Mortality in Concurrent Type 1 Diabetes and Anorexia Nervosa

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OBJECTIVE — Previous studies in this field report early occurrence of diabetic complications, but excess mortality, though expectable, has not been reported. We combined information from earlier studies to estimate the mortality for this group of patients.

RESEARCH DESIGN AND METHODS — The observed mortality is analyzed using crude mortality rate (a percentage), standardized mortality ratio (SMR), incidence rate ratio, risk difference, and survival analysis.

RESULTS — After ~10 years of follow-up, 13 of 510 females with type 1 diabetes, 43 of 658 females with anorexia nervosa (AN), and 8 of 23 concurrent case subjects had died. Mortality rate was 2.2 (per 1,000 person-years) for type 1 diabetes, 7.3 for AN cases, and 34.6 for concurrent cases. Crude mortality rates were 2.5, 6.5, and 34.8%, respectively. SMR was 4.06 in type 1 diabetes, 8.86 in AN, and 14.5 in concurrent cases. Survival analysis indicated between-group differences in mortality.

CONCLUSIONS — Concurrent type 1 diabetes and AN is a rare but serious condition in females. All indexes of mortality evidence excess mortality in this preliminary study. Vigorous and well-directed treatment efforts seem vital for this subpopulation. Collaboration between diabetologists and eating disorder specialists is warranted. The implications of other eating disorders and subclinical eating disorders in diabetic populations need to be analyzed, especially because these conditions are more frequent than clinical eating disorders.

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Despite suggestions of excess mortality in subjects with concurrent eating disorder (ED) and type 1 diabetes (1,2), we have not been able to locate any quantitative reports on this subject. Bryden et al. (3) reported two deaths in the original cohort of 76 adolescents at the 8-year follow-up. It is not stated whether this mortality is "excessive" or "expectable." Because controlled studies (4–7) and a meta-analysis (2) indicate early and severe neurovascular complications in these patients, excess mortality is expectable. Furthermore, ED might lead to unstable or "brittle" diabetes, a condition with high mortality and a high frequency of diabetes complications (8). Emborg's (9) finding of 8 dead out of 29 case subjects with concurrent type 1 diabetes and ED led to the present detailed scrutiny of mortality in these cases. We estimated the mortality in this clinical subpopulation using information from the Danish psychiatric and somatic hospital admission registers and the centralized person registry. The necessary information was available because of ongoing research (2,9–12; A.G.M., K. Nørgaard, K. Borch-Johnsen, B. Christau, M. Davidsen, J. Nerup, unpublished data). We want to emphasize the dire consequences of clinical ED in female type 1 diabetic patients. We also want to inspire clinical collaboration and further research, preferably in the form of repeated follow-ups of controlled studies.

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Abbreviations: AN, anorexia nervosa; CMR, crude mortality rate; ED, eating disorder; ED-NOS, ED not otherwise specified; ICD, International Classification of Diseases; OR, odds ratio; RD, risk difference; RR, rate ratio; SMR, standardized mortality ratio.

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

RESEARCH DESIGN AND METHODS

— In this register-based study (13), we had access to the following variables: sex, date of birth, date of index admission, *International Classification of Diseases* (ICD)-8 (14) diagnoses, type of exit (death or censoring), and date of exit. Population data from the Danish Central Bureau of Statistics permit computation of standardized mortality ratio (SMR) controlling for the effects of age, sex, and time period. Males were excluded.

Diabetic population

Data originate from two population-based studies (12; A.G.M., K. Nørgaard, K. Borch-Johnsen, B. Christau, M. Davidsen, J. Nerup, unpublished data). The study population was limited to juvenile-onset (0–29 years) type 1 diabetes. Time of entry was defined as the date of the first insulin injection.

Anorexia nervosa population

The data source (10) was the Danish nationwide psychiatric admission case register (13). The entry period was 1 January 1970 to 31 December 1984. Time of entry was the date of the first diagnosis of anorexia nervosa (AN).

Subpopulation: concurrent AN and type 1 diabetes

Data (9) stem from the Danish nationwide psychiatric admission register (13). From 1 January 1977, the data were supplemented with information from the Danish nationwide somatic admission register. Entry was defined as the first occurrence of a type 1 diabetes diagnosis in a female psychiatric AN inpatient or the first psychiatric admission of a female type 1 diabetic patient with an AN diagnosis. Entry periods were 1 January 1970 to 31 December 1993 for psychiatric admissions

Table 1—*Characteristics of the three samples*

	Type 1 diabetes	AN	Concurrent cases
Source	Christau et al. (12) Mølbak et. al. (unpublished data)	Møller-Madsen et al. (10)	Emborg (9)
Sex	F	F	F
Sample size	510	658	23
Type of study	Catchment area, 1.5 million population	Register study, psychiatric, nationwide	Register study, psychiatric and somatic, nationwide
Entry period(s)	1970–1976 1980–1984	1970–1984	1970–1993
Age at entry (years)			
Mean ± SD	15.8 ± 7.9	22.2 ± 8.5	26.1 ± 13.4
Range	0–29	8.5–64.5	8–59
Length of follow-up (years)			
Mean ± SD	11.6 ± 4.97	8.97 ± 4.16	10.06 ± 4.94
Range	0.0–18.2	0.2–17.1	0.5–22
End point of study	8 March 1988	15 November 1987	31 December 1993

and 1 January 1977 to 31 December 1993 for somatic admissions. The characteristics of the different samples are summarized in Table 1.

We used the following indexes of mortality: crude mortality rate (CMR) (a percentage), SMR, rate ratio (RR) (mortality per 1,000 person-years of observation), risk difference (RD), and survival analysis. We use established methods (15,16) in the analyses for SMR, RR, and RD, including 95% CIs. Data handling and analysis involved EXACTMA (available from http://www.sph.emory.edu/~haustin.exactma.html) (17), STATISTIX (Analytical Software, Tallahassee, FL) (18), SPSS for Windows (SPSS, Chicago) (19), CIA (BMJ Publishing Group, London) (20), and StatXact4 (Cytel Software, Cambridge, MA) (21). Full documentation of the statistical methods used in this study can be found in the manuals of the computer programs.

All background studies obtained the approval of the relevant Danish committees on ethical aspects of scientific research.

RESULTS

Study populations

Of the AN case subjects, 85% (n = 561) had their first psychiatric admission for AN before age 30 years and only 4% (n = 26) after age 40 years. Of the 29 case subjects with concurrent ICD-8 (14) ED and type 1 diabetes reported by Emborg (9), 3 were AN males, one was a female coded 306.58 (other eating disorder, specified), and two were females coded 306.59 (eating disorder, unspecified). After excluding these six case subjects, 23 AN females remained who also had type 1 diabetes.

CMR and incidence rate ratio

Basic data and findings are summarized in Table 2. CMR is not homogeneously distributed across diagnostic category (Fisher statistic 31.20; df = 2; $P < 0.001$) (21). When comparing AN with type 1 diabetes, Fisher statistic is 10.38 (df = 1; P = 0.001). Odds ratio (OR) for premature death is 2.67 (95% "exact" CI 1.4–5.5; P_{OR} = 0.002) (21). That is, the odds of death is ~2.5 times higher for AN subjects than for type 1 diabetic subjects. Comparing concurrent cases with AN gives a Fisher statistic of 16.07 (df = 1; $P < 0.001$). OR for premature death is 7.63 (95% "exact" CI 2.6–20.3; $P_{OR} < 0.001$) (21). Finally, when comparing concurrent cases with type 1 diabetes, Fisher statistic is 27.60 (df = 1; $P < 0.001$). OR for premature death is 20.39 (95% "exact" CI 6.2–62.2; $P_{OR} < 0.001$) (21).

Incidence RR is significantly increased in all pair-wise analyses: AN versus type 1 diabetes 3.35 (95% CI 1.8–6.3), z-score 4.053, $P < 0.001$; concurrent cases versus AN 4.75 (95% CI 2.4–9.4), z-score 4.465, $P < 0.001$; concurrent cases versus type 1 diabetes 15.88 (95% CI 6.6–38.3), z-score 8.31, $P < 0.001$.

RD (difference of proportions)

For AN versus type 1 diabetes, RD = 0.04 (95% CI 0.01–0.07) and P_{RD} = 0.03

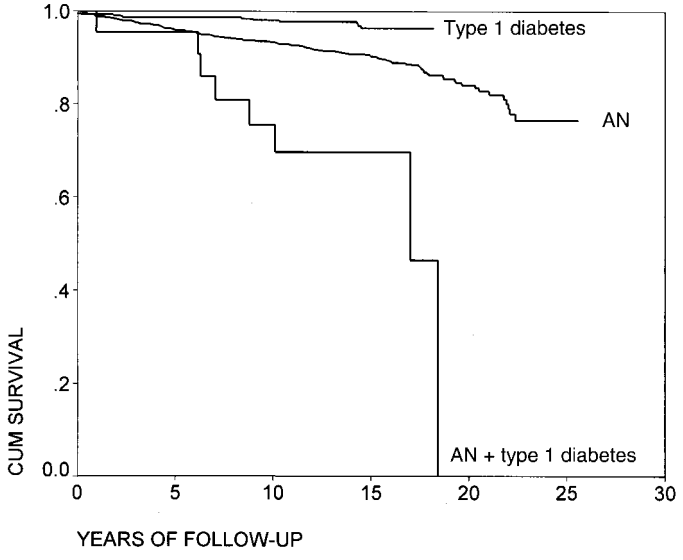

Figure 1—*Survival functions in females. Both pair-wise and global analysis confirm the visual impression of a different pattern of survival in the three groups (see details in text). AN + type 1 diabetes, comorbid AN and type 1 diabetes; CUM, cumulative.*

Table 2—*Mortality of the different samples*

Diagnosis	Dead	Alive	Total	Person-years	RR*	Percentage†
Type 1 diabetes	13	497	510	5,926	2.2	2.5
AN	43	615	658	5,900	7.3	6.5
Concurrent cases	8	15	23	231.3	34.6	34.8

*RR = mortality per 1,000 person-years; †crude mortality rate (percent of total).

(21), i.e., probands with AN have a 4% higher CMR than probands with type 1 diabetes. For concurrent cases versus AN, RD = 0.28 (95% CI 0.10–0.54) and P_{RD} = 0.01 (21), i.e., concurrent cases have a 28% increase in CMR compared with probands with AN. Finally, for concurrent cases versus type 1 diabetes, RD = 0.32 (95% CI 0.14–0.58) and P_{RD} = 0.004 (21), i.e., concurrent cases have a 32% increase in CMR compared with type 1 diabetes.

SMR

Pertinent data and basic analysis are sumarized in Table 3. All groups had significantly elevated SMR. SMR is not homogeneous across the three strata ("exact" [17], $P = 0.005$). Inspection of the 95% CIs shows considerable overlap for the AN and concurrent case subject strata, and formal testing (17) does not reject a hypothesis of homogeneity of SMRs for these two strata (exact, $P = 0.24$). Pairwise analysis of the ratio of the two SMRs (20) yielded the following results: AN versus type 1 diabetes 2.18 (95% CI 1.15–4.42), concurrent cases versus AN 1.63 (0.66–3.52), and concurrent cases versus type 1 diabetes 3.56 (1.28 to 9.27).

Survival analysis

We used the Kaplan-Meier method (19). The survival functions for the different subgroups are shown in Fig. 1.

Analyzing the 1970–1984 AN (10) and type 1 diabetes (12, Mølbak et al., unpublished data) cohorts for equality of survival distributions gave the following results: log-rank test statistic 15.19; df = 1; $P < 0.001$. That is, significantly higher mortality exists for AN subjects than for type 1 diabetic subjects. Survival in Emborg's (9) 1970–1993 cohort was analyzed in two subpopulations: AN subjects without type 1 diabetes (n = 2,197; 179 deaths; 2,018 censorings) and AN subjects with type 1 diabetes (n = 23; 8 deaths; 15 censorings). Analysis for equality of survival distributions gave these results: log-rank test statistic 22.53; df = 1; $P < 0.001$. The probability of survival was much smaller in the concurrent case subjects than in the AN cohort. This trend is even more pronounced for the comparison of type 1 diabetes and concurrent cases: log-rank test statistic 51.01; df = 1; $P < 0.001$. The visual impression of differences in the three survival functions is confirmed by the log-rank test: 46.81 (df = 2; $P < 0.001$).

Causes of death in concurrent cases

Type 1 diabetes was listed as the cause of death on all eight death certificates—in four cases as the primary cause of death (one case, coma diabeticum; one case, uremia; two cases, type 1 diabetes). In two cases, type 1 diabetes was listed as a contributory cause of death, and in a further two cases, as an underlying or tertiary cause of death. No unnatural deaths (accidents, suicides, or homicides) were recorded.

Table 3—*SMR by diagnosis*

		Mortality					
Diagnosis	n	OBS	EXP	SMR	95% CI_{SMR}	Test statistic	P‡
Type 1 diabetes	510	13	3.20	4.06	2.26–6.77	3.945*	<0.001
AN	658	43	4.854	8.86	6.5–11.8	292†	<0.001
Concurrent cases	23	8	0.553	14.5	6.7–27.5	4.886*	<0.001

*Standard normal deviate (z-score); †χ^2; df = 1; ‡two-tailed. OBS, observed; EXP, expected.

CONCLUSIONS — This is a preliminary study using an indirect method to obtain estimates of mortality in the different diagnostic subgroups. Our efforts at quantification yielded the following findings.

AN has higher mortality than type 1 diabetes on all indexes of mortality. The occurrence of type 1 diabetes in AN patients does not seem to increase mortality significantly, whereas the occurrence of AN in a type 1 diabetic population leads to a significant increase in mortality for this group. This main finding is in agreement with intuition and with other researchers' findings of early appearance of severe neurovascular complications in these patients (4–7). Furthermore, most of the fatalities in concurrent case subjects occurred after 6–10 years of observation (Fig. 1), which is 5–10 years earlier than in a type 1 diabetic cohort (22).

A strength of the present study is the comprehensive statistical analysis of data from well-established registers with high ascertainment rates. The study has some inherent weaknesses, limiting the inference that can be drawn confidently from the findings. First, in a register study, we have limited clinical information. Second, Denmark adheres to the ICD-8 (17) diagnostic system in the period under study; therefore, AN is the only reliably diagnosed eating disorder. Other relevant eating disorders, i.e., bulimia nervosa, eating disorder not otherwise specified (ED-NOS), and "subclinical" or "subthreshold" eating disorders, cannot be studied. Third, the sample size of concurrent cases is small, a not altogether unexpected finding because existing evidence does not indicate an increased occurrence of AN in type 1 diabetic subjects (2).

A common pathway to early occurrence of diabetes complications and premature death is the widespread use of an osmotic purge of calories via a reduction in insulin (2,23). Because clinical and subclinical ED might be an important element in "brittle" diabetes, collaboration between diabetologists and ED specialists is warranted. Treatment of these cases is difficult (2,24).

The course of subclinical ED and ED-NOS in type 1 diabetic patients should be elucidated because these conditions are more frequent than AN and bulimia nervosa (2,23,25). In cases of brittle diabetes, a formal evaluation for ED might be helpful. Forthcoming studies should be designed to elucidate the complex relationships between physical and mental health status and history, health knowledge, health care behavior, and outcome.

It is important to control for obesity and to use the best available instruments for evaluating diabetes-specific behavior.

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