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All-cause and cardiovascular mortality risk in U.S. adults with and without type 2 diabetes: Influence of physical activity, pharmacological treatment and glycemic control ☆

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ABSTRACT

Aims: This study determined the joint association between physical activity, pharmacotherapy, and HbA1c control on all-cause and cardiovascular disease (CVD) mortality risk in adults with and without type 2 diabetes (T2D).
Methods: 12,060 adults from NHANES III and NHANES continuous (1999–2002) surveys were used. Cox proportional hazards analyses were included to estimate mortality risk according to physical activity, pharmacotherapy, and glycemic control (HbA1c <7.0%) status, with physically active, treated and controlled (goal situation) as the referent.
Results: Compared to the referent, adults with T2D who were uncontrolled, or controlled but physically inactive had a higher all-cause mortality risk ($p < 0.05$). Compared to the referent, only adults with T2D who were physically inactive had a higher CVD mortality risk, regardless of treatment or control status ($p < 0.05$). Normoglycemic adults had a similar all-cause and CVD mortality risk as the referent ($p > 0.05$).
Conclusions: Physical activity and glycemic control are both associated with lower all-cause and CVD mortality risk in adults with T2D. Adults with T2D who are physically active, pharmacologically treated, and obtain glycemic control may attain similar mortality risk as normoglycemic adults.

1. Introduction

Type 2 diabetes (T2D) is an established risk factor for myocardial infarction, stroke, lower extremity amputation, blindness, kidney failure, and premature mortality (Centers for Disease Control & Prevention, 2011). Cardiovascular disease (CVD) is a major complication of T2D and is the leading cause of death in this population (National Institutes of Health, 1995). Type 2 diabetes affects 11.3% of the U.S. adult population, of which 84% are receiving antihyperglycemic therapy (Centers for Disease Control & Prevention, 2011), with approximately half of adults and two thirds of older adults achieving glycemic control as defined as HbA1c <7.0% (53 mmol/mol) (Shaya et al., 2010). For the management of hyperglycemia, pharmacotherapy is recommended, as well as lifestyle modification, which includes participating in regular physical activity (Nathan et al., 2009). Physical activity has been reported to be associated with decreased baseline glycosylated hemoglobin (HbA1c) levels (Umpierre et al., 2011) and decreased mortality risk in individuals with T2D (Hu et al., 2005). There is also substantial evidence that pharmacotherapy for T2D can significantly reduce HbA1c (Inzucchi, 2002). However, evidence regarding mortality outcomes of achieving a controlled HbA1c (<7.0% (53 mmol/mol), is equivocal, as some have reported lower mortality risk (Davidson, 2004; Davila, Florez, Trepka, Fleming, & Niyonsenga, 2011), no effect on mortality risk (Tkac, 2009), as well as increased mortality risk (Boussageon et al., 2011; The ACCORD Study Group, 2011). There is also mixed evidence regarding if antihyperglycemic treatment lowers mortality risk to that of normoglycemic populations (Almdal, Scharling, Jensen, & Vestergaard, 2004; Juutilainen, Lehto, Ronnemaa, Pyorala, & Laakso, 2008; Lutgers, Gerrits, Sluiter, Ubink-Veltmaat, & Landman, 2008).

Although physical activity and pharmacological therapy are both recommended for T2D management, to our knowledge the joint association between physical activity, pharmacological treatment of T2D, and control of HbA1c with mortality risk has not been investigated. Therefore, the objectives of this study were to determine the joint associations between physical activity, antihyperglycemic treatment, and glycemic control on all-cause, and CVD mortality risk.

There are no conflicts of interest to disclose.
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2. Subjects, materials and methods

Data were obtained from persons in the United States who participated in the NHANES III survey (1988–1994; n = 33 994), and NHANES Continuous surveys 1999–2000 (n = 9 965) and 2001–2002 (n = 11 039). A detailed explanation of the data collection methods has been previously reported (Centers for Disease Control, Prevention, and National Center for Health Statistics, 1994; Centers for Disease Control, Prevention, and National Center for Health Statistics, 1999; National Center for Health Statistics, Center for Disease Control and Prevention, 1996). Mortality information for NHANES III and NHANES Continuous survey participants was provided by the National Centre for Health Statistics using probabilistic record matching with death certificate data found in the National Death Index (NCHS Linked Mortality File) through December 31, 2006. All participants gave written informed consent prior to participation, and the methods were approved by the National Centre for Health Statistics. The total number of participants from all three surveys was 54 998. Individuals were excluded if they were considered to have type 1 diabetes as defined as self-report diagnosis of diabetes before the age of 30 and taking insulin since diagnosis (Davila et al., 2011) (n = 148), if they were younger than 40 years (n = 36 910), or if they had missing information for HbA1c (n = 22 287), or years since diagnosis for adults with T2D (n = 1 562), leaving a final sample size of 12 060 men and women for this sample.

During the physical examination, height and weight were measured by a trained technician and BMI was calculated. HbA1c was measured using blood samples via venipuncture and plasma glucose was measured after a 6–12 h fast during the physical examination. In NHANES III only, an oral glucose tolerance test was conducted in mobile center examinees over the age of 40 years. Use of any prescription medications was reported during the household interview and T2D drugs were identified. Individuals reported if they had a doctor's diagnosis of T2D, and the length of time since diagnosis.

Physical activity in NHANES III was assessed as the monthly frequency of the following activities: walking, jogging, biking, swimming, calisthenics, gardening, weight lifting, aerobics, and dancing. Participants could also list up to four additional activities. In the NHANES continuous surveys, respondents reported physical activity frequency in terms of the number of times per day, week, or month, as they preferred. Participants were asked about transportation, home or yard physical activity, or any other moderate or vigorous leisure time activity. For the purpose of this analysis, monthly physical activity from all questionnaires was converted to weekly physical activity. Since it has been shown that engaging in physical activity just once a week is beneficial for mortality risk (Kushi et al., 1997; Sundquist, Qvist, Sundquist, & Johansson, 2004), physically active was defined as participating in ≥1 time/week of physical activity, and physical inactivity was defined as participating in no weekly physical activity.

Questionnaires were used to assess age, sex, education (less than high school, high school, more than high school), ethnicity (white or non-white), and smoking status (current, past, or never). Individuals were considered hypertensive if they had self-reported doctor's diagnosis of hypertension, if they were taking antihypertensive medications, if their systolic blood pressure was ≥ 140 mmHg (> 130 mmHg if had T2D), or if their diastolic blood pressure was ≥90 mmHg (> 80 mmHg if had T2D). Type 2 diabetes was defined as self-reported doctor's diagnosis of T2D, or taking antihyperglycemic drugs, or having an HbA1c of ≥ 6.5% (48 mmol/mol), or a fasting plasma glucose of > 7.0 mmol/L, or a 2-h plasma glucose of > 11.0 mmol/L after an oral glucose tolerance test. Individuals were considered dyslipidaemic if they were taking lipid medications, if their fasted cholesterol was ≥ 6.2 mmol/L, or if their fasted triglycerides were ≥ 2.3 mmol/L. History of cardiovascular disease (CVD) was defined as having a doctor's diagnosis of coronary heart disease, or prior diagnosis of a heart attack or stroke. For the purpose of this analysis, acceptable glucose control was defined as an HbA1c <7.0% (53 mmol/mol), while ≥ 7.0% (53 mmol/mol) was the criterion for uncontrolled glucose. Individuals were classified as either being treated or not being treated with antihyperglycemic drugs. Death was categorized as all-cause, or CVD (ICD-10 codes 53–75).

Group differences in subject characteristics were determined with one-way analysis of variance (ANOVA) and chi-square tests. Cox proportional hazards were used to estimate differences in all-cause and CVD mortality risk, according to physical activity level, antihyperglycemic treatment and HbA1c control. The proportional hazards assumption was verified for all models. Adults with T2D who were physically active, treated and controlled (goal situation) was the referent group. In a separate model hazard ratios stratified by glycemic control were adjusted for HbA1c to determine if baseline HbA1c differed between treatment and physical activity groups. Multivariate analyses were adjusted for age, sex, education, ethnicity, and smoking status in the first model, and then additionally adjusted for dyslipidaemia, CVD, hypertension, BMI, and years since diagnosis in the final, fully adjusted models. All statistical analyses were performed with SAS vs. 9.3 and results were considered statistically significant at $p < 0.05$.

3. Results

The average follow-up time was 9.2 ± 4.9 years, during which there were 3306 (27.4%) all-cause deaths, of which 45.6% were CVD related (n = 1509). Subject characteristics according to physical activity status, glycemic control, and antihyperglycemic treatment are presented in Table 1. There were 1511 (12.5%) adults with T2D, wherein 46% participated in physical activity at least once a week, 43% had glycemic control (HbA1c < 7.0%), and 71% were pharmacologically treated. The average number of years since T2D diagnosis was 10.9 ± 8.8 years. Adults with T2D, who were physically active, treated and controlled, had a higher HbA1c and BMI, and a higher prevalence of hypertension and CVD than normoglycemic adults ($p < 0.05$). All results were similar between the first multivariable model and the fully adjusted model for all-cause and CVD mortality, and thus only results for the fully adjusted models are reported. There were no interaction effects between physical activity, antihyperglycemic treatment, or HbA1c control for all-cause or CVD mortality ($p > 0.05$ for all).

There was a significant main effect of being physically active (all-cause HR, 95% CI = 0.71, 0.66–0.76, $p < 0.001$; CVD 0.64, 0.58–0.72, $p < 0.001$), and having glycemic control (all-cause 0.73, 0.63–0.86, $p < 0.001$; CVD 0.73, 0.58–0.93, $p < 0.01$) but not antihyperglycemic medication usage (all-cause 1.12, 0.96–1.31, $p = 0.14$; CVD 1.18, 0.94–1.47, $p = 0.16$). Adjustment for HbA1c within HbA1c control strata did not alter the significant effects of physical activity and antihyperglycemic treatment on all-cause or CVD mortality risk.

The hazard ratios for all-cause (Fig. 1) mortality risk are presented by physical activity, antihyperglycemic treatment, and HbA1c control. Compared to adults with T2D who were physically active, treated and controlled (goal referent), adults with T2D who were uncontrolled, regardless of physical activity or treatment status, or controlled but physically inactive, had a higher all-cause mortality risk ($p < 0.05$). Physically active, untreated and controlled adults with T2D, and normoglycemic adults, had a similar all-cause mortality risk as compared to the referent ($p > 0.05$) (Fig. 1).

The hazard ratios for CVD (Fig. 2) mortality risk are presented by physical activity, antihyperglycemic treatment, and HbA1c control. Compared to the referent, physically inactive adults with T2D had a higher CVD mortality risk. Conversely, physically active adults had a similar CVD mortality risk, regardless of treatment or control status ($P > 0.05$). Normoglycemic adults had a similar CVD mortality risk as the referent regardless of physical activity status ($p > 0.05$) (Fig. 2).