 20 times lower than that in Finland) (28). The first report of the DERI observational study in 1991 demonstrated that Japanese patients with T1D had a much worse prognosis than did similar patients in Finland, the USA, and Israel, with the most frequent causes of death being the acute complications of diabetes and end-stage renal disease (ESRD) (29-31). A possible reason discussed for the higher mortality rate in Japan is the low incidence of T1D itself in this country, which probably causes difficulties in the diagnosis and treatment of the disease. On the other hand, the EURODIAB study shows no significant relationship of mortality with the country's incidence rate or gross domestic product (7).

Much higher is also the number of deaths in the cohort from the USA in comparison with the European countries from the population-based studies included. The significant impact of the disease on the overall mortality is demonstrated by the high SMR of 6.9, compared with the European countries, where the SMR varies between 2 and 4 (9,5,8,24-26). These geographical differences could be due to the high-cost healthcare in the USA, which is probably an obstacle for a frequent contact of some patients with a physician. Another possible reason could be the higher mortality rate in African Americans (a part of the population in Allegheny County) (9,14).

Time Trends in Mortality (Impact of Year of Diagnosis on Mortality)

The influence of calendar year of diagnosis on mortality is examined in the population-based studies from Norway, Finland, Japan, and the USA. No significant difference in cumulative survival is found in Norway when the cases diagnosed between 1978 and 1982 are compared over 20 years of disease duration with those diagnosed between 1973 and 1977 (0.96 vs 0.97, p=0.52) (8). Another population-based Norwegian study including childhood-onset T1D subjects diagnosed in 1973-1982 and 1989-2012, and followed up until 2013, shows more contemporary data (32). Temporal trends in mortality assessed by cox regression analysis show that it decreased significantly by 49% (HR 0.51, 95% CI 0.28-0.93; p=0.03) for those diagnosed in 1999-2012 compared with subjects diagnosed in 1973-1982. However, the follow-up time of both groups is different. Improved survival of patients with later calendar year of diagnosis is also observed by Harjutsalo et al. in Finland (5). The 20-year cumulative mortality in the groups of patients diagnosed in 1970-1974, 1975-1979, 1980-1984, and 1985-1989 is 4.7% (3.7% to 5.8%), 4.3% (3.3% to 5.2%), 3.6% (2.8% to 4.5%), and 2.7% (1.9% to 3.4%), respectively. However, the follow-up time of the last

group has not yet reached 20 years. In the same cohort, SMR decreases by 4.3% per year of diagnosis, after adjustment for duration and age at onset of diabetes. Furthermore, an improvement in mortality due to chronic complications is observed - a significant decline from 10.0 (5.8 to 13.1)/10 000 in patients diagnosed in 1970-1974 to 2.2 (0.9 to 4.5)/10 000 in those diagnosed in 1985-1989 (p<0.001). On the other hand, mortality due to acute complications (non-alcohol related) shows a non-significant tendency to increase from 2.1 (0.8 to 4.6)/10 000 to 4.1 (1.9 to 6.5)/10 000.

Noticeable is the improvement in T1D mortality in Japan. The 15-year survival increases from 87.6% for the subjects diagnosed in 1965-1969 to 96% for those diagnosed in 1975-1979 (33). This beneficial influence of the calendar year of diagnosis is preserved even for longer period of follow-up. SMR observed at the 25th year of follow-up declines from 19.3 in the 1965-1969 diagnosis group to 6.6 in the 1975-1979 diagnosis group (10). Improvement in patient prognosis is also observed in the representative cohort from the USA with T1D onset after 1965-1969. Significantly higher mortality rates from diabetes-related causes are registered for the 1965-1969 cohort in comparison with the 1975-1979 cohort (RR 1.5, p=0.05). In addition, further analysis by diabetes duration reveals that the 1975-1979 cohort has a significantly lower mortality rate compared with the 1965-1969 diagnosis group over the first 20 years of disease duration (RR 0.45, p=0.01) (14).

Unlike Finland and the USA, where overall mortality rates continue to rise, as would be expected with increasing age and T1D duration, in Japan the overall mortality rates decline with longer period of follow-up (11, 34). This is further an indicator of the dramatic improvements in T1D care in Japan after 1980.

Effect of Age at Onset of T1D on Mortality

Three of the long-term studies included in the present review assess the effect of age at diabetes onset on overall mortality. Skrivarhaug et al. find a significantly higher mortality rate in individuals with diabetes onset at age 10-14 years in Norway than in those with onset below 10 years of age (2.85/1000 vs 1.73/1000; RR 1.70, 95% CI 1.15-2.51) (8). A similar tendency is observed in Finland and Japan regarding T1D patients diagnosed in 1965-1979 and followed up until 1994 (2 of the cohorts in the DERI study, 11). It is found that the absolute mortality is almost two times higher in patients with diabetes onset at pubertal age (≥11 years for girls, ≥12 years for boys) than in those with diagnosis in prepubertal age (9.41/1000 vs 4.56/1000 in Japan, 4.46/1000 vs 2.78/1000 in Finland). The effect of diagnosis in pubertal age is no longer significant after adjustment for mortality in the corresponding age groups of the general population. The SMR for pubertal and prepubertal age is 16.4 (12.7-20.9) and 10.8 (8.4-13.6) in Japan, and 3.7 (3.2-4.3) and 3.6 (3.1-4.3) in Finland, respectively. This is an expression of the higher mortality in pubertal age in the general population as well.

Laron-Kenet et al. find no relationship between overall T1D mortality in Israel and age at diagnosis (under and over 12 years). However, the death of the patients diagnosed before 12 years of age occurred at a younger age than those diagnosed at 12 years or later (log-rank 5.8; p=0.016) (23). An effect of age at diagnosis on absolute mortality is also observed in the short-term study from Wales - higher mortality risk for those diagnosed in teenage years than those who developed T1D younger (OR per additional year of age 1.16 (1.05-1.28); p=0.005) (25).

Causes of Death

When studying the causes of death among T1D subjects in the long-term studies observed, the violent death (accidents, suicides, intoxications) appears to be the most common in the cohorts from Norway and Finland (for the diagnosed in 1970-1989 in Finland), accounting for around 30% of all death cases (5, 8). They are followed by acute (22.6%) and chronic diabetes complications (28.7%) in Finland, and acute complications (22.3%), sudden death (16.5%), and cardiovascular (CV) death (14.6%) in Norway. On the other hand, in the study from Israel, which is with a significantly shorter observational time, the leading mortality causes are DKA (21.6%), infections (21.6%), and chronic diabetes complications (24.3%) (23). The most common cause of death in the cohort from Allegheny County is CV mortality (36.2%), followed by acute metabolic complications (16.13%), infections (16%) and renal diseases (13.26%) (14). Most frequent for the Japanese population is the mortality due to ESRD (22.87%), followed by CV mortali-

ty (17.94%), acute metabolic complications (17.04%), and infections (15.25%) (10).

Scrivarhaug et al. analyze the causes of death in T1D subjects in Norway according to age at death (8). They find acute metabolic complications (38%) and violent death (23%) to be the most common causes before the age of 20 years. The same two remain most frequent (28% and 33%, respectively) among subjects aged 20-30 years, while after the age of 30 years CV death is predominant (30%). The impact of disease duration on the causes of death has been studied in the same population. Dominant in the first 10 years of T1D are acute metabolic complications (42%), while after that - violent death (29%). Acute metabolic complications (22%) turn out to be the second most common cause of death after 10-19 years and CV diseases (26%) - after 20 years of diabetes duration. The influence of disease duration on the leading causes of death in T1D subjects is also assessed in the USA, Allegheny County, by Secrest et al. (14). Within the first 10 years of diabetes onset, > 70% of all deaths are due to acute diabetes complications, while after 10 years of diabetes, the same become a minor but persistent (9–15%) cause of death in this population. On the other hand, after 10 years of diabetes, CV mortality becomes the leading cause of death, eventually accounting for 40% of all deaths after 20 years of duration. Renal disease does not contribute to any deaths until after 10 years of diabetes duration, when it contributes to about half of all deaths in the same cohort. Similar to the other population-based studies, acute diabetes complications are the most common cause of early mortality also in Japan (40% of the death cases followed for less than 10 years), while mortality due to ESRD dominates in the subjects with a longer follow-up time (10-19 years) (10). The percentage of CV death also increases with longer duration of T1D, becoming the leading mortality cause after 30-35 years of observation.

A comparison between the causes of death among T1D subjects and the general population in Norway demonstrates about 20-fold higher mortality rates for ischemic heart disease (IHD) and cerebrovascular disease for the patients with T1D, while SMR for violent death is significantly lower (3.3 for men, 1.7 for women) (8). ESRD is responsible for a small number (8%) of all deaths in the same study. Nevertheless, SMR is especially high for this cause - 220 for males and 155 for females. In Finland, SMR for IHD is high, while that for cerebrovascular disease is significantly lower (17.4 and 5.1, respectively) (5). In Finland and Norway, the mortality from suicide is not significantly greater in patients with diabetes compared with the general population (5,8). However, it accounts for 10-20% of all deaths.

Similar are also the observations for the diabetic populations in Allegheny County (USA) and Japan - high SMR for CV diseases and renal diseases, but also for infections (14, 10). On the other hand, deaths from non-diabetes-related causes occur at similar rates in T1D to the age-, sex-, and race-matched general population (SMR for accidents/suicides and neoplasms - 1.2 in the USA, 2.1 and 0.5 in Japan, respectively).

DKA is the leading diabetes-related cause of death in the short-term studies from Wales, Northern Ireland, and Sweden (24-26). On the other hand, the chronic diabetes complications are responsible for a small percentage of mortality in these cohorts, which is most probably a result of the shorter follow-up time and the relatively young age of the patients. It is worth noting that the so called dead-in-bed syndrome is the second most common cause of death among diabetic subjects in Sweden, comprising 22% of all deaths in this cohort (24).

CONCLUSION

In conclusion, childhood-onset T1D is still associated with premature mortality even in societies with well-organized health care systems and unrestricted access to treatment of diabetes and its complications. Higher is the absolute mortality among males in the majority of the population-based studies included in the review. On the other hand, the relative mortality is female-dominated in almost all the cohorts, thus demonstrating that diabetes greatly attenuates, or may even reverse, the protective effect of female sex. Especially high is the mortality rate in Japan and the USA, unlike, for example, the Scandinavian countries, where the incidence of T1D is the highest. On the other hand, the dissimilarities in the study methods and the characteristics of the examined cohorts (including the longer period of follow-up for the Allegheny County population) make comparisons difficult. There are common trends for longer survival with later calendar year of diagnosis and

for higher mortality with pubertal (compared with prepubertal) onset of disease in most of the long-term studies. The leading causes of death among T1D subjects appear to be the acute and chronic diabetes complications. However, in some cohorts a large number of death cases are also due to violent death, including suicides and intoxications. That should focus the attention on the psychological health of childhood-onset T1D as well. The worldwide increase in incidence of the disease, as well as the continuous technological progress in diabetology, raise the importance of conducting long-term contemporary mortality studies in order to establish the efficacy of T1D treatment over time.

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