Cause-Specific Mortality in Type 2 Diabetes

The Verona Diabetes Study

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OBJECTIVE — This population-based study, carried out in the framework of the Verona Diabetes Study, investigated mortality from specific causes in known type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A cohort of 7,148 known type 2 diabetic patients (3,366 men and 3,782 women) was identified on 31 December 1986 and followed up for 5 years (1987–1991). Underlying causes of death were obtained from death certificates and were coded according to the *International Classification of Diseases, Ninth Revision*. Cause-specific death rates of diabetic subjects were compared with those of the inhabitants of Verona. By 31 December 1991, 1,550 diabetic subjects (744 men and 806 women) had died.

RESULTS — The standardized mortality ratio (SMR) for all causes of death was 1.42 (95% CI 1.35–1.50). The highest SMRs were for the following specific causes: diabetes (SMR 4.47 [3.91–5.10]), gastrointestinal diseases (1.83 [1.50–2.21])—particularly liver cirrhosis (2.52 [1.96–3.20])—and cardiovascular diseases (1.34 [1.23–1.44]), particularly cerebrovascular (1.48 [1.25–1.73]) and ischemic heart diseases (1.41 [1.24–1.62]). A significantly higher than expected risk of mortality for cardiovascular causes was already present in the first 5 years after diagnosis and decreased with age. Type 2 diabetic patients treated with insulin had a higher risk of dying than those treated orally or by diet.

CONCLUSIONS — The highest SMRs in the diabetic cohort were for diabetes and liver cirrhosis. The mortality risk for cardiovascular diseases, although significantly higher than expected, was much lower in Italian type 2 diabetic patients than that reported for American patients. The evidence of an early effect on mortality suggests that prevention, early diagnosis, and treatment should be improved.

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It has been reported that diabetic subjects are at a greater risk of mortality (1–3) from heart diseases and stroke (4,5) than are nondiabetic subjects, whereas the association between cancer and diabetes has shown a controversial pattern (6).

In the U.S., cardiovascular diseases are the most frequent causes of death in people with diabetes. The relative risk of dying (diabetic versus nondiabetic individuals) from heart disease and ischemic heart disease was higher than the relative risk of mortality due to all causes combined (7).

To our knowledge, no reliable data on mortality from specific causes of diabetic patients are available in southern Europe for comparison with data from other countries. We have previously reported that in a well-characterized population of southern Europe (Verona, Italy), diabetes was associated with a higher mortality from all causes with respect to the general population (8). The purpose of the present analysis was to investigate the mortality from specific causes in type 2 diabetic patients of the Verona Diabetes Study. Cause-specific mortality rates of this cohort of diabetic patients were compared with those of the general population of Verona.

RESEARCH DESIGN AND METHODS

— The design of the study (Verona Diabetes Study) has been described elsewhere (8–10). Briefly, this survey used three different sources of ascertainment (diabetes clinics, family physicians, and the drug consumption database) to identify known diabetic patients who were alive and residing in the Social Health Unit of Verona (Verona SHU) on 31 December 1986. In this way, a cohort of 7,148 known type 2 diabetic patients were identified at the baseline. A total of 4,047 patients (56.6%) were ascertained from the records of all patients attending the two diabetic clinics in the area; 2,165 patients (30.3%), who were not attending the diabetes clinics, were identified by family physicians, using the National Diabetes Data Group criteria for diabetes diagnosis (11); 936 patients (13.1%), not included in the previous sources, were identified through the drug consumption database as having had more than two prescriptions for diabetes within 6 months in 1986. According to the capture-recapture method, this cohort represents about 80.5% of the whole known type 2 diabetic population of Verona (12).

The life status of the diabetic cohort was ascertained on 31 December 1991 using the mortality records of Verona SHU. The underlying cause of death stated on the death certificates was coded according to the *International Classification of Diseases, Ninth Revision*. A total of 161 patients, corresponding to 2.25% of the cohort, were not traced and for statistical purposes were considered alive at the end of the follow-up. The cause of death was not ascertained in 73 patients (4.7%).

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Abbreviations: OHD, oral hypoglycemic drug; SMR, standardized mortality ratio; Verona SHU, Social Health Unit of Verona.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Number of subjects in the cohort, person-years, number of deaths, and crude mortality rate according to sex, age, therapy, and time since diagnosis at the beginning of the follow-up (1 January 1987)*

	n (%)	Person-years	Number of deaths	Crude rate × 1,000
Sex				
Men	3,366 (47.1)	14,978	744	49.7
Women	3,782 (52.9)	16,927	806	47.6
Age at baseline (years)				
<55	1,017 (14.2)	3,860	36	9.3
55–64	1,920 (26.7)	7,895	187	23.7
65–74	2,305 (32.2)	10,623	447	42.1
≥75	1,906 (26.7)	9,548	880	92.2
Therapy				
Diet	860 (12.0)	4,082	98	14.0
OHD	5,821 (81.4)	25,835	1,310	50.7
Insulin	437 (6.1)	1,854	135	72.8
Time since diagnosis (in tertiles)				
<5.5	2,057 (28.8)	9,529	334	35.1
5.5–12.5	2,024 (28.3)	9,240	375	40.6
≥12.5	1,965 (27.5)	8,613	491	57.0

Information on therapy was missing in 30 patients (7 deceased). Information on time since diagnosis was missing in 1,102 patients (350 deceased).

Standardized mortality ratios (SMRs) were computed by means of the program PYRS (person-years) version 1.3 (13), using the general population of 301,519 inhabitants of Verona as reference. Byar's approximation was used to calculate 95% CI for SMR (14). To compare SMRs, Gail's test (15) was used, and χ^2 for trend was performed to evaluate age-related trends in the observed/expected ratios (14).

The Poisson regression model was used to evaluate the effect of sex, age, time since diagnosis, and treatment on mortality from all causes and from specific causes (14).

For the analysis, the time since diagnosis was computed at the baseline and recoded in tertiles, whereas the treatment was coded in three levels—diet, oral hypoglycemic drugs (OHD), and insulin, alone or in association with OHD.

RESULTS — At the beginning of the study (Table 1), most patients (81.4%) were treated with OHD, 6.1% with insulin, and 12% with diet only. Women were significantly older (69.2 ± 10.7 vs. 63.7 ± 11.0 years, $P < 0.001$) and more frequently treated with insulin (7.0 vs. 5.2%) than men, whereas men were more frequently treated with diet (13.6 vs. 10.8%). The crude mortality rate increased with age at the baseline. The rate was higher in patients treated with insulin alone or in association with OHD, and it increased as the disease progressed (time since diagnosis).

By the end of follow-up, 1,550 (21.7%) patients had died—22.1% of the men (744 of 3,366) and 21.3% of the women (806 of 3,782). The main causes of death were cardiovascular diseases, malignancies, diabetes, and gastrointestinal diseases, which accounted for 40.4, 20.9, 14.4, and 6.9% of the deaths, respectively (Table 2).

The diabetic cohort had a higher mortality risk than the general population (Table 3), with an overall SMR of 1.42 (95% CI 1.35–1.50). The highest SMRs were for diabetes (SMR 4.47), gastrointestinal diseases (SMR 1.83)—particularly liver cirrhosis (SMR 2.52)—and cardiovascular diseases (SMR 1.34), particularly cerebrovascular (SMR 1.48) and ischemic

Table 2—International Classification of Diseases, Ninth Revision, *codes and observed number of deaths from the main causes of death*

Cause of death	ICD-9 codes	Men	Women	Total
All causes	—	744 (100.0)	806 (100.0)	1,550 (100.0)
Malignant neoplasms	140–208	194 (26.1)	130 (16.1)	324 (20.9)
Diabetes	250	84 (11.3)	140 (17.4)	224 (14.4)
Cardiovascular	390–459	275 (37.0)	351 (43.5)	626 (40.4)
Ischemic	410–414	111 (14.9)	99 (12.3)	210 (13.5)
Cerebrovascular	430–438	57 (7.7)	96 (11.9)	153 (9.9)
Gastrointestinal	520–579	63 (8.5)	44 (5.5)	107 (6.9)
Chronic liver disease and cirrhosis	571	47 (6.3)	21 (2.6)	68 (4.4)
Pancreas	577	3 (0.4)	0 (0.0)	3 (0.2)
Other gastrointestinal causes	520–570, 572–576, 578–579	13 (1.7)	23 (2.8)	36 (2.3)
Respiratory	460–519	40 (5.4)	43 (5.3)	83 (5.3)
Injury and poisoning	800–999	29 (3.9)	22 (2.7)	51 (3.3)

Data are ICD-9 codes or *n* (%). ICD-9, *International Classification of Diseases, Ninth Revision.*

Table 3—*SMRs (95% CI) for all and specific causes of death for men, women, and the overall cohort*

Cause of death	Men	Women	Total
All causes	1.40 (1.31–1.51)	1.44 (1.34–1.54)	1.42 (1.35–1.50)
Malignant neoplasms	1.08 (0.93–1.24)	1.02 (0.85–1.21)	1.05 (0.94–1.17)
Diabetes	4.76 (3.80–5.90)	4.31 (3.63–5.09)	4.47 (3.91–5.10)
Cardiovascular	1.35 (1.19–1.52)	1.33 (1.19–1.47)	1.34 (1.23–1.44)
Ischemic	1.42 (1.18–1.71)	1.41 (1.16–1.72)	1.41 (1.24–1.62)
Cerebrovascular disease	1.35 (1.02–1.74)	1.57 (1.27–1.92)	1.48 (1.25–1.73)
Gastrointestinal	2.17 (1.67–2.78)	1.49 (1.08–2.00)	1.83 (1.50–2.21)
Chronic liver disease and cirrhosis	2.82 (2.08–3.76)	2.04 (1.26–3.12)	2.52 (1.96–3.20)
Pancreas	3.27 (0.66–9.53)	0.00 (0.00–0.00)	2.61 (0.52–7.62)
Other gastrointestinal causes	1.13 (0.66–1.93)	1.21 (0.81–1.82)	1.18 (0.85–1.63)
Respiratory	0.98 (0.70–1.34)	1.35 (0.97–1.81)	1.14 (0.91–1.42)
Injury and poisoning	1.26 (0.84–1.80)	0.82 (0.51–1.24)	1.02 (0.76–1.34)

Data are SMRs (95% CI).

heart diseases (SMR 1.41). Mortality from malignancies, respiratory diseases, pancreatic diseases, and injury and poisoning was not significantly higher in the diabetic cohort than in the general population.

The sex- and age- specific observed/expected ratios for all causes and for the main specific causes of death are reported in Fig. 1*A* (men) and *B* (women). In both sexes, the risk of mortality from ischemic heart diseases and liver cirrhosis decreased significantly as age increased (χ^2 for trend, $P < 0.001$ and $P \leq 0.05$, respectively), following the pattern of all-cause mortality ($P < 0.001$); this age trend was more pronounced in women than in men. No significant age trend for cerebrovascular mortality was observed. After 75 years of age, the mortality risk from all causes, although markedly reduced, was still significantly higher than in the general population, both in men and in women; the same pattern was observed for cirrhosis in men and for cerebrovascular diseases in women.

The increased mortality risk from all and specific causes was also detectable in subjects with a shorter duration of diabetes (time since diagnosis <5.5 years) (Fig. 2).

Table 4 shows the relative risk of mortality from all and specific causes according to different therapeutic regimens. After adjusting for sex, age, and time since diagnosis, diabetic patients treated with insulin had a threefold higher risk of dying from all causes during the 5-year follow-up than patients treated only with diet (relative risk = 2.95). However, the risk of death from ischemic heart diseases was higher in subjects treated with OHD (vs. diet) than in those treated with insulin (vs. diet). On the contrary, insulin treatment was associated with a particularly high risk of mortality from liver cirrhosis (relative risk = 6.84).

CONCLUSIONS — This study was aimed at analyzing the mortality from specific causes in a well-characterized type 2 diabetic cohort. This is the first population-based study on this subject carried out in Italy and southern Europe. It gives the opportunity to compare diabetes-related mortality in this region with mortality in other countries.

In agreement with previous studies (16–19), we observed a 42% increased risk of mortality in known type 2 diabetic patients, with respect to the general population. Previous studies (20) reported that aging was associated with a steady decline in the observed/expected ratios of death. In contrast, an increased risk of mortality was already present when the disease was diagnosed, and there was no substantial change thereafter. It should be remembered that the latency between the onset of type 2 diabetes and its clinical diagnosis seems to be 7–10 years (21). In addition, it has been reported that the mortality risk during this latency period is similar to, or even higher than, the mortality risk of known diabetic patients (22). This finding strongly suggests that diabetic patients should be identified and treated in the earlier stages of the disease to reduce complications and, hence, mortality.

In our study, the relative risk of death from all causes was in the lower part of the range reported in the current literature (23–25).

The leading cause of death in type 2 diabetic patients was cardiovascular disease, which accounted for 40% of all deaths in diabetic patients. The SMRs for cardiovascular and ischemic heart diseases were 1.34 and 1.41, respectively, consistent with those obtained in a recent study performed in Scotland, which reported a ~50% higher mortality risk for cardiovascular diseases in diabetic than in nondiabetic subjects (17). However, these SMRs are remarkably lower than those reported in U.S. studies, in which the risk of dying from cardiovascular/ischemic diseases was two/four times higher in people with diabetes than in the general population (7,26). Furthermore, the SMRs for cardiovascular and ischemic heart diseases in our study were similar to those from all causes, suggesting that type 2 diabetic patients in Italy are exposed to a moderately increased risk of death, compared with the general population, that is not largely accounted for by cardiovascular diseases, as in other countries. In fact, after the exclusion of cardiovascular diseases, the SMR for all causes was 1.49 (1.40–1.59), which was higher than that for cardiovascular and ischemic heart diseases.

Some methodological features of our study—such as the choice of the general population as the reference rather than the nondiabetic population or the fact that only people with known diabetes were included in the cohort—are expected to slightly underestimate the mortality risk of the diabetic cohort (24,25). However, such methodological differences could explain only to a minor extent the striking difference between the results of our study and the U.S. studies. The observed discrepancy in the risk of cardiovascular mortality could reflect an artifact due to differences in the certification or coding of the causes

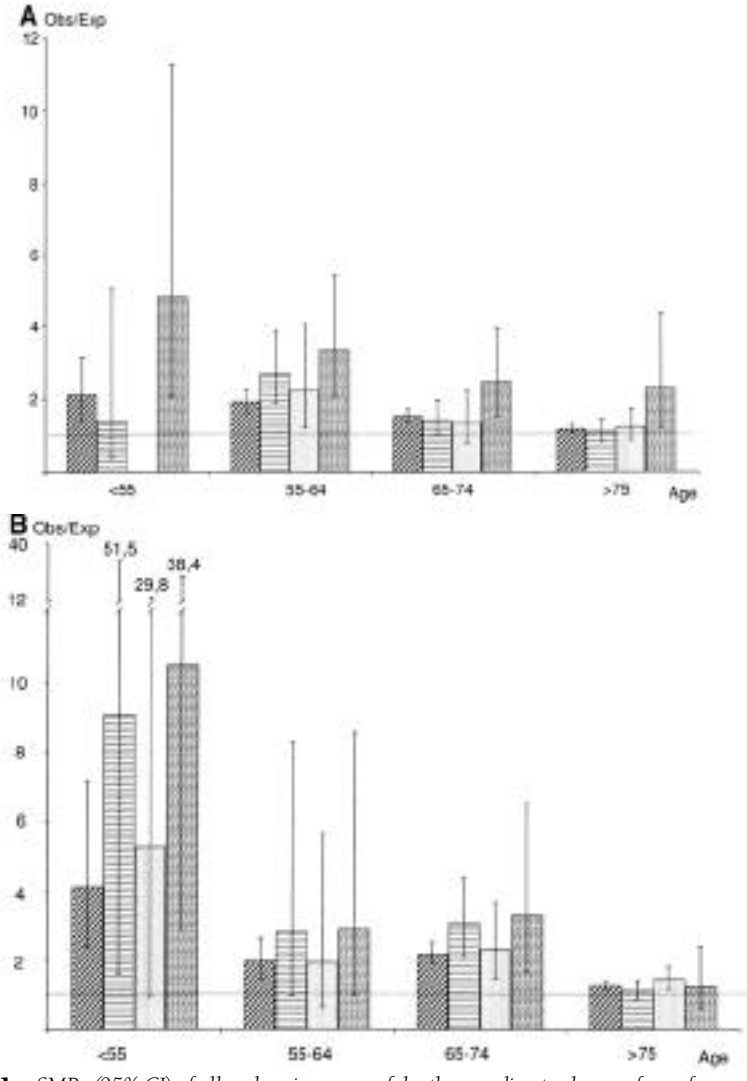

Figure 1—*SMRs (95% CI) of all and main causes of death according to classes of age, for men* (A) *and women* (B). ▨*, All causes;* ▤*, ischemic heart disease;* ⊡*, cerebrovascular disease;* ⊠*, cirrhosis.*

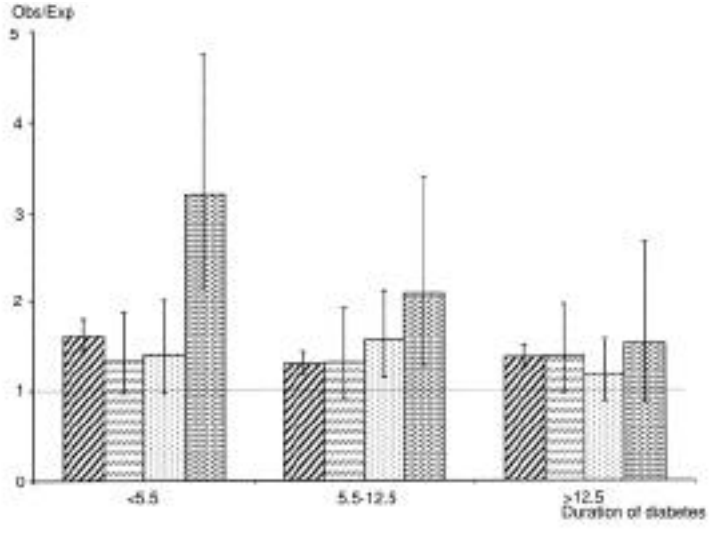

Figure 2—*SMRs (95% CI) of all and main causes of death stratified by tertiles of time since diagnosis.* ▨*, All causes;* ▤*, ischemic heart disease;* ⊡*, cerebrovascular disease;* ⊠*, cirrhosis.*

of death. In this case, it would be expected that an underreporting of cardiovascular diseases on death certificates could be counterbalanced by an overreporting of other causes, particularly diabetes, as the underlying cause of death (1,16,27). However, in our study, diabetes was selected as the underlying cause of death in 14% of diabetic deaths, a figure similar to those reported in U.S. studies. Thus, alternative explanations should be invoked to explain the apparent discrepancy in mortality rates for cardiovascular diseases. For instance, this discrepancy could reflect differences in the accessibility of health services and in the severity of the disease. In Italy, where health care for diabetic patients is mainly provided freely by the public health services, virtually all known diabetic patients are treated, whereas in the U.S., where diabetes care is mainly provided by private institutions, 25% of diabetic patients are left untreated (28). This difference in the management of the disease is likely to affect survival. In fact, it has been reported that mortality from all causes and from cardiovascular diseases is lower when the diabetic patients are managed by diabetic clinics or specialists (10,29) and is higher in the lowest social classes (30–32). Another possible explanation could be that type 2 diabetes is, on average, more severe in the U.S. than in Italy, as could be argued by the difference in the treatment pattern. In fact, our data, consistent with those of another recent Italian study (33), pointed out that <10% of type 2 diabetic patients are treated with insulin. On the contrary, in the U.S., >25% patients are insulin treated (28).

Only a few population-based studies have investigated the mortality from cerebrovascular diseases among people with diabetes. In agreement with these studies (17,18), we found an increased mortality risk from cerebrovascular diseases, especially in diabetic women. This sex-related pattern could reflect the fact that diabetes has a different effect on hypertension and other risk factors for cerebrovascular diseases in men and women (20,34,35).

A more than twofold risk of dying from liver cirrhosis was found in the Verona diabetic cohort compared with the general population. In both sexes, the observed/expected ratios decreased as age progressed, and the highest mortality risk was found in patients of the first tertile of time since diagnosis. The association between liver cirrhosis and diabetes was

Table 4—*Relative risk of dying according to therapeutic regimens for some specific causes of death, after adjusting for sex, age, and time since diagnosis (in tertiles)*

	OHD (vs. diet)	Insulin (vs. diet)
All causes	1.68 (1.36–2.1)*	2.95 (2.2–3.9)*
Ischemic heart disease	1.80 (1.02–3.20)†	1.55 (0.65–3.67)
Cerebrovascular disease	1.35 (0.72–2.5)	1.41 (0.5–3.7)
Cirrhosis	4.93 (1.19–20.4)†	6.84 (1.2–38.0)†

Data are relative risks (95% CI). *$P < 0.001$; †$P < 0.05$.

noted years ago (36,37). It has been reported that when multiple causes of death are considered, women are more likely to have diabetes listed as the underlying cause, and men are more likely to have cirrhosis listed as the underlying cause (38). In our cohort, however, both sexes have a significantly increased risk of dying from cirrhosis. This suggests that our results are not influenced by a coding artifact. Alcohol consumption could be an important confounding variable in this context (39). In fact, an association exists between alcohol consumption and serum glucose levels; moreover, alcoholic patients with liver disease frequently have reduced glucose tolerance. Recently, Balkau and colleagues (40,41), in the context of the Paris Prospective Study, showed a very high risk of death due to alcohol-related diseases in diabetic men. Furthermore, hepatitis infections could be invoked as another determinant of the increased risk of dying from cirrhosis in our cohort. In fact, a high prevalence of the hepatitis C infection in diabetic patients has been reported (42), and a recent study in Italy showed that nearly 40% of cirrhosis may be attributed to hepatitis infections (43). Unfortunately, in the present study, these hypotheses cannot be tested because the information on alcohol and hepatitis infections was not available.

The overall SMR from diabetes found in our cohort was 4.47. The reliability of this estimate (as others reported) is likely to be very poor due to the general and well-known drawback of studies that rely on death certificates. In fact, as a cause of death, diabetes is largely underreported, because certifying physicians are more likely to record other common conditions, such as ischemic heart diseases, as the underlying cause of death in diabetic patients rather than diabetes itself (1,16,27). In addition, our reference population included diabetic patients, and this could have led to a further underestimation of the risk of dying from diabetes.

Mortality from cancer was evaluated in several studies (1,17,18,34). Compared with mortality in the reference population, cancer mortality in diabetic patients has been reported to be higher, comparable, or even lower in different studies. In our study, the diabetic cohort showed a mortality from cancer comparable to that of the reference population.

In the multivariate model, we found that diabetic patients treated with insulin or OHD had a poorer survival prognosis than those treated only with diet. The latter association has already been reported in other studies (8,20), and it may be related to the severity of the disease. In fact, insulin treatment is started when the disease cannot be controlled by diet or OHDs. Accordingly, diabetic patients on insulin have a greater risk of complications (19). In our study, it is of interest to note that subjects treated with OHD had a higher mortality risk from cardiovascular diseases than did subjects treated with diet only, whereas this was not found in subjects treated with insulin alone. A particularly strong association was found between insulin treatment and mortality from cirrhosis.

In conclusion, our study shows that diabetic patients are exposed to a 42% greater risk of mortality from all causes than the general population. In contrast to the U.S. studies, the increased mortality in diabetic patients was not explained simply by an increased mortality from cardiovascular diseases. Other causes of death, such as cirrhosis and diabetes, contributed to increase the risk of mortality. Mortality from malignancies was similar in the diabetic cohort and in the general population. Insulin treatment was strongly associated with mortality from all causes and cirrhosis. The evidence of an increased mortality risk from all causes and from cardiovascular diseases in subjects with an apparently short duration of diabetes suggests that prevention, early diagnosis, and treatment should be implemented.

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