Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk)

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Abstract

Objective To examine the value of glycated haemoglobin (HbA_{1c}) concentration, a marker of blood glucose concentration, as a predictor of death from cardiovascular and all causes in men.
Design Prospective population study.
Setting Norfolk cohort of European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk).
Subjects 4662 men aged 45-79 years who had had glycated haemoglobin measured at the baseline survey in 1995-7 who were followed up to December 1999.
Main outcome measures Mortality from all causes, cardiovascular disease, ischaemic heart disease, and other causes.
Results Men with known diabetes had increased mortality from all causes, cardiovascular disease, and ischaemic disease (relative risks 2.2, 3.3, and 4.2, respectively, $P < 0.001$ independent of age and other risk factors) compared with men without known diabetes. The increased risk of death among men with diabetes was largely explained by HbA_{1c} concentration. HbA_{1c} was continuously related to subsequent all cause, cardiovascular, and ischaemic heart disease mortality through the whole population distribution, with lowest rates in those with HbA_{1c} concentrations below 5%. An increase of 1% in HbA_{1c} was associated with a 28% ($P < 0.002$) increase in risk of death independent of age, blood pressure, serum cholesterol, body mass index, and cigarette smoking habit; this effect remained (relative risk 1.46, $P = 0.05$ adjusted for age and risk factors) after men with known diabetes, a HbA_{1c} concentration ≥7%, or history of myocardial infarction or stroke were excluded. 18% of the population excess mortality risk associated with a HbA_{1c} concentration ≥5% occurred in men with diabetes, but 82% occurred in men with concentrations of 5%-6.9% (the majority of the population).
Conclusions Glycated haemoglobin concentration seems to explain most of the excess mortality risk of diabetes in men and to be a continuous risk factor through the whole population distribution. Preventive efforts need to consider not just those with established diabetes but whether it is possible to reduce the population distribution of HbA_{1c} through behavioural means.

Introduction

The global prevalence of diabetes is predicted to rise from 135 million in 1995 to 300 million by 2025.[1–3] In the United Kingdom, diabetes and associated complications cost the NHS £4.9bn a year, about a tenth of its entire budget.

Various blood glucose threshold concentrations have been proposed for the diagnosis of diabetes,[4–7] based on the relation to risk of microvascular complications of diabetes, particularly retinopathy.[8] However, people with diabetes are also at increased risk of macrovascular diseases such as coronary heart disease and stroke,[9] and it is uncertain whether the relation between blood glucose concentration and such diseases has a threshold or is a continuum.

Glycated haemoglobin (HbA_{1c}) concentration is an indicator of average blood glucose concentration over three months and has been suggested as a diagnostic or screening tool for diabetes.[8 10] Meta-regression analyses of several studies suggest a continuous relation between fasting or two hour glucose concentration and macrovascular events even below accepted thresholds for diabetes, but data for glycated haemoglobin have been limited by the few prospective studies in which it has been measured in people without diabetes.

We examined the relation between glycated haemoglobin concentrations, diabetes, and subsequent mortality in men.

Participants and methods

We studied men in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition. The cohort comprises 25 623 men and women aged 45-79 years resident in Norfolk, recruited from general practice age-sex registers.[11] Additional data were collected for the Norfolk cohort to enable us to examine the determinants of chronic disease. At the baseline survey between 1993 and 1997

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participants completed a detailed health and lifestyle questionnaire. People with established diabetes were defined as those who responded "yes" to the diabetes option of the question: "Has a doctor ever told you that you have any of the following?" followed by a list of conditions including diabetes, heart attack, and stroke. Smoking history was derived from responses to the questions "Have you ever smoked as much as one cigarette a day for as long as a year?" and "Do you smoke cigarettes now?"

Participants attended a health examination carried out by trained nurses. Body mass index was estimated as weight (kg)/(height (m))^2. Blood pressure was measured with an Accutorr blood pressure monitor[12] after the participant had been seated resting for five minutes; the mean of two readings was used for analysis. Plasma and serum samples were obtained from blood taken by venepuncture. From November 1995, an additional EDTA-anticoagulated blood sample was taken for measurement of HbA_{1c}. Blood samples were assayed at the department of clinical biochemistry, Cambridge University. Serum total cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations were measured by colorimetry (RA 1000, Bayer Diagnostics, Basingstoke), and low density lipoprotein cholesterol concentrations were calculated by the Friedewald formula.[13] Glycated haemoglobin assays used a Biorad Diomat high pressure liquid chromatography analyser. The coefficient of variation was 3.6%.

All participants were flagged for death certification at the Office of National Statistics. We present results for mortality follow up to December 1999. Death certificates were coded by trained nosologists at the Office of National Statistics according to the International Classification of Disease (ICD), 9th revision. Cardiovascular death was defined as ICD 400-438 and ischaemic heart disease death as ICD 410-414 anywhere on the death certificate.

The study was approved by the Norwich District Health Authority ethics committee, and all participants gave signed informed consent.

The analysis reported here includes all men aged 45-79 years who completed the baseline health examination and had HbA_{1c} measured. There were not enough events in women with HbA_{1c} measurements for robust analyses. We divided the men into five categories: those with established diabetes, those with previously undiagnosed diabetes (defined as those without a history of diabetes but with a HbA_{1c} concentration $\geq 7\%$[8]), and then the remainder by approximate thirds of HbA_{1c} concentration using clinically applicable cut off points. We calculated age adjusted death rates by cause in these categories using χ^2 for linear trend to assess statistical significance.[14] We used the Cox proportional hazards model to determine the contribution of risk factors to mortality.[15]

We also calculated the population distribution of HbA_{1c} concentration and diabetes and estimated the population attributable risk associated with diabetes or HbA_{1c} above the lowest category less than 5%, assuming the death rates for those with a HbA_{1c} concentration less than 5% applied to the whole population.

Results

Table 1 shows the characteristics of the 4662 men according to concentration of HbA_{1c} and self reported diabetes. Men with self reported diabetes or previously undiagnosed diabetes were older and had higher levels of risk factors for cardiovascular disease than the rest of the population.

Table 2 shows age adjusted mortality by concentration of HbA_{1c} and self reported diabetes. Men with established or undiagnosed diabetes had greater risk of dying from all causes, cardiovascular disease, or ischaemic heart disease compared with men without diabetes. Risk of death increased through the range of HbA_{1c} concentrations, with lowest rates in those with HbA_{1c} concentrations less than 5% and a gradient of increasing rates through the whole distribution.

Table 3 shows the independent multivariate relation between HbA_{1c} concentration or diabetes status and mortality with the Cox proportional hazards model after adjustment for age alone and for age, systolic blood pressure, serum cholesterol concentration, body mass index, cigarette smoking habit, and history of myocardial infarction or stroke. In separate models diabetes status significantly predicted death from all causes, cardiovascular disease, and ischaemic heart disease and HbA_{1c} concentrations predicted all cause, cardiovascular, ischaemic heart disease, and

Table 1 Characteristics of study population by concentration of glycated haemoglobin and self reported diabetes. Values are mean (SD) unless stated otherwise

	Glycated haemoglobin (%)				Self reported diabetes (n=160)
	<5 (n=1204)	5-5.4 (n=1606)	5.5-6.9 (n=1611)	≥7 (n=81)	
Age (years)	57.5 (8.6)	58.8 (9.0)	61.1 (8.5)	64.0 (7.9)	64.4 (7.4)
HbA_{1c} (%)	4.57 (0.34)	5.20 (0.14)	5.82 (0.31)	8.35 (1.52)	7.98 (1.87)
Body mass index (kg/m^2)	26.2 (3.0)	26.5 (3.2)	26.8 (3.5)	28.6 (3.4)	27.7 (3.8)
Systolic blood pressure (mm Hg)	136.3 (16.7)	136.9 (16.8)	138.4 (17.7)	143.8 (16.0)	143.4 (19.3)
Diastolic blood pressure (mm Hg)	84.8 (10.6)	84.7 (10.9)	85.2 (11.1)	87.3 (10.2)	86.2 (12.5)
Cholesterol (mmol/l)	5.88 (1.07)	6.01 (1.04)	6.11 (1.10)	6.22 (1.04)	5.9 (1.21)
LDL cholesterol (mmol/l)	3.81 (0.94)	3.89 (0.95)	3.95 (0.94)	3.90 (0.93)	3.65 (10.2)
HDL cholesterol (mmol/l)	1.26 (0.34)	1.26 (0.36)	1.24 (0.33)	1.10 (0.28)	1.15 (0.28)
Triglycerides (mmol/l)	1.91 (1.08)	2.00 (1.12)	2.14 (1.27)	2.80 (1.78)	2.60 (1.78)
Cigarette smoking habit (No (%))					
Never	476 (39.8)	564 (35.4)	448 (27.9)	21 (25.9)	31 (19.5)
Former	620 (51.8)	860 (54.0)	881 (55.0)	50 (61.7)	116 (73.0)
Current	100 (8.4)	168 (10.6)	274 (17.1)	10 (12.3)	12 (7.5)
No (%) with history of heart attack or stroke	50 (4.2)	89 (5.5)	142 (8.8)	15 (18.5)	32 (20.0)

P<0.001 for differences between categories for all variables except diastolic blood pressure.

Table 2 Age adjusted rates for all cause, cardiovascular, ischaemic heart disease, and non-cardiovascular death by glycated haemoglobin concentration and self reported diabetes in men aged 45-79 years, 1995-9

Cause of death	Glycated haemoglobin (%) <5 (n=1204)	5-5.4 (n=1606)	5.5-6.9 (n=1611)	⩾7 (n=81)	Self reported diabetes (n=160)	χ^2 (linear trend), P value
All causes (n=135)						
Age adjusted rate/100 (No of events)	1.65 (18)	2.33 (35)	3.43 (61)	4.35 (5)	5.92 (16)	40.8,
Relative risk	1.00	1.41	2.07	2.64	3.59	<0.001
Cardiovascular disease (n=60)						
Age adjusted rate/100 (No of events)	0.50 (5)	1.27 (19)	1.24 (22)	2.54 (3)	4.11 (11)	31.8,
Relative risk	1.00	2.53	2.46	5.04	8.16	<0.001
Ischaemic heart disease (n=42)						
Age adjusted rate/100 (No of events)	0.31 (3)	0.86 (13)	0.87 (15)	1.63 (2)	3.43 (9)	29.0,
Relative risk	1.00	2.74	2.77	5.20	10.91	<0.001
Non-cardiovascular disease (n=75)						
Age adjusted rate/100 (No of events)	1.15 (13)	1.06 (16)	2.19 (39)	1.81 (2)	1.82 (5)	11.8,
Relative risk	1.00	0.92	1.91	1.58	1.58	<0.001

non-cardiovascular mortality independently of age and known risk factors. When diabetes status and HbA_{1c} concentration were both included in the same model, diabetes no longer significantly independently predicted mortality. The increased risk of mortality in men with diabetes was largely mediated through HbA_{1c} concentration. An increase of 1% in HbA_{1c} concentration was associated with roughly a 30% increase in all cause and 40% increase in cardiovascular or ischaemic heart disease mortality. After men with a history of diabetes or with a HbA_{1c} concentration ⩾7% and those with a history of heart disease and stroke (n=522) were excluded, the relative risk of all cause mortality for a 1% increase in HbA_{1c} was 1.49 (95% confidence interval 1.03 to 2.17, P=0.03) adjusted for age and 1.46 (1.00 to 2.12, P=0.05) adjusted for age and risk factors.

Table 4 shows the distribution of HbA_{1c} concentration and self reported diabetes in these men. It also shows the population attributable risk, an estimate of the excess mortality associated with diabetes or HbA_{1c} concentration ⩾5%. About 37% (48/131) of the total deaths in this population could be attributed to excess mortality in men with HbA_{1c} concentrations ⩾5%. The prevalence of established or newly diagnosed diabetes was about 5% in the study population. Although this group had greatly increased relative risk of mortality, they contributed only 18% of the excess deaths from all causes relating to HbA_{1c} >5%; men with HbA_{1c} concentrations of 5%-6.9%, who form the majority of the population, contributed about 82% of the excess mortality. Table 4 also shows the estimated effect on prevalence distributions if HbA_{1c} concentrations were lowered by 0.1% or 0.2% in everyone in the population (excluding those with self reported diabetes). An estimated 12% (6/48) of the excess deaths could potentially be prevented by lowering the population mean HbA_{1c} concentration by 0.1%, and 25% (13/48) could be prevented by lowering the population mean by 0.2%. The reduction in total deaths would be 5% (6/131) and 10% (13/131) respectively.

Table 3 Cox multivariate regression for 4662 men aged 45-79 years for all cause, cardiovascular, ischaemic heart disease, and non-cardiovascular mortality, 1995-9. Effects of glycated haemoglobin and diabetes status were modelled separately (models 1 and 2) and together (model 3)

Cause of death		Relative risk adjusted for age (95% CI)	P value	Relative risk adjusted for age and risk factors* (95% CI)	P value
All causes (131 events†)					
Model 1	HbA_{1c} (per 1% increase)	1.32 (1.18 to 1.47)	0.0001	1.29 (1.14 to 1.45)	0.0001
Model 2	Diabetes history (yes *v* no)	2.56 (1.49 to 4.40)	0.0006	2.15 (1.23 to 3.77)	0.007
Model 3	HbA_{1c} (per 1% increase)	1.27 (1.10 to 1.47)	0.001	1.28 (1.09 to 1.49)	0.002
	Diabetes history (yes *v* no)	1.33 (0.66 to 2.67)	0.42	1.08 (0.52 to 2.25)	0.83
Cardiovascular disease (60 events)					
Model 1	HbA_{1c} (per 1% increase)	1.41 (1.21 to 1.64)	0.0001	1.38 (1.18 to 1.61)	0.001
Model 2	Diabetes history (yes *v* no)	3.91 (1.97 to 7.73)	0.0001	3.31 (1.61 to 6.8)	0.001
Model 3	HbA_{1c} (per 1% increase)	1.29 (1.05 to 1.59)	0.01	1.29 (1.05 to 1.60)	0.01
	Diabetes history (yes *v* no)	1.96 (0.78 to 4.90)	0.15	1.63 (0.62 to 4.23)	0.32
Ischaemic heart disease (41 events†)					
Model 1	HbA_{1c} (per 1% increase)	1.51 (1.29 to 1.77)	0.0001	1.44 (1.21 to 1.71)	0.0001
Model 2	Diabetes history (yes *v* no)	4.85 (2.23 to 10.55)	0.0001	4.24 (1.92 to 9.35)	0.0003
Model 3	HbA_{1c} (per 1% increase)	1.40 (1.12 to 1.74)	0.003	1.31 (1.02 to 1.67)	0.03
	Diabetes history (yes *v* no)	1.90 (0.67 to 5.37)	0.22	2.69 (1.34 to 5.43)	0.21
Non-cardiovascular causes (75 events)					
Model 1	HbA_{1c} (per 1% increase)	1.23 (1.04 to 1.46)	0.02	1.20 (1.01 to 1.44)	0.04
Model 2	Diabetes history (yes *v* no)	1.52 (0.61 to 3.80)	0.36	1.34 (0.54 to 3.36)	0.52
Model 3	HbA_{1c} (per 1% increase)	1.26 (1.02 to 1.55)	0.03	1.26 (1.01 to 1.59)	0.04
	Diabetes history (yes *v* no)	0.80 (0.26 to 2.44)	0.70	0.70 (0.22 to 1.59)	0.54

*Risk factors are systolic blood pressure, serum cholesterol concentration, body mass index, cigarette smoking, and history of myocardial infarction or stroke.
†Some data were missing for multivariate analysis.

Table 4 Prevalence of self reported diabetes and glycated haemoglobin concentration and percentage population excess mortality associated with glycated haemoglobin 5% or higher in men 45-79 years, 1995-9

	Glycated haemoglobin (%)				Self reported diabetes (n=160)
	<5 (n=1204)	5-5.4 (n=1606)	5.5-6.9 (n=1611)	≥7 (n=81)	
Prevalence in study population (%)	25.8	34.4	34.6	1.7	3.4
% contribution to excess mortality from					
All causes	—	23	59	4	14
Cardiovascular disease	—	39	38	5	18
Ischaemic heart disease	—	37	38	4	21
Prevalence if population mean lowered by 0.1% HbA_{1c} (%)	32.4	34.8	27.7	1.6	3.4
Prevalence if population mean lowered by 0.2% HbA_{1c} (%)	38.5	38.8	17.7	1.5	3.4

Discussion

Glycated haemoglobin concentration significantly predicted mortality, with increasing risk throughout the whole range of concentrations, even below the threshold commonly accepted for diagnosis of diabetes. This effect was independent of known risk factors and consistent after men with existing diabetes, heart disease, and stroke were excluded. The predictive value of HbA_{1c} for total mortality was stronger than that documented for cholesterol concentration, body mass index, and blood pressure. The mortality risk of established diabetes seemed to be mediated largely through HbA_{1c} concentration.

People with diabetes have increased risk of vascular disease,[9 16–18] and in these people blood concentration of glucose or HbA_{1c} predicts subsequent microvascular and macrovascular events.[19 20] High glucose concentrations might accelerate atherosclerotic processes through several plausible mechanisms such as oxidative stress and protein glycation of vessel walls.[21] Reductions in blood glucose or HbA_{1c} concentrations through tight blood glucose control in people with diabetes also reduces the risk of microvascular disease.[22–25] However, whether the relation of increasing blood glucose with adverse clinical outcomes exists only above a threshold or is a continuous relation across the whole population distribution is still debated.[26–32] For microvascular complications, studies report a flat relation below a threshold for fasting and post challenge glucose concentration as well as for HbA_{1c}.[8] The relation with macrovascular outcomes, coronary heart disease, and stroke, is less clear.[26–32] A review[33] and meta-regression analysis of 20 prospective studies[34] (94% male) concluded that the progressive relation between glucose concentrations and cardiovascular disease extends below the diabetic threshold.

Importance of glycated haemoglobin in people without diabetes

HbA_{1c} concentration is related to prevalent coronary disease or carotid intimal thickening in non-diabetic people.[35 36] Two prospective studies reported that HbA_{1c} predicts cardiovascular disease in non-diabetic people, but they focused on the top end of the distribution, which may contain people with undiagnosed diabetes.[37 38] In the Norfolk cohort, the effect of HbA_{1c} concentration on mortality was evident even at the lower end of the population distribution, and there was no apparent threshold effect: men with HbA_{1c} concentrations above 5% had greater risk than men with concentrations below 5%. Glycated haemoglobin seems to resemble blood pressure and blood cholesterol in terms of the continuous relation with cardiovascular risk.[39]

Clinical implications

Clinical attention has focused on microvascular complications of diabetes. However, rates of myocardial infarction and stroke in diabetic people are about twice the rates of microvascular events,[40] and control of other cardiovascular risk factors such as hypertension is particularly beneficial.[41] Treatment trials have shown the effectiveness of lowering blood pressure and cholesterol concentration in reducing cardiovascular events. Since blood pressure and cholesterol are continuously related to mortality,[39] prevention of cardiovascular disease has moved from single risk factor intervention at fixed thresholds to identifying overall cardiovascular risk in individuals. Lower treatment thresholds are recommended for people at high absolute risk, as estimated by age, sex, and cardiovascular risk factors such as diabetes, blood pressure, blood cholesterol, smoking, and family history.[42 43] Our data indicate that raised glycated haemoglobin concentration, even in men without diabetes, is a marker of greater absolute risk, and preventive treatment with blood pressure or cholesterol lowering drugs should be considered in such patients.

A diagnostic classification for diabetes based on fasting glucose concentration has been challenged by studies that show that glucose concentration two hours after a glucose load has greater predictive value for mortality.[44–46] However, glucose loading is unsuitable for repeated monitoring. Detection and monitoring of hyperglycaemia would be enhanced by a test such as glycated haemoglobin.

Public health implications

Concentrations of glycated haemoglobin are roughly normally distributed in the population. The lowest death rates were in men with HbA_{1c} concentrations below 5% (25% of our population). Established diabetes is associated with increased mortality, but the prevalence of diabetes is low (5% in the population), whereas about 70% of the population have HbA_{1c} concentrations between 5% and 6.9%. As table 4 shows, 82% of the population excess mortality occurred in this large group of the population compared with 18% in those with diabetes. Large numbers of people exposed to a small increase in risk contribute more events to the population than a small number of people exposed to a large increase in risk.[47] The intensive individual medical management and tight glucose control that has been achieved in treatment trials for diabetic patients would not be feasible, or necessarily beneficial, in people who do not have diabetes. However, if it were possible to lower the population mean distribution of HbA_{1c} concentration by lifestyle means such as diet or physical activity, many people could shift into lower risk categories. As shown in table 4, after men with diabetes are excluded, a reduction of just 0.1% HbA_{1c} in the whole population would reduce the prevalence of men with concentrations of 5%-6.9% from 79% to 63%, and a population reduction of 0.2% HbA_{1c} would reduce the prevalence to 57%. If the same

What is already known on this topic

Diabetes mellitus increases cardiovascular disease risk

HbA_{1c} concentrations predict cardiovascular risk in people with diabetes

What this study adds

HbA_{1c} concentrations predict mortality continuously across the whole population distribution in people without diabetes and at concentrations below those used to diagnose diabetes

People with high HbA_{1c} concentration may benefit from control of blood pressure and cholesterol concentration

HbA_{1c} may provide a practical screening tool for diabetes or impaired glucose tolerance

Over 80% of the population excess mortality associated with HbA_{1c} concentrations above 5% occurred in 70% of the population with HbA_{1c} concentrations of 5%-6.9%

death rates are assumed to apply, these reductions in population prevalence would reduce total mortality by 5% and 10% respectively.

Whether it is possible to shift the whole population distribution of glycated haemoglobin concentration is unknown. However, huge secular trends and migrant studies showing rapidly increasing prevalence of diabetes suggest that glucose tolerance in the population is susceptible to environmental changes and may be viewed as a societal problem. Studies have implicated nutrition and physical activity as important determinants of diabetes and glycaemia in populations.[48 49] The challenge is to identify how much risk can be affected by small changes in the determinants of glycaemia at the population level and to devise strategies for bringing about these changes.[50–52]

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Contributors: K-TK, ND, and SB originated and designed the EPIC-Norfolk population study. NW introduced the glycated haemoglobin measurements and diabetes component. SO is study coordinator and organised data collection including quality control of blood samples and measurement procedures. AW contributed to data collection and analysis. RL was responsible for data management and computing and assisted with analyses. K-TK conducted the data analyses and wrote the paper with NW and ND. K-TK is guarantor for this paper.

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