Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study

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Abstract

Objective To determine the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.
Design Prospective observational study.
Setting 23 hospital based clinics in England, Scotland, and Northern Ireland.
Participants 4585 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk.
Outcome measures Primary predefined aggregate clinical outcomes: any end point or deaths related to diabetes and all cause mortality. Secondary aggregate outcomes: myocardial infarction, stroke, amputation (including death from peripheral vascular disease), and microvascular disease (predominantly retinal photocoagulation). Single end points: non-fatal heart failure and cataract extraction. Risk reduction associated with a 1% reduction in updated mean HbA_{1c} adjusted for possible confounders at diagnosis of diabetes.
Results The incidence of clinical complications was significantly associated with glycaemia. Each 1% reduction in updated mean HbA_{1c} was associated with reductions in risk of 21% for any end point related to diabetes (95% confidence interval 17% to 24%, $P<0.0001$), 21% for deaths related to diabetes (15% to 27%, $P<0.0001$), 14% for myocardial infarction (8% to 21%, $P<0.0001$), and 37% for microvascular complications (33% to 41%, $P<0.0001$). No threshold of risk was observed for any end point.
Conclusions In patients with type 2 diabetes the risk of diabetic complications was strongly associated with previous hyperglycaemia. Any reduction in HbA_{1c} is likely to reduce the risk of complications, with the lowest risk being in those with HbA_{1c} values in the normal range (<6.0%).

Introduction

The UK prospective diabetes study (UKPDS), a clinical trial of a policy of intensive control of blood glucose after diagnosis of type 2 diabetes, which achieved a median haemoglobin A_{1c} (HbA_{1c}) of 7.0% compared with 7.9% in those allocated to conventional treatment over a median 10.0 years of follow up, has shown a substantial reduction in the risk of microvascular complications, with a reduction in the risk of myocardial infarction of borderline significance.[1] Complementary information for estimates of the risk of complications at different levels of glycaemia can be obtained from observational analyses of data during the study.

In patients with type 2 diabetes previous prospective studies have shown an association between the degree of hyperglycaemia and increased risk of microvascular complications,[2 3] sensory neuropathy,[3 4] myocardial infarction,[2 5 6] stroke,[7] macrovascular mortality,[8–10] and all cause mortality.[9 11–14] Generally, these studies measured glycaemia as being high or low or assessed glycaemia on a single occasion, whereas repeated measurements of glycaemia over several years would be more informative.

The existence of thresholds of glycaemia—that is, concentrations above which the risk of complications markedly increases—has not been studied often in patients with type 2 diabetes. The relative risk for myocardial infarction seems to increase with any increase in glycaemia above the normal range,[15 16] whereas the risk for microvascular disease is thought to occur only with more extreme concentrations of glycaemia.[17–19] The diabetes control and complications trial (DCCT) research group showed an association between glycaemia and the progression of microvascular complications in patients with type 1 diabetes for haemoglobin A_{1c} over the range of 6-11% after a mean of six years of follow up.[20] No specific thresholds of glycaemia were identified above which patients were at greater risk of progression of retinopathy, increased urinary albumin excretion, or nephropathy.[19–21] Nor has any threshold of fasting plasma glucose concentration been identified for cardiovascular deaths.[22 23]

We evaluated the relation between exposure to glycaemia over time and the development of macrovascular and microvascular complications and compared this with the results of the UKPDS trial of a policy of intensive control of blood glucose control.[1]

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Methods

Participants recruited to the UKPDS

Details are presented in the companion paper (UKPDS 36) published in this issue (see page 412).

Participants in observational analysis

Of 5102 patients, 4585 white, Asian Indian, and Afro-Caribbean patients who had haemoglobin A_{1c} (HbA_{1c}) measured three months after the diagnosis of diabetes were included in analyses of incidence rates. Of these, 3642 with complete data for potential confounders were included in analyses of relative risk. Complete data were required for all participants included in the multivariate observational analyses. For this reason there are fewer (3642) participants in these analyses than in the clinical trial, despite the inclusion of patients not randomised in the trial. Their characteristics are presented in table 1.

Participants in UKPDS blood glucose control study

After a three month dietary run-in period patients were stratified on the basis of fasting plasma glucose concentration and body weight. The 3867 patients who had fasting plasma glucose concentrations between 6.1 and 15.0 mmol/l and no symptoms of hyperglycaemia were randomised to a policy of conventional glucose control, primarily with diet, or to an intensive policy with sulphonylurea or insulin.[1 24–26] The aim in the group allocated to conventional control (n = 1138) was to obtain fasting plasma glucose concentration < 15 mmol/l, but if concentrations rose to ≥15 mmol/l or symptoms of hyperglycaemia developed patients were secondarily randomised to non-intensive use of these pharmacological treatments, with the aim of achieving fasting plasma glucose concentrations < 15 mmol/l without symptoms. The aim in the group allocated to intensive control (n = 2729) was to achieve fasting plasma glucose concentration < 6 mmol/l, primarily with a single pharmacological treatment. Details of treatments and their effect on glucose control have been published elsewhere.[1]

Biochemical methods

Biochemical methods have been reported previously.[27] Haemoglobin A_{1c} was measured by high performance liquid chromatography (Biorad Diamat automated glycosylated haemoglobin analyser), the range for people without diabetes being 4.5% to 6.2%.[27 28] Baseline variables are quoted for measurements after the initial dietary run-in period.

Table 1 Characteristics of patients included in proportional hazards model measured after three month dietary run-in after diagnosis of diabetes and those included in UKPDS glucose control study.[1] Figures are means (SD) unless stated otherwise

	Proportional hazards model of observational data (n=3642)	Clinical trial of intensive *v* conventional blood glucose control policy (n=3867)
Age (years)	53 (8)	53 (9)
Proportion of men (%)	60	61
Ethnicity (% white/Asian Indian/Afro-Caribbean/ other)	82/10/8/0	81/10/8/1
Body mass index (kg/m^2)	27.7 (5.3)	27.5 (5.2)
Fasting plasma glucose (mmol/l)*	7.9 (6.6-10)	8.0 (7.1-9.7)
Haemoglobin A_{1c} (%)	7.1 (1.8)	7.1 (1.5)
Systolic blood pressure (mm Hg)	135 (19)	135 (20)
Low density lipoprotein cholesterol (mmol/l)	3.5 (1.0)	3.5 (1.0)
High density lipoprotein cholesterol (mmol/l)	1.06 (0.24)	1.07 (0.24)
Triglyceride (mmol/l)†	1.5 (0.9-2.5)	1.5 (0.9-2.5)
Albuminuria (%)‡	13.3	11.4

*Median (interquartile range).
†Geometric mean (1 SD range).
‡>50 mg/l in single morning sample.

Glycaemic exposure

Exposure to glycaemia was measured firstly at baseline as haemoglobin A_{1c} concentration and secondly over time as an updated mean of annual measurements of haemoglobin A_{1c} concentration, calculated for each individual from baseline to each year of follow up. For example, at one year the updated mean is the average of the baseline and one year values and at three years is the average of baseline, one year, two year, and three year values.

Clinical complications

The clinical end points and their definitions are shown in the box in the companion paper (UKPDS 36) published in this issue (see page 412).

Statistical analysis

Incidence rates by category of glycaemia

The unadjusted incidence rates were calculated by dividing the number of people with a given complication by the person years of follow up for the given complication within each category of updated mean haemoglobin A_{1c} concentration and reported as events per 1000 years of follow up.[29] The categories were defined (median values in parentheses) as: < 6% (5.6%), 6- < 7% (6.5%), 7- < 8% (7.5%), 8- < 9% (8.4%), 9- < 10% (9.4%), and ≥ 10% (10.6%) over the range of updated mean haemoglobin A_{1c} of 4.6-11.2% (1st-99th centile). Follow up time was calculated from the end of the initial period of dietary treatment to the first occurrence of that complication or loss to follow up, death from another cause, or to the end of the study on 30 September 1997 for those who did not have that complication. Hence, follow up time is equivalent to duration of diabetes. For myocardial infarction and stroke for participants who had a non-fatal followed by a fatal event, the time to the first event was used. The rates were therefore for single and not recurrent events. The median follow up time for all cause mortality was 10.4 years.

We calculated adjusted incidence rates for each category of updated mean haemoglobin A_{1c} using a Poisson regression model adjusted for male sex, white ethnic group, age at diagnosis 50-54 years, and duration of diabetes 7.5-12.5 years and expressed in events per 1000 person years of follow up. These parameters were chosen to reflect the median age and duration of diabetes and the modal ethnic group and sex.

Hazard ratio and risk reduction

To assess potential associations between updated mean haemoglobin A_{1c} and complications we used proportional hazards regression (Cox) models. Potential confounding risk factors included in all Cox models were sex, age, ethnic group, smoking (current/ever/never) at time of diagnosis of diabetes, and baseline high and low density lipoprotein cholesterol, triglyceride, presence of albuminuria (> 50 mg/l measured in a single morning urine sample) measured after three months'

dietary treatment, and systolic blood pressure represented by the mean of measures at two and nine months after diagnosis. The hazard ratio was used to estimate the relative risk. At each event time, the updated mean haemoglobin A_{1c} value for individuals with an event was compared with the updated value of those who had not had an event by that time. The updated mean value was included as a time dependent covariate to evaluate glucose exposure during follow up.[20 29 30] It was included as a categorical variable in the categories of glycaemia listed above, with the lowest category (<6%) as the reference category assigned a hazard ratio of 1.0 and with the highest category ≥9%. (This is reflected in the point estimates as shown in figures 3 and 4.) Separate models, with updated mean haemoglobin A_{1c} as a continuous variable, were used to determine reduction in risk associated with a 1% reduction in haemoglobin A_{1c} (see regression lines in figures 3 and 4). We evaluated the presence of thresholds by visual inspection. The 95% confidence intervals were calculated on the basis of the floating absolute risk.[31] Log linear relations are reported by convention.[1 32] The risk reduction associated with a reduction of 1% updated mean haemoglobin A_{1c} was calculated as 100% minus the reciprocal of the hazard ratio expressed as a percentage. The risk reduction from the continuous variable model associated with a 1% reduction in observed haemoglobin A_{1c} was compared with the risk reduction seen in the UKPDS intervention trial of an intensive versus a conventional policy of blood glucose control, for which no adjustment for potential confounders was required as they were balanced by randomisation.[1]

To assess whether the association between mean updated haemoglobin A_{1c} and complications was independent of randomisation, separate models included mean updated haemoglobin A_{1c} and randomisation to either intensive or conventional policy, as well as all potential confounders listed above. The model for all end points related to diabetes included 3005 individuals.

Statistical analyses were performed with SAS version 6.12.[33]

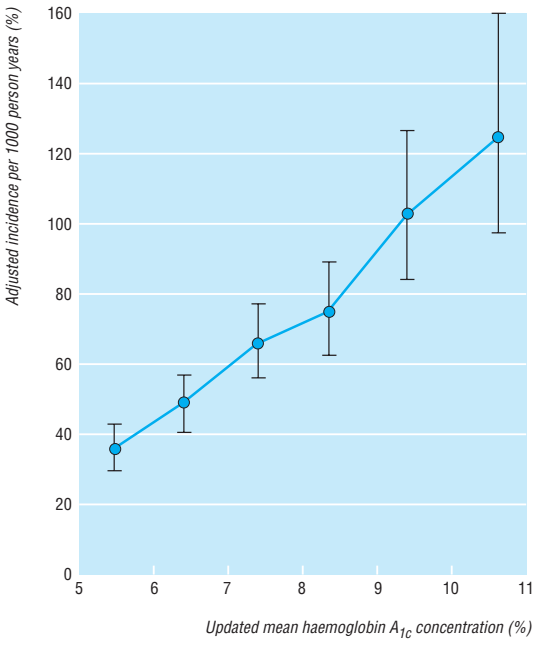

Fig 1 Incidence rate and 95% confidence intervals for any end point related to diabetes by category of updated mean haemoglobin A_{1c} concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years

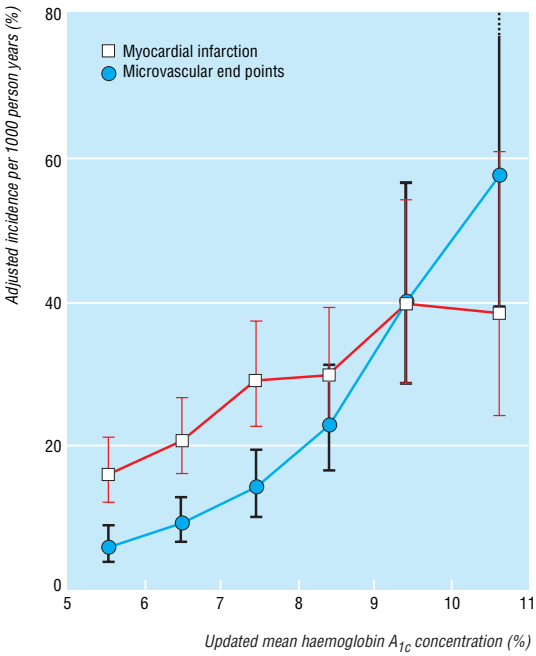

Fig 2 Incidence rates and 95% confidence intervals for myocardial infarction and microvascular complications by category of updated mean haemoglobin A_{1c} concentration, adjusted for age, sex, and ethnic group, expressed for white men aged 50-54 years at diagnosis and with mean duration of diabetes of 10 years

Results

The risk of each of the microvascular and macrovascular complications of type 2 diabetes and cataract extraction was strongly associated with hyperglycaemia as measured by updated mean haemoglobin A_{1c}. The incidence rates for any end point related to diabetes, adjusted for age, sex, ethnic group, and duration of diabetes, increased with each higher category of updated mean haemoglobin A_{1c}, with no evidence of a threshold and with a threefold increase over the range of updated mean haemoglobin A_{1c} of <6% (median 5.6%) to ≥10% (median 10.6%) (figs 1 and 2). The unadjusted and adjusted incidence rates are shown in table 2. Figure 2 shows the adjusted incidence rates for myocardial infarction and microvascular end points. The increase in the incidence rate for microvascular end points was greater over the range of increasing glycaemia than was the increase in the incidence rate for myocardial infarction. Thus at near normal concentrations of updated mean haemoglobin A_{1c} the risk of myocardial infarction was twice to three times that of a microvascular end point, whereas in the highest category of haemoglobin A_{1c} concentration (≥10%) the risks were of the same order.

Table 2 Incidence of complications in patients with type 2 diabetes by category of updated mean haemoglobin A_{1c} concentration (%). Rates per 1000 person years' follow up adjusted in Poisson regression model to white men aged 50 to 54 years at diagnosis of diabetes and followed up for 7.5 to <12.5 years, termed "10 years" (n=4585)

	<6%	6% to <7%	7% to <8%	8% to <9%	9% to <10%	≥10%
Aggregate end points						
Complications related to diabetes:						
Events/person years	229/9195	391/11 432	369/8464	268/5605	159/2542	88/1334
Unadjusted rate	24.9	34.2	43.6	47.8	62.5	65.9
Adjusted rate (95% CI)	35.9 (29.9 to 43.1)	48.7 (41.3 to 57.3)	65.5 (55.5 to 77.2)	74.5 (62.6 to 88.8)	103.2 (84.2 to 126.5)	124.9 (97.3 to 160.3)
Deaths related to diabetes:						
Events/person years	56/10 113	101/13 143	116/10 054	84/6595	47/3137	19/1537
Unadjusted rate	5.5	7.7	11.5	12.7	15.0	12.4
Adjusted rate (95% CI)	8.9 (6.3 to 12.7)	12.0 (8.9 to 16.3)	19.9 (14.8 to 26.7)	23.5 (17.2 to 32.0)	29.5 (20.4 to 42.6)	33.0 (19.8 to 55.1)
All cause mortality:						
Events/person years	112/10 113	207/13 143	188/10 054	123/6595	64/3137	26/1537
Unadjusted rate	11.1	15.8	18.7	18.7	20.4	16.9
Adjusted rate (95% CI)	17.0 (13.1 to 22.0)	23.3 (18.5 to 29.2)	30.0 (23.8 to 37.7)	31.8 (24.7 to 40.8)	37.0 (27.3 to 50.2)	40.7 (26.5 to 64.5)
Fatal or non-fatal myocardial infarction:						
Events/person years	100/9870	163/12 590	159/9579	101/6331	60/3016	23/1490
Unadjusted rate	10.1	13.0	16.6	16.0	19.9	15.4
Adjusted rate (95% CI)	16.0 (12.1 to 21.2)	20.8 (16.2 to 26.7)	29.2 (22.8 to 37.4)	30.0 (22.9 to 39.4)	39.6 (28.8 to 54.5)	38.6 (24.4 to 61.0)
Fatal or non-fatal stroke:						
Events/person years	32/9916	67/12 869	59/9822	32/6424	13/3062	9/1509
Unadjusted rate	3.2	5.2	6.0	5.0	4.2	6.0
Adjusted rate (95% CI)	4.3 (2.6 to 7.0)	6.6 (4.4 to 10.1)	8.3 (5.4 to 12.7)	7.4 (4.5 to 11.9)	6.7 (3.5 to 12.7)	12.0 (5.7 to 25.3)
Amputation or death from peripheral vascular disease:						
Events/person years	3/10 018	7/12 993	7/9897	9/6492	15/3061	7/1502
Unadjusted rate	0.3	0.5	0.7	1.4	4.9	4.7
Adjusted rate (95% CI)	1.2 (0.4 to 3.2)	1.2 (0.5 to 3.1)	2.6 (1.1 to 5.8)	4.0 (1.8 to 9.0)	10.9 (5.0 to 23.7)	12.2 (4.6 to 32.4)
Fatal or non-fatal microvascular disease:						
Events/person years	38/9814	77/12 707	86/9438	91/6185	73/2855	47/1432
Unadjusted rate	3.9	6.1	9.1	14.7	25.6	32.8
Adjusted rate (95% CI)	6.1 (4.1 to 9.0)	9.3 (6.7 to 12.9)	14.2 (10.3 to 19.5)	22.8 (16.7 to 31.3)	40.4 (28.9 to 56.5)	57.8 (39.3 to 85.1)
Single end points						
Heart failure:						
Events/person years	17/9967	34/12 928	36/9782	20/6432	10/3062	10/1514
Unadjusted rate	1.7	2.6	3.7	3.1	3.3	6.6
Adjusted rate (95% CI)	2.3 (1.2 to 4.5)	3.4 (1.9 to 5.8)	5.0 (2.9 to 8.6)	4.4 (2.4 to 8.2)	5.0 (2.3 to 10.6)	11.9 (5.5 to 25.8)
Cataract extraction:						
Events/person years	35/9841	59/12 763	49/9692	45/6355	19/3009	19/1495
Unadjusted rate	3.6	4.6	5.1	7.1	6.3	12.7
Adjusted rate (95% CI)	4.1 (2.5 to 6.5)	4.5 (3.0 to 6.9)	4.9 (3.1 to 7.6)	6.9 (4.4 to 10.8)	6.6 (3.8 to 11.6)	14.4 (8.1 to 25.7)

Person years, events, and unadjusted rates are for all patients.

The estimated hazard ratios associated with different categories of updated mean haemoglobin A_{1c} concentration, relative to the lowest category, are shown as log linear plots in figures 3 and 4. Mortality related to diabetes and all cause mortality were both strongly associated with glycaemia ($P<0.0001$). The risk of each of the complications evaluated rose with increasing updated mean haemoglobin A_{1c} concentration both before and after adjustment for baseline variables including age, sex, ethnic group, lipid concentrations, blood pressure, smoking, and albuminuria. The decrease in risk for each 1% reduction in updated mean haemoglobin A_{1c} concentration is shown in table 3 and figures 3 and 4. The glycaemia associated reduction in risk for microvascular end points and for amputation or death from peripheral vascular disease was greater (by 37% and 43% per 1% reduction in haemoglobin A_{1c} concentration, respectively, each $P<0.0001$) than it was for myocardial infarction, stroke, and heart failure (by 14% ($P<0.0001$), 12% ($P=0.035$), and 16% ($P=0.021$) per 1% haemoglobin A_{1c}, respectively) (fig 4). In models that included a variable for conventional control of blood glucose or intensive control with either sulphonylurea or insulin, updated mean haemoglobin A_{1c} remained associated with all complications, although for stroke and heart failure, where the numbers of events were lower than in the previous analyses, these were no longer significant. In these models, treatment of blood glucose per se had no association with any complication beyond that of mean updated haemoglobin A_{1c}.

There was no indication of a threshold for any complication below which risk no longer decreased nor a level above which risk no longer increased. The updated mean haemoglobin A_{1c} showed steeper relations than did baseline haemoglobin A_{1c} (table 3), and when both glycaemic variables were included in a model for all complications of diabetes only updated mean haemoglobin A_{1c} reached significance ($P<0.0001$).

Discussion

This observational analysis shows highly significant associations between the development of each of the complications of diabetes, including mortality, across the wide range of exposure to glycaemia that occurs in patients with type 2 diabetes. This association

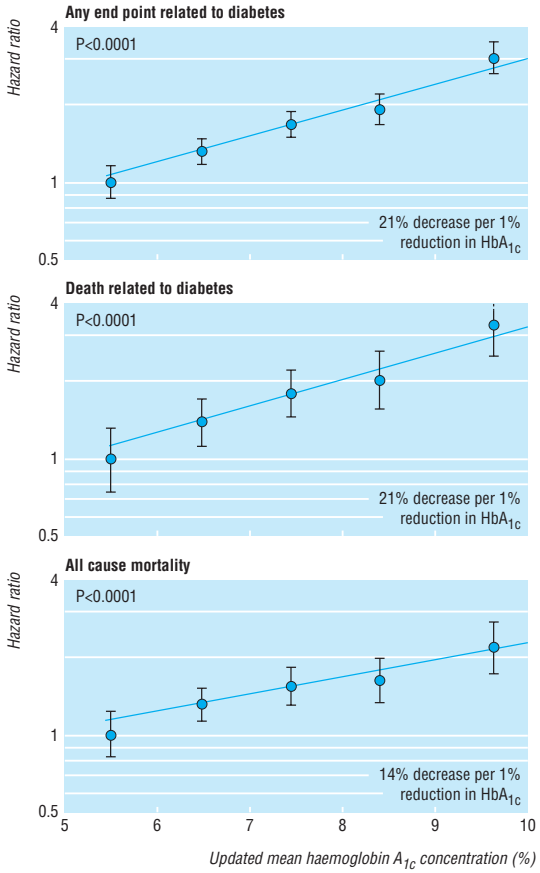

Fig 3 Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A_{1c} concentration and any end point or deaths related to diabetes and all cause mortality. Reference category (hazard ratio 1.0) is haemoglobin A_{1c} <6% with log linear scales. P value reflects contribution of glycaemia to multivariate model. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides

remained after adjustment for other known risk factors, including age at diagnosis, sex, ethnic group, systolic blood pressure, lipid concentrations, smoking, and albuminuria. Each 1% reduction in haemoglobin A_{1c} was associated with a 37% decrease in risk for microvascular complications and a 21% decrease in the risk of any end point or death related to diabetes. The association with glycaemia was less steep for stroke and heart failure, for which blood pressure is a major contributing factor.[32 34 35] In patients within the lowest category of updated mean haemoglobin A_{1c} the incidence of myocardial infarction was higher than that of microvascular disease.[5] These results suggest that, in these people, the effect of hyperglycaemia itself may account for at least part of the excess cardiovascular risk observed in diabetic compared with non-diabetic people beyond that explained by the conventional risk factors of dyslipidaemia, hypertension, and smoking.[36] The rate of increase of relative risk for microvascular disease with hyperglycaemia was greater than that for myocardial infarction, which emphasises the crucial role of hyperglycaemia in the aetiology of small vessel disease and may explain the greater rate of microvascular complications seen in populations with less satisfactory control of glycaemia.

Relation to trial data

This observational analysis provides an estimate of the reduction in risk that might be achieved by the therapeutic lowering of haemoglobin A_{1c} by 1.0%, but it is important to realise that epidemiological associations cannot necessarily be transferred to clinical practice. Tissue damage from previous hyperglycaemia may not promptly be overcome, but the results are not inconsistent with those achieved by the policy of intensive glucose control in the clinical trial.[1] This suggests that the reduction in glycaemia obtained over a median 10 years of follow up of the trial, comparing median haemoglobin A_{1c} 7.0% with 7.9%, provided much of the benefit that could be expected from that degree of improved glycaemic control. Our results suggest that intensive treatment with sulphonylurea or insulin does not have an effect beyond that of lowering blood glucose concentration with respect to altering risk. The 16% risk reduction (P = 0.052) in myocardial infarction in the clinical trial in the group allocated to a policy of intensive blood glucose control (associated

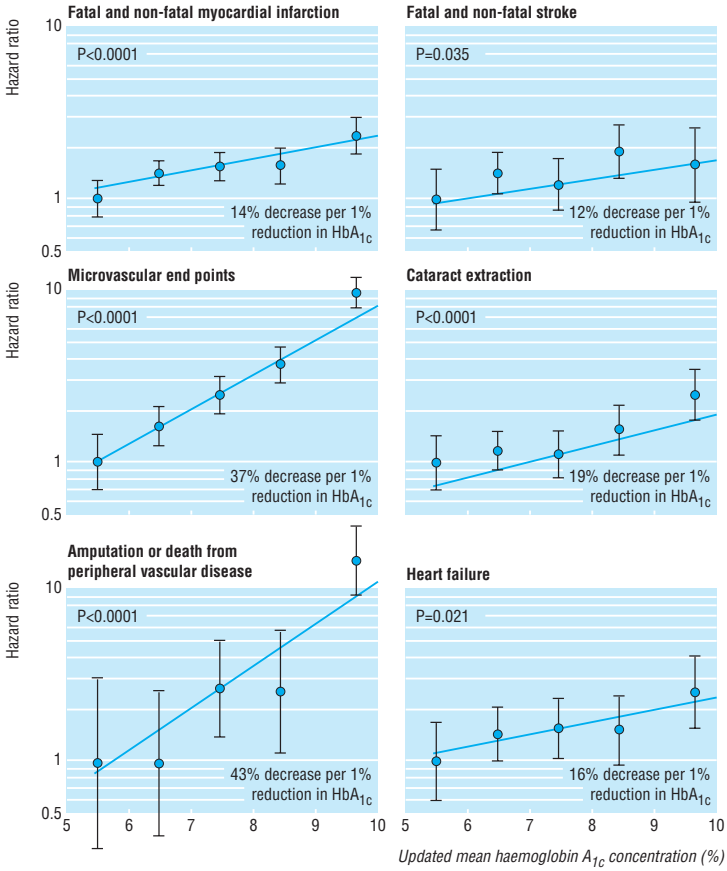

Fig 4 Hazard ratios, with 95% confidence intervals as floating absolute risks, as estimate of association between category of updated mean haemoglobin A_{1c} concentration and myocardial infarction, stroke, microvascular end points, cataract extraction, lower extremity amputation or fatal peripheral vascular disease, and heart failure. Reference category (hazard ratio 1.0) is haemoglobin A_{1c} <6% with log linear scales. P value reflects contribution of glycaemia to multivariate model. Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides

Table 3 Observational analysis of relation between glycaemic exposure and complications of diabetes as estimated by decrease in risk for 1% reduction in haemoglobin A_{1c} (HbA_{1c}) concentration, measured at baseline and as updated mean, controlled for age at diagnosis of diabetes, sex, ethnic group, smoking, albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol, and triglycerides (n=3642) compared with results of clinical trial of intensive *v* conventional glucose control policy (n=3867)[1]

	Observational analysis					Clinical trial of intensive *v* conventional policy[1]		
	Baseline HbA_{1c}			Updated mean HbA_{1c}				
	No of events	Decrease in risk (%)/1% reduction (95% CI)	P value	Decrease in risk (%)/1% reduction (95% CI)	P value	No of events	Decrease in risk (%) seen for 0.9% difference in HbA_{1c} (95% CI)	P value
Aggregate end points								
Any end point related to diabetes	1255	11 (8 to 13)	<0.0001	21 (17 to 24)	<0.0001	1401	12 (1 to 21)	0.029
Deaths related to diabetes	346	9 (3 to 14)	0.0018	21 (15 to 27)	<0.0001	414	10 (–11 to 27)	0.34
All cause mortality	597	6 (2 to 10)	0.0081	14 (9 to 19)	<0.0001	702	6 (–10 to 20)	0.44
Myocardial infarction	496	5 (0 to 9)	0.067	14 (8 to 21)	<0.0001	573	16 (0 to 29)	0.052
Stroke	162	–4 (–14 to 6)	0.44	12 (1 to 21)	0.035	203	–11 (–49 to 19)	0.52
Peripheral vascular disease*	41	28 (18 to 37)	<0.0001	43 (31 to 53)	<0.0001	47	35 (–18 to 64)	0.15
Microvascular disease	323	23 (20 to 27)	<0.0001	37 (33 to 41)	<0.0001	346	25 (7 to 40)	0.0099
Single end points								
Heart failure	104	0 (–12 to 11)	0.99	16 (3 to 26)	0.016	116	9 (–35 to 39)	0.63
Cataract extraction	195	9 (2 to 16)	0.013	19 (11 to 26)	<0.0001	229	24 (0 to 42)	0.046

*Lower extremity amputation or fatal peripheral vascular disease.

with a 0.9% difference in haemoglobin A_{1c}) was similar to the 14% risk reduction seen in the epidemiological analysis, which was associated with a 1% reduction in concentration of updated mean haemoglobin A_{1c}. The UKPDS clinical trial evaluated a policy of intensive glucose control based primarily on single pharmacological treatments to enable evaluation of the individual treatments. Now that the UKPDS has shown that improved glucose control reduces the risk of complications and that the treaments used are safe in clinical practice, a larger reduction in haemoglobin A_{1c} might be achieved by the earlier use of combination treatments or by the use of newer treatments, which could further reduce the risk of myocardial infarction.

The observational analysis extends the range of hyperglycaemia studied in the UKPDS by including participants who, throughout the study, had near normal glucose concentrations on dietary treatment alone and participants who could never be treated by dietary treatment alone.[37] The UKPDS population was likely to be at lower risk of complications than other diabetic populations. Hence, the incidence rates we report are perhaps lower than might be observed in other diabetic populations as the cohort was newly diagnosed with diabetes, excluded old or ill patients, and contained a small proportion (6%) of participants with impaired fasting glycaemia.[38] None the less, the decrease in relative risk is unlikely to be different from other diabetic populations.

What is already known on this topic

The risk of developing complications of diabetes increases with increasing concentrations of hyperglycaemia

Reduction of hyperglycaemia in these individuals reduces the risk of complications

What this study adds

There is a direct relation between the risk of complications of diabetes and glycaemia over time

No threshold of glycaemia was observed for a substantive change in risk for any of the clinical outcomes examined

The lower the glycaemia the lower the risk of complications

The rate of increase of risk for microvascular disease with hyperglycaemia is greater than that for macrovascular disease

Lack of thresholds

We observed no thresholds of glycaemia for any type of complication of diabetes. This suggests that there is no specific target value of haemoglobin A_{1c} for which one should aim but that the nearer to normal the haemoglobin A_{1c} concentration the better. In reality, it is difficult to obtain and maintain near normal concentrations of haemoglobin A_{1c} in patients with type 2 diabetes, particularly in those with a high concentration of haemoglobin A_{1c} at diagnosis of diabetes.[37] Intensification of treatment by adding insulin to improve the relatively modest reduction in glycaemia achieved with oral hypoglycaemic treatments can be constrained by reluctance from patients and providers because, in part, of side effects such as hypoglycaemia or weight gain. These observational analyses, together with the results of the clinical trial, however, indicate that any improvement in a raised haemoglobin A_{1c} concentration is likely to reduce the risk of diabetic complications.

The magnitude of the risk reduction associated with a 1% reduction in haemoglobin A_{1c} concentration for myocardial infarction and microvascular disease (mostly retinopathy) was consistent with that observed in a cohort of patients from Wisconsin.[2] As in this analysis, a stronger association with haemoglobin A_{1c} concentration was observed for amputation than for ischaemic heart disease, possibly because glycaemia increases the risk of microvascular disease, neuropathy,

and peripheral arterial disease, each of which increases the risk of amputation.[4 8 18 39–41] The estimated 14% decrease in all cause mortality per 1% reduction in haemoglobin A_{1c} concentration was similar to that seen in other studies that have assessed glycaemia as haemoglobin A_{1c} as a continuous variable (per 1% change) in multivariate proportional hazards models.[9]

Summary

Both the observational and clinical trial analyses of an intensive glucose control policy suggest that even a modest reduction in glycaemia has the potential to prevent deaths from complications related to diabetes as cardiovascular and cerebrovascular disease account for 50-60% of all mortality in this and other diabetic populations.[8 42–47] Individuals with very high concentrations of glycaemia would be most likely to benefit from reduction of glycaemia as they are particularly at risk from the complications of type 2 diabetes, but the data suggest that any improvement in glycaemic control across the diabetic range is likely to reduce the risk of diabetic complications.

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Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study

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Abstract

Objective To determine the relation between systolic blood pressure over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes.
Design Prospective observational study.
Setting 23 hospital based clinics in England, Scotland, and Northern Ireland.
Participants 4801 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk.
Outcome measures Primary predefined aggregate clinical outcomes: any complications or deaths related to diabetes and all cause mortality. Secondary aggregate outcomes: myocardial infarction, stroke, lower extremity amputation (including death from peripheral vascular disease), and microvascular disease (predominantly retinal photocoagulation). Single end points: non-fatal heart failure and cataract extraction. Risk reduction associated with a 10 mm Hg decrease in updated mean systolic blood pressure adjusted for specific confounders
Results The incidence of clinical complications was significantly associated with systolic blood pressure, except for cataract extraction. Each 10 mm Hg decrease in updated mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes (95% confidence interval 10% to 14%, $P<0.0001$), 15% for deaths related to diabetes (12% to 18%, $P<0.0001$), 11% for myocardial infarction (7% to 14%, $P<0.0001$), and 13% for microvascular complications (10% to 16%, $P<0.0001$). No threshold of risk was observed for any end point.
Conclusions In patients with type 2 diabetes the risk of diabetic complications was strongly associated with raised blood pressure. Any reduction in blood pressure is likely to reduce the risk of complications, with the lowest risk being in those with systolic blood pressure less than 120 mm Hg.

Introduction

The UK prospective diabetes study (UKPDS) has shown that a policy of tight control of blood pressure, which achieved a median blood pressure of 144/82 mm Hg compared with 154/87 mm Hg over median 8.4 years of follow up, substantially reduced the risk of microvascular disease, stroke, and deaths related to diabetes,[1] but not myocardial infarction. Complementary information for estimates of the risk of complications including myocardial infarction at different levels of blood pressure can be obtained from observational analysis of the UKPDS data. This information can help to estimate the expected reduction in the risk of diabetic complications from a given change in blood pressure. It can also help to assess whether or not thresholds in blood pressure exist below which the risk of complications is substantially reduced. Such thresholds would have substantial influence on the establishment of guidelines on clinical care.

People with type 2 diabetes have a greater incidence of cardiovascular disease, cerebrovascular disease, and renal disease than the general population. Epidemiological studies suggest that relative hyperglycaemia accounts for part but not all of the increased risk.[2–7] Raised blood pressure is more common in people with type 2 diabetes than in the general population,[8–12] and in people without diabetes it is a major risk factor for myocardial infarction and stroke.[13 14] Epidemiological studies of the role of blood