Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Glycaemic control in people with diabetes influences the beneficial role of physical activity on cardiovascular mortality. Prospective data from the HUNT Study, Norway

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ARTICLE INFO

Article history:
Received 13 August 2014
Received in revised form
8 April 2015
Accepted 22 April 2015
Available online 19 May 2015

Keywords:
Cardiovascular mortality
Epidemiology
Diabetes
Physical activity
Glycaemic control

ABSTRACT

Aim: To examine whether glycaemic control in people with diabetes, measured as glycated haemoglobin (HbA_{1c}), influences the role of leisure time physical activity on the increased risk of death from cardiovascular disease.

Methods: We prospectively examined the joint association of diabetes according to glycemic control, measured as glycated haemoglobin (HbA_{1c}), and physical activity with cardiovascular mortality. A total of 53,549 were followed up for 12 years through the Norwegian Cause of Death Registry. Cox proportional adjusted hazard ratios (HRs) with 95% confidence intervals (CI) were estimated.

Results: Overall, 1710 people died from cardiovascular disease during the follow-up. Compared to the reference group of inactive people without diabetes, people with diabetes and $HbA_{1c} < 8.0\%$, had a hazard ratio (HR) of 1.46 (95% CI: 0.96, 2.21) if they were physically inactive and a HR of 1.33 (95% CI: 0.81, 2.19) if they were physically active. Among people with diabetes and $HbA_{1c} \geq 8.0\%$, the corresponding comparison gave HRs 2.69 (95% CI: 2.11, 3.42) and 0.93 (95% CI: 0.64, 1.36), respectively.

Conclusions: The data suggest that physical activity should be more strongly encouraged as a therapeutic measure additional to medical treatment, especially among those with most severe hyperglycemia.

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http://dx.doi.org/10.1016/j.pcd.2015.04.007
1751-9918/

1. Introduction

Diabetes approximately doubles the risk of death from cardiovascular disease [1–6], with the highest risk among those with most severe hyperglycaemia [7–10].

Physical activity is recommended in the management of diabetes [11,12] and may improve glycaemic control, insulin sensitivity, as well as conventional cardiovascular risk factors such as blood pressure and blood lipids [13–16]. Studies have shown that people with diabetes who are physically active have substantially lower risk of death from cardiovascular disease, compared to inactive people with diabetes [17,18]. In a recent study, we found that even modest physical activity may cancel out the excess risk of cardiovascular death associated with diabetes [19]. However, whether the beneficial effect of leisure time physical activity on cardiovascular mortality among people with diabetes is modified by glycemic control, is not known.

The objective of this large population-based cohort study was therefore to assess whether glycaemic control in people with diabetes, measured as glycated haemoglobin (HbA_{1c}), influences the role of leisure time physical activity on the increased risk of death from cardiovascular disease.

2. Materials and methods

2.1. Subjects

The HUNT Study is a large population-based health study in Nord-Trøndelag County in Norway. Between 1995 and 1997, all inhabitants aged 20 years or older (94,194) were invited to participate in the second wave of the study (HUNT2 Survey) and a total of 64,961 (70%) accepted the invitation, completed questionnaires, and attended a clinical examination. All participants in the HUNT2 Survey gave a written informed consent upon participation and the Survey was recommended by the Regional Committee for Ethics in Medical Research, and approved by the Norwegian Data Inspectorate For the purpose of the present study, a total of 11,412 participants were excluded at baseline; 5186 who reported prevalent cardiovascular disease (angina, myocardial infarction, and/or stroke), 108 without sufficient information on diabetes (diagnosis and/or HbA_{1c}), 5630 without information on leisure time physical activity, and 488 without information on potentially confounding factors (i.e. systolic blood pressure, total serum cholesterol or body mass index). After these exclusions, 53,549 participants (25,139 men and 28,410 women) were available for statistical analyses. Compared to participants included in the study, the 6226 persons with missing information on central variables were on average older (mean age 63.6 versus 46.4 years).

2.2. Follow-up

Individual person time at risk of death was calculated from the date of participation in HUNT2 (1995–1997) until the date of death or until the end of follow-up (31st December 2008), whichever occurred first. The mandatory reporting of death to the Cause of Death Registry in Norway constitutes the basis for the coding of underlying cause of death. Deaths were classified according to the International Classification of Disease (ICD-9 and ICD-10). Cardiovascular disease was defined by ICD-9: 390–459 and ICD-10: I00–I99.

2.3. Study variables

A detailed description of selection procedures, questionnaires, and measurements can be found at http://www.ntnu.edu/hunt and in a report by Holmen et al. [20]. Briefly, information was collected on a range of lifestyle and health related factors, including medical history, physical activity, smoking status, alcohol consumption and educational attainment. At the clinical examination, standard anthropometric measures were obtained in standing subjects without shoes and outdoor clothing (height to the nearest centimetre, weight to the nearest half kilogram, and waist and hip circumferences to the nearest centimetre). Body mass index was calculated as weight (kg) divided by the squared value of height (m). Blood pressure was measured three times using a Dinamap 845XT (Critikon, Tampa, USA), and the mean of the second and third measure was calculated. A non-fasting whole blood sample was drawn from all participants at the screening site. Blood was separated by centrifuging before the serum samples were transported in a cooler to the Central Laboratory at Levanger Hospital and analyzed on a Hitachi 911 Auto-analyzer (Hitachi, Mito, Japan). Glucose was measured using an enzymatic hexokinase method and total cholesterol using an enzymatic colorimetric cholesterolesterase method.

2.3.1. Diabetes and glucose measures

Participants who answered 'Yes' to the question 'Do you have or have you had diabetes?' were defined as having diabetes ($N = 1002$). Among these, an extra tube of whole blood was drawn for analyses of glycated haemoglobin (HbA_{1c}). For the purpose of the statistical analyses, we stratified people with diabetes into two groups according to their measured HbA_{1c}: $HbA_{1c} \geq 8.0$ and $HbA_{1c} < 8.0$. The cut-off was chosen because it provided the necessary statistical power for the analyses and because the mean HbA_{1c} value was 8% among the people with diabetes. Those confirming diabetes in the questionnaire were also invited to a follow-up investigation. A total of 783 individuals took part in these investigations, where blood glucose, serum C-peptide and GADA were measured in a fasting state. In addition, GADA was analyzed in cases declaring diabetes but not attending the follow-up and having serum available from a non-fasting state ($N = 182$). Among those attending the follow-up information, those with an anti-GAD level > 8.0 or an anti-GAD < 8.0 and/or a C-peptide < 150 pmol/l were classified as having type 1 diabetes. Among those not attending the follow-up, only the former diagnostic criteria (anti-GAD level > 8.0) were used to classify type 1 diabetes. This resulted in a total of 172 persons being classified as having type 1 diabetes.

2.3.2. Leisure time physical activity

Information on leisure time physical activity was obtained from the standard questionnaire. Participants were asked to report their usual weekly hours of light and/or hard leisure time physical activity during the past year, with four response