

Relationship Between Insulin Exposure and All-Cause Mortality

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Background

Although the benefits of insulin therapy on blood glucose control and risk of microvascular complications are well known in type 2 diabetes; the impact on mortality remains unclear.

Objective

We aimed to compare population-based rates of all-cause mortality in newly treated type 2 diabetes patients according to insulin exposure levels.

Methods

Study Population

- Using the retrospective administrative databases of Saskatchewan Health, 12,272 new users of oral antidiabetic therapy were identified between 1991-1996.
- Eligible subjects were ≥ 30 years of age; at least 1 year continuous prescription coverage prior to index date.
- These subjects were prospectively followed until death, termination of Saskatchewan Health Coverage, or until December 31, 1999, whichever occurred first.

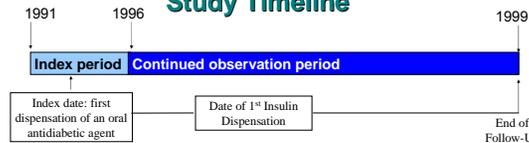
Exposure and Outcome Definition

- Our independent variable of interest was insulin exposure classified on an ordinal scale.
- Individuals were grouped according to level of insulin exposure based on the mean number of insulin dispensations per year: **NO** clinically meaningful exposure (0 to <3) (reference group); **LOW** exposure (3 to <9); **MEDIUM** exposure (9 to <15); **HIGH** exposure (15 to <21); **VERY HIGH** exposure (≥ 21).
- The primary outcome was time to all-cause mortality.

Statistical Analysis

- Time-varying, multivariate Cox proportional hazards models were used to examine the relationship between insulin exposure level and all-cause mortality.
- Covariates included in the model were age, sex, chronic disease score, severity of diabetes (based on absence or presence of microvascular and macrovascular complications), and relevant medications (statins, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, diuretics, antiplatelets, anticoagulants, antiarrhythmics, and pentoxifylline).
- Multiple sensitivity analyses were performed: Low Insulin exposure as the reference group; Exclusion of subjects who died in the first 6 and 12 months; Exclusion of subjects never exposed to insulin.

Study Timeline



Results

- Average length of follow-up was 5.1 years (SD 2.2) and 10% of subjects initiated insulin therapy.
- We found a graded increase in mortality associated with increasing insulin exposure.

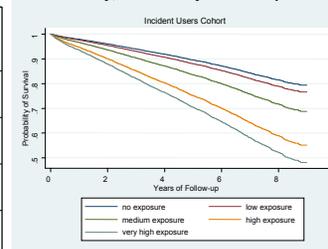
Table 1. Characteristics of Baseline Cohort

	Overall Cohort	No insulin	Low	Medium	High	Very High
Number of Subjects (n)	12 272	11 064	257	450	286	215
Age (mean yrs (SD))	65 (14)	66 (13)	60 (15)	60 (15)	59 (14)	58 (14)
Sex (%male)	55%	56%	50%	55%	47%	46%
CDS (mean (SD))	9 (4)	8 (4)	9 (5)	9 (5)	9 (4)	10 (4)
Micro- & macrovascular complications (%)	46%	46%	45%	47%	43%	49%

Table 2. Mortality Events and HR* for Primary Analysis

Insulin Exposure †	Events (n/N)	Mortality Rate‡	HR* (95% CI)
No exposure	2456/11064	58	1.00
Low	36 / 257	46	1.16 (0.83 – 1.61)
Medium	89 / 450	72	1.62 (1.31 – 2.01)
High	57 / 286	81	2.58 (1.98 – 3.37)
Very High	43 / 215	100	3.17 (2.33 – 4.31)

Figure 1. Adjusted* Survival for all-cause mortality, stratified by insulin exposure.



* HR adjusted for age, sex, CDS, severity of diabetes, oral diabetes medications, use of selected medications. Oral diabetes medication regimen was treated as a time-varying covariate. † time-varying covariate (The amount of person-time follow-up was classified based on time spent unexposed or subsequently exposed to insulin. ‡ Adjusted mortality rate per 1000 person-years.

Table 3. HR* and 95% CI for Sensitivity Analyses on Insulin Exposure Definition and Survival

Insulin Exposure †	Low Exposure as Reference	Excluding Subjects who died within 6 months	Excluding Subjects who died within 12 months
No exposure	n/a	1.00	1.00
Low	1.00	1.67 (1.13 – 2.48)	1.67 (1.12 – 2.49)
Medium	1.40 (0.95 – 2.07)	2.59 (1.92 – 3.50)	2.57 (1.89 – 3.49)
High	2.23 (1.47 – 3.39)	2.96 (2.10 – 4.17)	2.97 (2.10 – 4.19)
Very High	2.74 (1.76 – 4.72)	3.18 (2.16 – 4.65)	3.07 (2.08 – 4.54)

Discussion:

- Potential reasons for observed graded risk in mortality associated with increasing insulin exposure:
 - Net harmful effect of insulin
 - Insulin itself has been associated with several adverse physiological cardiovascular effects including vasculature dysfunction, weight gain, and exacerbation of hypertension, and dyslipidemia.
 - In one of the few RCTs conducted, The Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA-CSDM), high versus standard doses of insulin therapy was examined in 253 patients with type 2 diabetes. The study reported 24 patients (32%) who were randomly assigned to high dose insulin therapy compared to 16 patients (20%) randomly assigned to standard dose insulin therapy, who experienced a cardiovascular (CV) event ($p=0.10$). Our findings are broadly consistent with this trial.
 - Confounding by disease severity whereby insulin simply serves as a marker for more severe diabetes.
 - Individuals being dispensed insulin more frequently may have poorer glycemic control and this alone accounts for our observed association between insulin exposure and mortality.
 - This is improbable because there is minimal randomized trial evidence that better glycemic control leads to better survival.
 - Even if we ignore the randomized trial evidence, observational data from the UKPDS reported a 14% decrease in all-cause mortality for every 1% reduction in A1C.
 - We observed an approximate 200% increase in risk among subjects exposed to very high levels of insulin compared to no insulin exposure, implying A1C differences between these groups in excess of 14%. A difference in A1C of this magnitude is implausible.
 - Furthermore, we attempted to adjust for diabetes severity using a categorical variable that identified the presence of both macrovascular and microvascular disease, suggesting all insulin users had comparable degree of diabetes severity.

Strengths:

- Unique approach to quantifying insulin exposure
- Time-dependent approach avoids immortal time bias
- Consistent association found in sensitivity analysis
- Data were collected in the 1990's where the variability of insulin formulations was considerably less than today

Limitations:

- True level of insulin exposure unknown
- Limited clinical variables in dataset
- Potential for residual confounding
- Observed association must not be interpreted as a true causal association

Conclusions:

- Our findings suggest that increasing amounts of insulin exposure are associated with higher mortality in older patients with type 2 diabetes.
- Higher level evidence is needed to further evaluate the impact of insulin therapy on long-term outcomes in patients with type 2 diabetes.

Acknowledgements

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