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 photo› coagulation). 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 com› plications, 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 prospec› tive studies have shown an association between the degree of hyperglycaemia and increased risk of micro› vascular complications,[2 3] sensory neuropathy,[3 4] myo› cardial 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 myo› cardial 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 glycae› mia and the progression of microvascular complica› tions 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 gly› caemia over time and the development of macrovascu› lar 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

dietary treatment, and systolic blood pressure repre› sented 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 fig› ures 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%

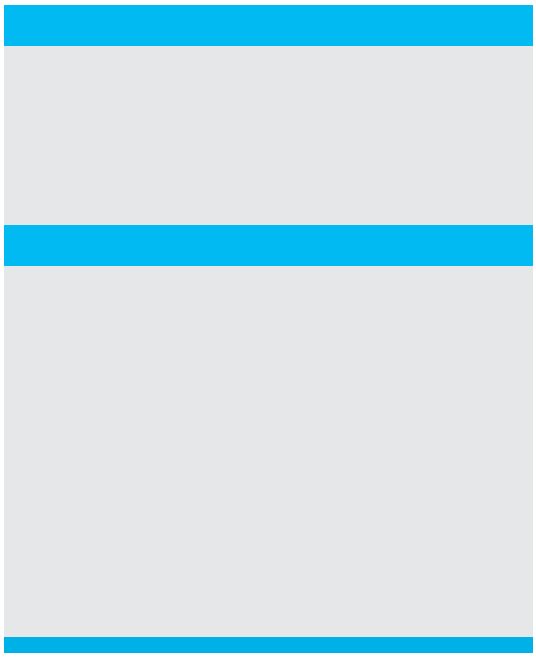
The estimated hazard ratios associated with different categories of updated mean haemoglobin A_{1c}

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

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 pharmaco› logical treatments to enable evaluation of the individual treatments. Now that the UKPDS has shown that improved glucose control reduces the risk of com› plications and that the treaments used are safe in clini›



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 concentra› tions 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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Contributors: IMS selected the methodology, carried out the statistical analyses, coordinated the writing of the paper, and participated in the interpretation of results. AIA assisted with the writing of the paper and interpretation of results. HAWN, DRM, and DH participated in interpretation and revision of the paper. SEM managed the biochemical aspects and participated in interpretation and revision of the paper. CAC participated in preparation of the database and interpretation and revision of the paper. RCT and RRH were the principal investigators, planned and designed the study, and participated in interpretation and revision of the paper. RCT was also responsi› ble for the initial draft of the paper. RRH is guarantor.

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