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ARTICLE

HbA_{1c} as predictor of all-cause mortality in individuals at high risk of diabetes with normal glucose tolerance, identified by screening: a follow-up study of the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION), Denmark

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Abstract
Aims/hypothesis Stepwise screening for type 2 diabetes will not only identify people with the disease or some other form of dysglycaemia (impaired fasting glucose or impaired glucose tolerance), but also many individuals who are phenotypically at high risk of developing diabetes, but currently have normal glucose tolerance (NGT). We therefore sought to assess whether HbA_{1c} adds prognostic information in relation to all-cause mortality in people who have NGT and a high risk of type 2 diabetes mellitus.
Methods In a Danish population-based stepwise screening programme for type 2 diabetes mellitus in general practice, we identified 15,634 persons at high risk of type 2 diabetes, who had NGT and a recorded HbA_{1c} measurement. As comparison groups, we included 1,401 people identified as having type 2 diabetes mellitus and 8,149 individuals characterised as being at low risk of diabetes. All individuals were followed from time of screening (April 2001 to December 2006) until death or 31 October 2009. Excess mortality was estimated using Cox proportional hazard models with all-cause mortality as the outcome measure.
Results Compared with individuals with NGT and HbA_{1c} below 6.0%, adjusted hazard ratios were: 1.21 (95% CI 0.95–1.56) for individuals with NGT and HbA_{1c} between 6.0% and 6.5%; 2.48 (95% CI 1.23–4.99) for individuals with NGT and HbA_{1c} 6.5% or above (in this group there were eight deaths among 68 individuals); 1.73 (95% CI 1.40–2.13) for individuals with type 2 diabetes mellitus.
Conclusions/interpretation HbA_{1c} level in people with NGT and at high risk of diabetes was clearly associated with increased all-cause mortality.

Keywords All-cause mortality · HbA_{1c} · Screening · Type 2 diabetes mellitus

Abbreviations

2hBG	2 h Blood glucose
ADDITION	The Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care
FBG	Fasting blood glucose
GP	General practitioner
ICD	International Classification of Diseases
NGT	Normal glucose tolerance

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Introduction

Stepwise screening for type 2 diabetes has been implemented in several countries following recommendations from international organisations [1–3]. This strategy will not only identify people with type 2 diabetes mellitus or some other form of dysglycaemia (impaired fasting glucose or impaired glucose tolerance), but also many individuals who have normal glucose tolerance (NGT) but are nevertheless phenotypically at high risk of developing diabetes due to one or more of the following: physical inactivity, high BMI, high amount of abdominal fat, family history of diabetes, hypertension or dyslipidaemia.

Some studies have demonstrated that HbA_{1c} is a risk factor for all-cause mortality in individuals with no prior diagnosis of diabetes [4–8]. In stepwise screening for type 2 diabetes mellitus, HbA_{1c} is often measured. Consequently, it could be beneficial to include HbA_{1c} in further risk stratification of individuals phenotypically at high risk of developing diabetes, potentially separating people into a very high-risk group and a group with 'near-normal' risk. Thus our aim was to study whether HbA_{1c} adds prognostic information in relation to all-cause mortality in people with NGT and at high risk of diabetes.

Methods

Study design The Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION) is a population-based, stepwise screening and intervention study for type 2 diabetes mellitus in general practice [9]. People from the Danish part of the ADDITION study are included in this paper. The study was approved by the local ethics committees and conducted in accordance with the Declaration of Helsinki, with participants giving written informed consent. Screening started in April 2001 and ended in December 2006. In Denmark, the screening process was a stepwise, high-risk strategy, including persons aged 40 to 69 years who were registered with the 190 participating practices in five counties in Denmark (Copenhagen, Ringkøbing, Ribe, South Jutland and Aarhus County). The individuals who met the inclusion criteria received an invitation with a risk score questionnaire. The questionnaire featured questions about sex, age, family history of diabetes, BMI, leisure time physical activity and whether respondents had (1) had diabetes that disappeared again and (2) been told that they had high blood pressure [10]. Persons at high risk of diabetes were advised to contact their general practitioner (GP) for further tests [10, 11]. In the second step, random capillary whole-blood glucose and HbA_{1c} were measured and individuals with the former ≥5.5 mmol/l or the latter ≥5.8% were invited for diagnostic testing, while the remaining participants were classified as having NGT and had no further tests. Step three was diagnostic testing for diabetes mellitus and included measurement of fasting blood glucose (FBG) (capillary whole blood; after at least 8 h fasting). An OGTT was performed on everyone with HbA_{1c} ≥5.8% or FBG 5.6 to 6.1 mmol/l. Capillary whole-blood samples were used to determine 2 h blood glucose (2hBG). All individuals with one diabetic value (FBG ≥6.1 and/or 2hBG ≥11.1 mmol/l) were re-invited for a confirmatory diagnostic test in accordance with WHO recommendations [12]. Individuals with FBG ≥6.1 and/or 2hBG ≥11.1 mmol/l on two different days were categorised as having type 2 diabetes mellitus. People with FBG <5.6 mmol/l and 2hBG <7.8 mmol/l were categorised as having NGT and pooled with individuals who had been categorised as NGT at the second step of the screening programme.

Capillary whole-blood glucose was analysed using a glucose analyser (HemoCue, Angelholm, Sweden). Calibration stability was checked on a daily basis using control cuvettes. All machines were registered with the HemoCue quality assurance scheme and calibrated externally at the start of screening and at regular intervals thereafter. The average result of two samples was used for diagnostic tests of type 2 diabetes mellitus (FBG and 2hBG after OGTT).

HbA_{1c} was analysed in venous blood at one of two laboratories (Aarhus County Hospital, Aarhus, Denmark or Steno Diabetes Center, Gentofte, Denmark). All samples were analysed on the day of arrival using ion-exchange high-performance liquid chromatography (Tosoh, Tokyo, Japan) (normal range 4.2–6.3%).

All 15,634 persons who fully attended the screening steps described above and were found to have NGT were included. As comparison groups we included 1,401 people identified as having type 2 diabetes mellitus and 8,149 individuals characterised as being at low risk of type 2 diabetes (on the basis of risk score questionnaire) stemming from a subsample of the invited population who had been asked to complete and return the risk score questionnaire regardless of their assessed risk [11].

All participants at high risk of diabetes had blood pressure, height and body weight registered at their first consultation (second screening step), and were asked to fill in a questionnaire about lifestyle, including smoking habits. To adjust for possible confounding resulting from comorbidity, we performed record-linkage with the Danish National Hospital Discharge Register (which covers all hospitalisations in Denmark), thus identifying all cases prior to screening of ischaemic heart disease (IHD) (International Classification of Diseases version 10 [ICD-10; www.who.int/classifications/icd/en/, accessed 1 March 2010]

I25.0–25.9), cerebrovascular disease (ICD-10: 60.0–69.8) and cancer (ICD-10: C00.0–97.9).

People at low risk of diabetes did not need to visit a GP, so we only have information on age and sex for this group.

Statistical analysis To estimate the prognostic impact of HbA_{1c} among individuals with NGT and at high risk of diabetes, those categorised as NGT were divided into three groups reflecting their HbA_{1c} level: HbA_{1c} <6.0%, 6.0% to <6.5% and ≥6.5%. Based on the unique Danish civil registration number, all individuals included were electronically linked to the nationwide Danish Civil Registration System (which comprises all Danes) to obtain information on death and/or emigration, and dates of those events. Survival was estimated by the Kaplan–Meier method. Possible excess mortality for individuals with NGT and at high risk of diabetes stratified by HbA_{1c} compared with individuals at low risk of diabetes were estimated with 95% CIs using Cox proportional hazard models. Adjustment was made for age and sex. Similarly, we estimated possible excess mortality for the different HbA_{1c} groups among individuals with NGT and at high risk of diabetes. Participants found to have type 2 diabetes mellitus at screening were included as a comparison group. Adjustment was made for age, sex, BMI, smoking, systolic BP, prior IHD, prior cerebrovascular disease and prior cancer. A stratified analysis with further adjustment for total cholesterol was performed on the 13,038 individuals included who had a cholesterol measurement.

The proportionality assumption was assessed graphically and tested using Schoenfeld residuals for each model.

The following variables were included as categorical: sex (male or female), smoking habits (smoker or non-smoker [including ex-smokers]), previous IHD (yes or no), previous cerebrovascular disease (yes or no) and previous cancer (yes or no). Time since screening was used as the time scale for individuals with NGT or type 2 diabetes mellitus; time since receipt of risk score questionnaire was used for people at low risk for diabetes. Each person was followed until death, emigration (censoring) or 31 October 2009, whichever came first. Analyses were performed using Stata version 10.1 (StataCorpLP, College Station, TX, USA).

Results

Baseline characteristics are shown in Table 1. The median follow-up time per individual was close to 2,500 days and did not differ between groups. In total 798 deaths occurred among individuals with NGT, 169 among individuals at low risk of diabetes and 118 among individuals with type 2 diabetes mellitus.

Mortality by HbA_{1c} level The impact of HbA_{1c} was analysed only in individuals with NGT, but with inclusion of two comparison groups, namely those at low risk of diabetes and those found to have type 2 diabetes mellitus. After stratification, individuals with an HbA_{1c} of 6.5% or above had lower survival and thereby higher all-cause mortality than all other groups (Fig. 1). HRs for individuals at low risk of diabetes and individuals with HbA_{1c} at 6.0% or below as respective reference groups are given in Table 2. Composed with individuals at low risk of diabetes and adjusting for age and sex, the highest HR was found for individuals with NGT and HbA_{1c} at 6.5% or above (HR 2.87, 95% CI 1.40–5.86). Likewise, composed with individuals found to have NGT and HbA_{1c} <6.0%, while adjusting for other potential confounders (i.e. besides age and sex: BMI, smoking, systolic BP, previous IHD, previous cerebrovascular disease and previous cancer), the highest HR was found for individuals with NGT and HbA_{1c} at 6.5% or above (HR 2.48, 95% CI 1.23–4.99). For both reference groups, and for the respective adjustments, we found a dose–response relationship between level of HbA_{1c} and mortality, although it was not statistically significant.

Within the group of high-risk individuals, further adjustment for total cholesterol produced similar results to those reported in Table 2 (data not shown).

Discussion

In this study the HbA_{1c} level was a significant predictor of mortality. Individuals with NGT, but with HbA_{1c} at 6.5% or above, and at high risk of diabetes had substantially increased all-cause mortality. Although, due to the low number of individuals with HbA_{1c} at 6.5% or above, our results are subject to some uncertainty, they do support previous findings of chronic hyperglycaemia being harmful [5, 13, 14] and also stress the significance of HbA_{1c} levels in the identification of risk groups. Carotid intima–media thickness is a well-established index of early atherosclerosis and is widely used as surrogate marker of cardiovascular disease [15]. A recent study found an independent relationship between HbA_{1c} and carotid intima–media thickness in individuals with NGT [16], although the former only contributed 4.4% to the variation of the latter. The authors suggest that glycaemic control might have a pathophysiological relevance in the development of atherosclerosis, even in individuals with NGT. It is not known whether cardiovascular disease is the main reason for the increased all-cause mortality in the present study. An international expert committee recently suggested use of HbA_{1c} as a diagnostic test for diabetes [17]. In the present study we found that individuals with NGT and HbA_{1c} at 6.5% or above have the same mortality as individuals with

Table 1 Characteristics of individuals included

Characteristic	NGT			Low risk of type 2 diabetes	Diagnosed with type 2 diabetes
	HbA_{1c} <6.0%	HbA_{1c} 6.0–6.4%	HbA_{1c} ≥6.5%		
n	14,521	1,045	68	8,149	1,401
Age (years)	58 (53–63)	60 (55–64)	61 (54–65)	48 (45–53)	59 (54–63)
Sex					
Women (%)	48.6	50.7	54.4	62.9	43.3
Men (%)	51.4	49.3	45.6	37.1	56.7
Smoking					
Yes (%)	28.9	45.0	41.2	–	35.2
No (%)	71.1	55.0	58.8	–	64.8
BMI (kg/m^2)	26.9 (24.4–29.6)	27.8 (25.0–30.7)	27.8 (23.8–33.0)	–	30.9 (27.5–34.3)
Systolic BP (mmHg)	135 (125–150)	135 (124–150)	130 (120–140)	–	140 (130–155)
IHD, *n* (%)[a]	671 (4.6)	65 (6.2)	8 (11.8)	–	120 (8.6)
Cerebrovascular disease, *n* (%)[a]	289 (2.0)	28 (2.7)	5 (7.4)	–	34 (2.4)
Cancer, *n* (%)[a]	655 (4.5)	49 (4.7)	2 (2.9)	–	56 (4.0)
HbA_{1c} (%)					
<6.0, *n* (%)	14,521 (100)	0 (0)	0 (0)	–	264 (19.3)
6.0– to <6.5, *n* (%)	0 (0)	1,045 (100)	0 (0)	–	428 (31.2)
6.5– to <7.0, *n* (%)	0 (0)	0 (0)	64 (94.1)	–	265 (19.3)
≥7.0, *n* (%)	0 (0)	0 (0)	4 (5.9)	–	413 (30.1)
FBG (mmol/l)	4.9[b] (4.6–5.2)	5.0 (4.7–5.2)	5.0 (4.7–5.3)	–	6.9 (6.4–7.8)
2hBG (mmol/l)	6.1[c] (5.2–6.7)	6.0 (5.1–6.8)	6.3 (5.4–7.0)	–	12.3 (10.5–14.0)
Follow-up (days)					
Median (min–max)	2,719 (16–3,142)	2,407 (82–3,134)	2,263 (253–3,078)	2,550 (1–3,092)	2,327 (133–3,139)
Total	34,861,329	2,414,179	150,343	20,501,495	3,081,405
Deaths, *n* (%)	721 (5.0)	69 (6.6)	8 (11.8)	169 (2.1)	118 (8.4)

Values are median (quartiles) unless indicated otherwise

[a] Prior screening

[b] Measurements from 5,919 individuals

[c] Measurements from 1,745 individuals

screen-detected type 2 diabetes mellitus. This supports the proposed use of HbA_{1c} at 6.5% or above as the threshold for diabetes when considering individuals who have NGT yet are at high risk of diabetes.

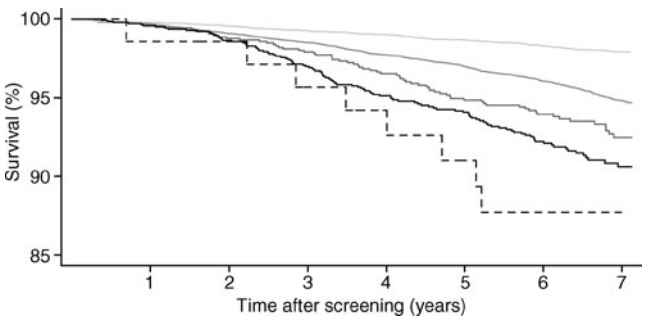

Fig. 1 Kaplan–Meier curves for all-cause mortality. Light grey line, low risk; medium grey line, NGT, HbA_{1c} <6.0%; dark grey line, NGT, HbA_{1c} 6.0– to <6.5%; black line, type 2 diabetes; dashed line, NGT, HbA_{1c} ≥6.5%

One strength of this study is that all individuals with HbA_{1c} at 6.0% or above had FBG measured and almost all had an OGTT (55 individuals with HbA_{1c} between 6.0 and 6.5% and one with HbA_{1c} above 6.5% had no OGTT performed. All of these 56 individuals had FBG below 5.6 mmol/l), ensuring that individuals categorised as NGT and with HbA_{1c} at 6.0% or above did not have dysglycaemia at screening. Other strengths are that this study was large, involving 15,634 individuals with NGT and at high risk of diabetes, and that the screening process was in accordance with a stepwise, high-risk strategy as recommended by international organisations, as well as by health authorities in certain countries. Follow-up moreover was complete, an achievement made possible by the unique personal Danish identification code and our access to record linkage with major national registries of vital status, emigration and hospitalisations [18, 19]. All measurements of BP, height and weight were standardised. Glucose was

Table 2 HRs for all-cause mortality according to HbA_{1c} level

Variable	*n*	Deaths (*n*)	Low-risk as reference group Adjusted HR[a] (95% CI)	Within the group of high-risk individuals Adjusted HR[b] (95% CI)
Low risk	8,149	169	1	–
NGT				
HbA_{1c} <6.0%	14,521	721	1.14 (0.94–1.39)	1
HbA_{1c} 6.0– to <6.5%	1,045	69	1.51 (1.12–2.03)	1.21 (0.95–1.56)
HbA_{1c} ≥6.5%	68	8	2.87 (1.40–5.86)	2.48 (1.23–4.99)
Type 2 diabetes	1,401	118	2.08 (1.61–2.69)	1.73 (1.40–2.13)

[a] Adjusted for age and sex; [b] adjusted for age, sex, BMI, smoking, systolic BP, IHD (prior to screening), cerebrovascular disease (prior to screening) and cancer (prior to screening)

measured locally by the GP, but using standardised equipment, quality control procedures and duplicate measurements that minimise measurement error to a level where the quality is comparable to that achieved in centralised laboratories [20]. HbA_{1c} analyses were done in one of two centralised laboratories.

A main limitation of the study is the small number of individuals with NGT and HbA_{1c} at 6.5% or above. Because of the small sample size in this group, the results are subject to some uncertainty. Another limitation is that people at high risk of diabetes and with HbA_{1c} below 5.8% and random blood glucose below 5.5 mmol/l did not have FBG measured or an OGTT performed; neither was an OGTT performed in individuals with HbA_{1c} below 5.8% and FBG below 5.6 mmol/l. Therefore we do not know whether some of those categorised as NGT with HbA_{1c} below 5.8% actually had some kind of dysglycaemia. If that were the case, then we have included individuals with dysglycaemia in the group of NGT individuals with HbA_{1c} below 6.0%. People with dysglycaemia are expected to have higher mortality than those with NGT and thereby the true mortality among NGT individuals with HbA_{1c} below 6.0% might be lower than that reported here. However, we expect the number of misclassified individuals to be very small. HbA_{1c} was measured centrally (and hence uniformly), while systolic BP was measured by the different GPs. Consequently, the effect of HbA_{1c} might be overestimated, while the effect of systolic BP might be underestimated. Since all GPs were expected to follow the guidelines for good clinical practice when measuring systolic BP, we expect this bias to be small. Smoking was assessed entirely on the basis of self-reported data. This might cause a misclassification of smoking status. Such a misclassification is most likely to have occurred randomly with regard to HbA_{1c} level, glucose tolerance status and mortality.

We have no information on lifestyle changes, pharmacological treatment, progression from NGT to type 2 diabetes mellitus or some other form of dysglycaemia, or on any changes in the included variables during follow-up. These considerations, however, are of great importance when investigating why people with NGT but at high risk of diabetes and with raised HbA_{1c} have high all-cause mortality.

The ADDITION study [9] focuses on people found to have type 2 diabetes mellitus. Due to initiation of lifestyle changes and pharmacological treatment, we did not include information on HbA_{1c} for individuals found to have type 2 diabetes mellitus. Thus this study does not determine whether HbA_{1c} is a predictor of mortality in individuals with type 2 diabetes mellitus. Approximately half of the individuals with type 2 diabetes mellitus in this study are enrolled in the intensive pharmacological intervention arm of the ADDITION study, and we expect that almost all individuals with type 2 diabetes mellitus will have received some kind of treatment during follow-up. This will probably have influenced their survival . Relevant results from the ADDITION study will be published in 2010.

The proportion of individuals with HbA_{1c} at 6.5% or above among individuals with NGT was low (in a total study population of 15,634 individuals with NGT and at high risk of diabetes, we found 68 individuals with HbA_{1c} at 6.5% or above). In the present study, measurement of HbA_{1c} was an integrated part of a step-wise screening programme for type 2 diabetes mellitus, for which reason identification of individuals with NGT and HbA_{1c} at 6.5% or above introduced no extra cost. Henceforth, when deciding whether to include HbA_{1c} in the identification of individuals with high mortality, economic considerations and clinical utility will have to be taken into account.

This study adds new and important information to consider when deciding on guidance and potential treatment of individuals at high risk of diabetes who are enrolled in targeted stepwise screening for type 2 diabetes mellitus and found to have NGT. In short, HbA_{1c} had a prognostic value for all-cause mortality in individuals at high risk of diabetes but with NGT. For individuals with HbA_{1c} at 6.5% or above, the mortality was just as high as for individuals with treated screen-detected type 2 diabetes

mellitus, although the sample sizes are small and these findings may be due to chance or underlying confounding factors that we have not accounted for. If the association is causal, we urge added awareness of individuals at high risk of diabetes and identified as having NGT during targeted screening for type 2 diabetes mellitus. This applies particularly to individuals with HbA_{1c} at 6.5% or above. New studies are needed to support our findings and to determine why this group has a high mortality rate.

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Duality of interest K. Borch-Johnsen is head of the Steno Diabetes Center, a hospital integrated in the Danish National Healthcare Service, but owned by Novo Nordisk, and holds shares in Novo Nordisk. During the last 5 years K. Borch-Johnsen has received honoraria for invited lectures from sanofi-aventis, the American Diabetes Association and academic societies. T. Lauritzen has received honoraria for invited lectures from industry, approximately €5,000, during the past year; he also holds shares in Novo Nordisk. A. Sandbaek and M. V. Skriver declare that for them there is no duality of interest associated with this manuscript.

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