Strict Glycemic Control and Mortality Risk Among US adults with Type 2 Diabetes

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Abstract

Objective: Assess the relationships between strict HbA1c levels and mortality risk among adults with type 2 diabetes by age, insulin therapy, and hypertension comorbidity.

Methods: Data of adult participants with type 2 diabetes from the third National Health and Nutrition Examination Survey (1988–1994) and its linked mortality file (with follow-up death up to 2000) were used.

Results: Having strict glycemic control (i.e. HbA1c ≤ 6.5%) was associated with a lower risk of mortality (hazards ratio= 0.69 [95% confidence interval=0.48–0.98]). However, among those with strict glycemic control levels, statistically significant results were not found.

Conclusion: Reaching strict glycemic control levels in the general US population with type 2 diabetes appears to be associated with lower mortality. Further research is needed as to how strict glycemic control affects certain diabetic groups.

Introduction

Strict glycemic control is associated with reductions in the incidence of microvascular complications by as much as 27% and increases in life expectancy, with a slight increase in complications due to longer survival time (Centers for Disease Control and Prevention Diabetes Cost-Effectiveness Group, 2002). Negative health outcomes due to strict glycemic control, such as increased mortality risk, have been recently reported in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (Cefalu & Watson, 2008). Individuals in the strict glycemic control arm, who achieved an average HbA1c of 6.4%, had more deaths than those in the standard group (HbA1c of 7.00–7.95%) (Cefalu & Watson,

2008). This unexpected finding resulted in early termination of the trial an suggested that strict glycemic control in certain individuals with type 2 diabetes could be harmful.

Because of recent controversies regarding optimal thresholds of glycemic control (Inzuchhi & Siegel, 2009; Hoogwerf, 2008; Soo Yean & Nesto, 2008), we assessed the relationships between all-cause mortality risk and strict HbA1c levels in various subgroups of US adults with type 2 diabetes who participated in the 1988–1994 National Health and Nutrition Examination Survey (NHANES III).

Methods

The NHANES was developed by the National Center for Health Statistics (NCHS) using a stratified, multi-stage complex probability design that allows for a nationally representative estimation of health outcomes for the non-institutionalized US population (NCHS, 2006). The NCHS performed a probabilistic match of information from NHANES III participants aged 17 years or older and the National Death Index through December 31, 2000 to determine mortality status (NCHS, 2007).

Individuals defined as having type 1 diabetes (i.e. self-report of diabetes diagnosis before age of 30 and taking insulin only since diagnosis) were excluded; the remaining sample was considered to have type 2 diabetes, as defined in a previous studies (Ong et al., 2008; Hertz et al., 2007; Fan et al., 2006), aged 20 years or older, and not pregnant were included in this study. HbA1c levels were categorized two ways: 6.0% versus > 6.0% (i.e., very strict glycemic control); and 6.5% versus > 6.5% (i.e., strict glycemic control). The threshold of 6.0% was used because it is a target used by many clinicians and in some research studies such as the ACCORD study while the threshold of 6.5% was used since it is a cut-off used by the American Association of Clinical Endocrinologist (AACE) for suboptimal glycemic control (AACE, 2000). Various subgroups were created: 1) the best health (i.e., less than 65 years of age, not diagnosed with hypertension, and not taking insulin; 2) the worst health (i.e., 65 years of age or older, being diagnosed with hypertension and under insulin therapy); and 3) intermediate subgroups. A categorical variable, "negative health factor", was created as follows: 1) having one negative health factor (i.e. 65 years of age or older, with insulin therapy, or diagnosed with hypertension); 2) having two negative health factors; and 3) having all three negative health factors.

Un-adjusted and adjusted (for sex, race/ethnicity, education, body mass index, and duration of diabetes) Cox proportional hazards regression analyses were conducted using each of the HbA1c thresholds. All-cause mortality was the outcome variable. Mortality from other causes was not investigated due to small sample size. The proportionality assumption for Cox proportional hazard analyses was also assessed and met. Potential confounders were assessed and interactions tested. Analyses were conducted using STATA 10.0 statistical software given its ability to account for the complex sample survey design.

Results

In fully adjusted Cox-proportional hazard models, a statistically significant direct relationship was found when using strict glycemic control levels. Having strict and very

strict glycemic control were associated with lower mortality risk among the general US population of adults with type 2 diabetes, (hazard ratio, HR = 0.72, 95% CI: [0.57–0.92] and HR = 0.69, 95% CI: [0.48–0.99], respectively) (Table). There were statistical significant interactions for strict glycemic control with age group and insulin therapy. Among diabetic subgroups, no statistically significant relationships were found between having a strict glycemic control and all-cause mortality risk. However, there were differences in the direction of the estimates of relationships between HbA1c and mortality risk depending on the subgroup. In fully adjusted hazard models among adults with type 2 diabetes with strict HbA1c levels, having 2 or 3 negative health factors, compared to having 1, was associated with greater mortality risk (HR = 2.46, 95% CI: [1.28–4.70] and HR = 4.27, 95% CI: [1.70–10.76], respectively).

Discussion

Several studies have assessed the relationships between glycemic control and all-cause risk, although these have led to conflicting findings and/or are based on non-nationally representative samples of adults with diabetes (Kovesdy et al., 2008; Menon et al., 2005; Kalantar-Zadeh et al., 2007). The only nationally representative study assessing glycemic control among adults with type 2 diabetes found that there was a curvilinear relationship between HbA1c levels and all-cause mortality risk but did not assess relationships within subgroups (Saydah et al., 2009).

We found that having strict and very strict glycemic control was associated with a lower mortality risk among the general population of US adults with type 2 diabetes. However, stratified analyses by subgroups did not show statistically significant associations between mortality risk and glycemic control. Nevertheless, the "best health" subgroup had a hazard ratio suggesting a lower mortality risk with strict glycemic control while the "worse health" subgroup had a hazard ratio suggesting a greater mortality risk with strict glycemic control. In addition, there was a trend towards greater mortality risk with greater negative health factors among adults who had strict glycemic control. Thus, the findings suggest that the effect of strict glycemic control on mortality risk may depend on: age, type of diabetes management (i.e., whether treated with insulin, suggesting loss of beta cell function), and presence of other comorbid conditions. Non-statistically significant findings may most likely be due to small sample sizes of subgroups. Moreover, HbA1c levels are only known at baseline. Therefore, there is potential misclassification of glycemic control at time of death.

There are some limitations that should be noted. Glycemic control was only based on baseline data, therefore leaving the possibility of misclassification of glycemic control at time of death; this misclassification is likely to be non-differential however. Also, although several potential confounders in the relationship between mortality risk and glycemic control were tested, only the ones found statistically and clinically significant were included in the hazard models in order to provide a parsimonious model. Having too many variables in the hazard model would have resulted in greater loss of power given the small sample size. Furthermore, only variables that would be relatively stable after 6–12 years of follow-up were considered as covariates given that these were only available at baseline and not follow-up. The inclusion of these covariates would have resulted in the probability of greater

misclassification. Cardiovascular death and cancer death were of interest but were not able to analyzed given the small sample size. The diabetic groups were somewhat arbitrarily chosen given the literature suggesting these individuals tend to be in frail health. There may be other diabetic groups that would have been importance but further stratification by these participant characteristics would have resulted in even smaller sample size and therefore loss of power. Finally, the cut offs of 6.5 and 6.0 for strict glycemic control were arbitrarily chosen based on the literature. Thus we performed sensitivity analyses using other cut-offs as well as using HbA1c as a continuous variable. The findings were similar, as the HbA1c level lowered, the mortality risk decreased as well (results not shown). However, when HbA1c levels were lower than 4.0%, the mortality risk increased, although these findings were not statistically significant (results not shown). These results were similar for all diabetic groups. Our findings suggest that strict glycemic control may indeed be beneficial in increasing survival among the general US population of adults with type 2 diabetes after a 6 to 12 year follow-up. These findings are in disagreement with recent findings from the ACCORD study (Cefaul & Watson, 2008). Further research studies are needed to determine if stricter HbA1c thresholds should be recommended for healthier adults with diabetes and less strict for those more chronically-ill

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Table.

Relationships between having very strict and strict HbA1c levels and all-cause mortality risk among adults with type 2 diabetes, and various diabetic subgroups (according to age, insulin therapy, and hypertension comorbidity)

HbA1c	All[†] (N=1381)	Diabetic subgroups						
		Best Health	Intermediate Health Groups					Worst Health
		< 65 yrs of age + not taking insulin + not diagnosed with hypertension (n=184)	65 yrs of age (n=620)	Diagnosed with hypertension (n=644)	Taking insulin (n=332)	65 yrs of age + diagnosed with hypertension (n=344)	65 yrs of age + taking insulin (n=189)	< 65 yrs of age + taking insulin + diagnosed with hypertension
Very strict								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	**0.69**[*]**(0.48– 0.98)**	0.35 (0.10–1.24)	0.76 (0.54–1.07)	0.83 (0.56–1.23)	0.98 (0.55–1.78)	0.95 (0.70–1.29)	1.13 (0.59–2.20)	1.42 (0.71–2.8)
Strict								
No	**1.00**	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	**0.72**[*]**(0.57– 0.92)**	0.51 (0.17–1.53)	0.73 (0.48–1.12)	0.84 (0.52–1.36)	0.95 (0.46–1.97)	0.87 (0.64–1.22)	1.05 (0.37–3.00)	1.41 (0.51–3.88)

[*] Statistically significant at the 0.05 alpha level

[†] Hazard ratios adjusted for age, sex, race/ethnicity, education, body mass index, and duration of diabetes.

Note: Data from NHANES III (1988–1994)