Impact of Sex and Age at Onset of Diabetes on Mortality From Ischemic Heart Disease in Patients With Type 1 Diabetes

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OBJECTIVE

To study whether ischemic heart disease (IHD) mortality among patients with type 1 diabetes (T1D) depends on the age at onset of diabetes and whether this effect is sex specific.

RESEARCH DESIGN AND METHODS

The study examined long-term IHD-specific mortality in a Finnish population-based cohort of patients with early-onset (0–14 years) and late-onset (15–29 years) T1D (*n* = 17,306).

RESULTS

During 433,782 person-years of follow-up, 478 deaths from IHD were observed. Within the early-onset cohort, the average crude mortality rate in women was 33.3% lower than in men, whereas in the late-onset cohort, mortality was only one-half that in men. In contrast, the standardized mortality ratio (SMR) was higher in women than in men (21.6 [95% CI 17.2–27.0] vs. 5.8 [5.1–6.6]). The difference in SMR between sexes was more striking in the early-onset cohort (women 52.8 [36.3–74.5], men 12.1 [9.2–15.8]). The SMR was also greater in women in the late-onset cohort (15.8 [11.8–20.7]) compared with men (5.0 [4.3–5.8]). The relative risk of dying from IHD was greatest in women aged <40 years and 40–60 years in the early- and late-onset cohorts, respectively.

CONCLUSIONS

The risk of mortality from IHD is exceptionally high in women with early-onset T1D compared with women in the background population. These observations underscore the importance of identifying risk factors early in women and delivering more-aggressive treatment after diagnosis.

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Diabetes is recognized as one of the major risk factors for the development of cardiovascular disease (CVD) both in men and women (1,2). A large body of evidence shows increased mortality from CVD, especially ischemic heart disease (IHD), in patients with diabetes compared with the general population (3–6). Unfortunately, these studies often pooled patients with type 1 diabetes (T1D) and type 2 diabetes, thus possibly masking potential differences in mortality rates between these two

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populations. Although a few large, long-term cohort studies examined the sex differences in mortality rates in patients with T1D, the reports showed great disparity in their conclusions and rarely examined mortality rates specifically from IHD, instead reporting them for overall CVD (3,7–11). Another frequently understudied topic is the stratification of mortality rates of IHD by age at onset of T1D. We have observed that not only is the long-term risk of developing microvascular complications different between men and women, but also the risk of microvascular complications greatly depend on the age at onset of T1D (12). Although others have also shown that the age at onset of diabetes plays a critical role in determining the overall cumulative risk of developing organ complications associated with diabetes (13–15), few studies have recognized that this effect may be sex specific. Thus, the aim of the current study was to examine sex differences in mortality from IHD according to the age at onset of diabetes in a cohort of 17,306 Finnish patients with T1D.

RESEARCH DESIGN AND METHODS

The study population included 17,306 Finnish patients given a diagnosis of T1D between 1970 and 1999 before 30 years of age. Follow-up started from the time of diagnosis of T1D and ended either at the time of death or at the end of 2011. The patients were identified from the Drug Reimbursement Register (DRR) of Finland. Because insulin for the treatment of T1D has been free of charge in Finland since 1964, the DRR includes all patients in Finland receiving insulin for T1D.

T1D was verified in the majority (74%) of patients as reported previously (16–19). The classification of the type of diabetes in the remaining patients (26%) was achieved following the procedure previously described (19). Briefly, the data on the patients from the DRR were linked to the Hospital Discharge Register (HDR) maintained by the National Institute for Health and Welfare. The HDR covers all hospital discharges nationwide since 1972 and includes up to four hospital discharge diagnoses (ICD codes) for each patient who had ever been admitted to a hospital. Cases in the HDR with a code indicating possible secondary diabetes were excluded. The ICD codes used to define patients as having T1D were 2500B–2508B, E10.0–E10.9, or O24.0. Vital status and causes of death were obtained from the Finnish Cause of Death Register (CDR). The register links were carried out by using personal identification codes. For the diagnosis of IHD, ICD-8, ICD-9, and ICD-10 codes 410–414 or I20–I25 were used.

Statistical Analysis

Crude age-specific mortality rates were calculated for each 5-year age-group after 20 years of age and expressed per 100,000 person-years. Standardized mortality ratios (SMRs) were calculated as the number of observed deaths to the number of expected deaths. The number of expected deaths from IHD was calculated by multiplying the number of person-years at risk by the 5-year age-group by calendar year–specific and sex-specific IHD mortality rates in the Finnish background population drawn from Statistics Finland and the National Institute for Health and Welfare. SMRs were calculated for the total cohort and separately for the early-onset (0–14 years, n = 10,492) and late-onset (15–29 years, n = 6,814) cohorts stratified by sex and attained age.

The SMR analysis was based on IHD as the primary cause of death to be consistent with the method used in the background population. However, crude mortality rates were calculated based on whether IHD was either a major or contributory cause of death.

Cumulative mortality was evaluated by Kaplan-Meier method, and differences between the groups were compared with the log-rank test. The impact of sex, age at onset stratified as early onset and late onset, year of diabetes diagnosis, and duration of diabetes on the risk of dying from IHD was studied by applying multivariate Poisson regression models, and corresponding mortality rate ratios (RRs) were derived. Statistical analyses were performed with SAS version 9.2 software (SAS Institute Inc., Cary, NC). This study was approved by the Ethical Committee of the National Institute for Health and Welfare, Finland.

RESULTS

Table 1 shows the characteristics of the study population. The median duration of diabetes was 24.4 (interquartile range 17.6–32.2) years. Over a 41-year study period totaling 433,782 person-years of follow-up, IHD accounted for 27.6% of the total 1,729 deaths. Specifically, IHD was identified as the cause of death in 478 patients, in whom IHD was the primary cause of death in 303 and a contributory cause in 175. Of the deaths from IHD as a primary cause, 83 were in the early-onset cohort and 220 in the late-onset cohort (Table 1). When IHD was accounted for as a contributory rather than a primary cause of death, the corresponding numbers of deaths were 72 and 103, respectively.

Within the early-onset cohort, the average crude mortality rate in women

Table 1—Number of patients, all deaths, deaths from IHD, and mortality rates in women and men in the early- and late-onset T1D cohorts

Cohort	No. patients (no. all deaths)	Median years of duration of diabetes (IQR)	No. IHD deaths as primary/any cause	Mortality per 100,000 person-years (95% CI)
Early onset				
All	10,488 (1,006)	25.1 (18.4–32.5)	83/155	109.1 (92.6–127.7)
Women	4,831 (259)	24.0 (17.1–32.1)	30/56	86.3 (65.2–112.1)
Men	5,657 (747)	24.1 (17.2–31.9)	53/99	128.2 (104.2–156.1)
Late onset				
All	6,818 (723)	24.0 (17.2–32.0)	220/323	190.8 (170.4–212.9)
Women	2,535 (260)	25.5 (18.5–32.8)	48/74	117.2 (92.0–147.1)
Men	4,283 (463)	24.9 (18.2–32.2)	172/249	239.7 (210.9–271.4)
Total	17,306 (1,729)	24.4 (17.6–32.2)	303/478	154.6 (141.1–169.1)

IQR, interquartile range.

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was 33.3% lower than in men (86.3 [95% CI 65.2–112.1] vs. 128.2 [104.2–156.1] per 100,000 person-years, respectively, $P = 0.02$). When adjusted for duration of diabetes and the year of diabetes diagnosis, the mortality RR between women and men of 0.64 was only of borderline significance ($P = 0.05$) (Table 2). In the late-onset cohort, crude mortality in women was, on average, only one-half that of men (117.2 [92.0–147.1] vs. 239.7 [210.9–271.4] per 100,000 person-years, respectively, $P < 0.0001$) (Table 1). An RR of 0.43 remained highly significant after adjustment for duration of diabetes and year of diabetes diagnosis. Every year of duration of diabetes increased the risk 10–13% (Table 2).

The number of deaths from IHD in the patients with T1D were compared with the number of deaths from IHD in the background population, and the SMRs were calculated. For the total cohort (early and late onset pooled), the SMR was 7.2 (95% CI 6.4–8.0) (Table 3). In contrast to the crude mortality rates, the SMRs were higher in women (21.6 [17.2–27.0]) than in men (5.8 [5.1–6.6]). When stratified by the age at onset of diabetes, the SMR was considerably higher in patients with early onset (16.9 [13.5–20.9]) than in those with late onset (5.9 [5.2–6.8]). In both the late- and the early-onset cohorts, there was a striking difference in the SMRs between women and men, and this was especially evident in the early-onset cohort where the SMR for women was 52.8 (36.3–74.5) compared with 12.1 (9.2–15.8) for men. This higher risk of death from IHD compared with the background population was evident in all women, regardless of age. However, the most pronounced effect was seen in women in the early-onset cohort <40 years of age, who were 83 times more likely to die of IHD than the age-matched women in the background population. This compares with a 37 times higher risk of death from IHD in women aged >40 years. The corresponding SMRs for men aged <40 and ≥40 years were 19.4 and 8.5, respectively. In contrast to the early-onset cohort, the SMR in the late-onset cohort was higher in women ≥40 years compared with those <40 years of age (16.8 [12.5–22.3] vs. 6.4 [1.1–21.2], respectively) (Table 2). In contrast, in the late-onset cohort, the SMRs were not different between men aged <40 and men aged ≥40 years.

Overall, the 40-year cumulative mortality for IHD was 8.8% (95% CI 7.9–9.7%) in all patients (data not shown). Figure 1 compares cumulative mortality rates from IHD in the early-onset and late-onset cohorts according to sex. The 40-year cumulative IHD mortality in the early-onset cohort was 6.3% (4.8–7.8%) for men and 4.5% (3.1–5.9%) for women ($P = 0.009$ by log-rank test) (Fig. 1*A*). In the late-onset cohort, the corresponding cumulative mortality rates were 16.6% (14.3–18.7%) in men and 8.5% (6.5–10.4%) in women ($P < 0.0001$ by log-rank test) (Fig. 1*B*).

Table 2—Poisson regression analyses for the effect of age at onset of diabetes, sex, duration of diabetes, and year of diabetes diagnosis on the risk of dying from IHD

	Early onset	*P* value	Late onset	*P* value
All				
Sex				
Male	1.0		1.0	
Female	0.64 (0.41–1.01)	0.05	0.43 (0.31–0.60)	<0.0001
Year of diabetes diagnosis	0.95 (0.90–0.99)	0.05	0.96 (0.94–0.99)	0.01
Duration of diabetes	1.11 (1.07–1.15)	<0.0001	1.12 (1.10–1.14)	<0.0001
Women				
Year of diabetes diagnosis	0.93 (0.85–1.01)	0.08	0.94 (0.88–1.041)	0.08
Duration of diabetes	1.11 (1.05–1.148)	0.0002	1.13 (1.09–1.18)	<0.0001
Men				
Year of diabetes diagnosis	0.96 (0.90–1.042)	0.15	0.97 (0.94–1.00)	0.04
Duration of diabetes	1.11 (1.06–1.146)	<0.0001	1.11 (1.09–1.13)	<0.0001

Data are mortality RR (95% CI).

CONCLUSIONS

This study provides novel information about mortality rates and SMRs from IHD, taking into account sex and age at onset of diabetes. The major findings of the current study are that women with early-onset T1D are exceptionally vulnerable to dying from IHD, which is especially evident in those receiving a T1D diagnosis during the prepubertal and pubertal years. Crude mortality rates were similar for women compared with men, highlighting the loss of cardioprotection in women. These observations suggest that sex and age at onset of T1D are important determinants of mortality from IHD. The fact that IHD is a major cause of death in patients with T1D, accounting for approximately one-quarter of all deaths, has previously been reported by many others (3–7).

Although men of all ages have greater crude mortality rates than women regardless of the age at onset of T1D, the current study shows that mortality from IHD attributable to diabetes is much more pronounced in women than in men. These observations highlight the loss of female sex as a protective factor in the setting of diabetes. Greater relative risk of mortality from IHD in women with T1D has also been observed by others (3,7,9,20), albeit these studies did not stratify by age at onset of diabetes. This high risk of mortality in women may not be so surprising because in the general population, premenopausal women exhibit a low risk of CVD and a low relative mortality from CVD compared with age-matched men (21,22). Estrogen, the predominant female hormone, is generally believed to offer cardioprotection in women of reproductive age; thus, the loss of ovarian hormones after menopause increases the risk of CVD. Thus, it is conceivable that one of the underlying reasons for the loss of female sex as a protective factor against the development of CVD in the setting of diabetes may be the loss of ovarian hormones. Indeed, women with T1D have been shown to have reduced levels of plasma estradiol compared with age-matched nondiabetic women (23) possibly because of idiopathic ovarian failure or dysregulation of the hypothalamic-pituitary-ovarian axis.

One of the novelties of the present study is that the risk of death from IHD

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Table 3—Age-specific SMRs for IHD between women and men according to age at diabetes onset (early 0–14 years, late 15–29 years) and attained age

	Women and men together			Women			Men		
Age-group	No. deaths from IHD	Expected no. deaths	SMR (95% CI)	No. deaths from IHD	Expected no. deaths	SMR (95% CI)	No. deaths from IHD	Expected no. deaths	SMR (95% CI)
All									
<40	63	5.77	10.9 (8.5–13.9)	18	0.50	35.8 (21.9–55.5)	45	5.27	8.5 (6.3–11.3)
40–69	239	36.20	6.6 (5.8–7.5)	60	3.11	19.3 (14.9–24.7)	179	33.09	5.4 (4.7–6.2)
All ages	302	41.97	7.2 (6.4–8.0)	78	3.61	21.6 (17.2–27.0)	224	38.35	5.8 (5.1–6.6)
Early onset									
<40	44	1.64	26.9 (19.8–35.8)	16	0.19	83.4 (49.4–132.5)	28	1.45	19.4 (13.1–27.6)
40–59	38	3.21	11.8 (8.5–16.1)	14	0.38	37.2 (21.2–61.0)	24	2.84	8.5 (5.5–12.4)
All ages	82	4.85	16.9 (13.5–20.9)	30	0.57	52.8 (36.3–74.5)	52	4.28	12.1 (9.2–15.8)
Late onset									
<40	19	4.13	4.6 (2.8–7.0)	2	0.31	6.4 (1.1–21.2)	17	3.82	4.4 (2.7–7.0)
40–69	201	32.98	6.1 (5.3–7.0)	46	2.73	16.8 (12.5–22.3)	155	30.25	5.1 (4.4–6.0)
All ages	220	37.11	5.9 (5.2–6.8)	48	3.04	15.8 (11.8–20.7)	172	34.07	5.0 (4.3–5.8)

highly depends on the age at onset of T1D. The data show that the SMR was considerably higher in early-onset (0–14 years) than in late-onset (15–29 years) T1D in both sexes. The longer duration of diabetes in the early-onset diabetes cohort may partly explain the higher mortality because IHD developed in these patients at earlier ages when there are fewer cases of IHD deaths in the background population. Of note, in the early-onset cohort, the relative risk of dying from IHD was greatest in women <40 years of age, whereas in the late-onset cohort, the greatest risk was observed in women >40 years of age. Although the latter may be explained through changes in the hormonal profile as these women enter menopause, the risk in women <40 years of age in the early-onset cohort is more difficult to explain. However, it is conceivable that even younger women with T1D experience hormonal changes that may contribute to the risk for IHD. Indeed, studies have shown that women with T1D often present with hormonal disturbances that lead to menstrual abnormalities and infertility (24,25).

The strength of the current study is that the patients comprised a population-based cohort of those with known T1D, and their causes of death were obtained from the Finnish CDR. Thus, the identification of patients with diabetes was not done through death certificates, which would have been problematic because diabetes is consistently under-recorded as the immediate cause of death (26). Another strength is that this study is the first to our knowledge to include a large number of patients as well as a long follow-up period (433,782 person-years) to examine the risk of mortality from IHD according to the age at diabetes onset and sex.

However, the study is a register study and has the limitations connected with this type of research. Some cases of type 2 diabetes might have been falsely classified as T1D, but because we used several sources of information, the number of such cases is likely to be very small; therefore, the effect on the results should be small. With regard to deaths from IHD, the reliability of the Finnish CDR has been considered to be high (27). However, because the patients with T1D often have multiple diseases, IHD is not always the major cause of death. Therefore, we took into consideration IHD as also a contributory cause of death. The study was also unable to examine the relationship between mortality and menopausal status of women.

In summary, this study finds that the risk of dying from IHD is high in both women and men receiving a diagnosis of T1D at a young age. Although men still have higher crude mortality rates than women, the increased risk of dying from IHD as a result of T1D is more pronounced in women. These observations underscore the importance of identifying risk factors

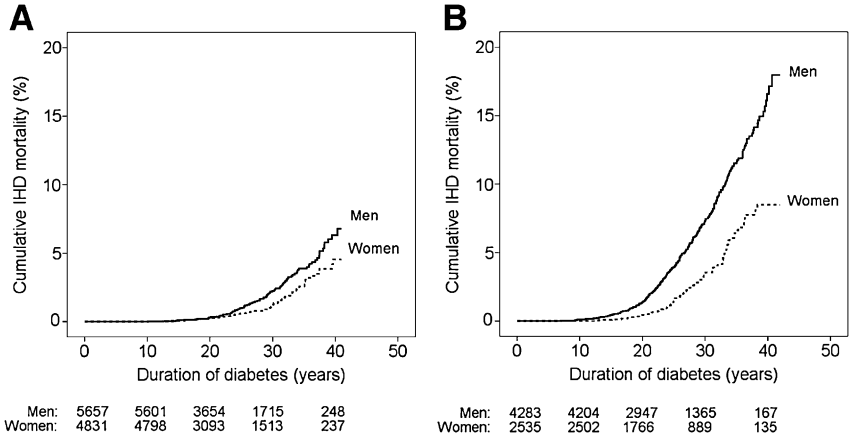

Figure 1—Cumulative mortality from IHD in patients with T1D according to sex. *A*: Early-onset T1D (0–14 years of age). *B*: Late-onset T1D (15–29 years of age).

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early in women and delivering more-aggressive treatment after diagnosis.

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Author Contributions. V.H. designed the research, performed the analyses, and wrote the manuscript. C.M.-B. designed the research and wrote the manuscript. C.F. reviewed the manuscript and contributed to the discussion. P.-H.G. reviewed and edited the manuscript. V.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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