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The relationship of acute insulin sensitivity to the progression of vascular disease in long-term Type 1 (insulin-dependent) diabetes mellitus

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Summary. In 51 individuals with Type 1 (insulin-dependent) diabetes mellitus initially of more than 15 years' duration, the acute hypoglycaemic effect of intravenous insulin (0.11 IU/kg) was related to outcome over 18 years. This acute insulin sensitivity, or glucose assimilation index, was reproducible over the period of study.

At 18-year follow-up, initial low glucose assimilation index (< 0.082 mmol $\cdot l^{-1} \cdot min^{-1}$ was significantly ($p < 0.01$) associated with death from vascular disease. Low glucose assimilation index was similarly significantly ($p < 0.01$) associated with progression of atherosclerotic disease, but not with microangiopathy alone. Hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure $>$ 95 mmHg) was the only other parameter significantly ($p <$ 0.01) related to outcome, but this relationship was no longer significant once glucose assimilation index had been taken into account. A linear logistic analysis confirmed that acute insulin sensitivity was independently associated with outcome. Neither initial clinical control of diabetes nor glycosylated haemoglobin level in the 26 survivors was related to vascular prognosis.

Key words: Vascular disease, acute insulin sensitivity, long duration Type 1 (insulin-dependent) diabetes.

The determinants of the increased mortality and morbidity in individuals with Type 1 (insulin-dependent) diabetes mellitus due to atherosclerosis and microangiopathy are unresolved. The revived focus on the importance of continued hyperglycaemia as a cause of microvascular disease has extended the earlier evidence of an association between poor diabetic control and microvascular disease [1–7]. Nevertheless, there does not appear to be a consensus of opinion. Exceptions to the general rule are recognized; atherosclerotic disease, which is the major cause of death, does not conform well to the hypothesis [8–12].

This department previously reported an association between insensitivity to the acute hypoglycaemic effect of intravenous insulin in long-term Type 1 diabetes mellitus and the presence of clinical atherosclerosis and microangiopathy [11]. This association was found to be related to progression of disease over a 7-year follow-up [12]. We now report the outcome of these 51 individuals with long-term Type 1 diabetes after 18 years follow-up.

Subjects and methods

The 51 individuals were selected as having Type 1 diabetes on clinical grounds as previously described [11–13], with the criteria that they were non-obese and duration of diabetes was greater than 15 years at the commencement of the study in 1966. Subsequent experience has not altered the clinical classification of any of the patients as ketosis-prone Type 1 diabetic patients, and in 30 patients tested after 11 years of follow-up plasma C-peptide was not detectable [14]. The clinical parameters assessed in relation to outcome at the initial and subsequent examinations were age, sex, duration of diabetes, ponderal index, systolic and diastolic blood pressure, and plasma cholesterol.

The 26 survivors were reassessed in 1984, and records were available to determine the cause of death in all of the 25 who had died. Details of treatment and records of control of diabetes were available in all who, except for three, had been followed in the Diabetic Clinic of The Royal Melbourne Hospital.

At 1984 review, the previous protocol of clinical assessment of both atherosclerotic and microvascular disease was followed [11, 12]. This included full clinical examination, including resting ECG and ophthalmological examination with retinal angiography in 18 of 26 survivors, plasma cholesterol (total) and triglycerides, and assessment of renal function by creatinine clearance, 24-h urine protein and microscopy of urine. Glycosylated haemoglobin (HbA_1) was determined using a Corning kit, for which the laboratory determined normal range was 4.5 to 9.0%. At this review, control of diabetes was determined by the average of estimations of HbA_1 in the preceding 12 months; an assessment of clinical control was not attempted.

Acute insulin tolerance was performed by the injection of a bolus of 0.1 IU/kg glucagon free crystalline insulin in the fasting state in 18 of the 26 survivors as previously described [11–13]. As in our previous reports, the arithmetic expression of Glucose Assimilation Index (GAI, maximum percentage fall of blood glucose concentration per 10 min of observation over 1 h) was used, as the fall in glucose was not always linear. The correlation between the more conventional expression of logarithmic glucose fall (KITT) and GAI in this series is very

Table 1. Age, duration of diabetes and glycosylated haemoglobin at review in survivors, and age and duration of diabetes at death from vascular disease in 46 patients with long-term Type 1 (insulin-dependent) diabetes mellitus

	Deceased	Survivors			
		Severe vascular disease	Moderate vascular disease	Severe and moderate disease	Minimal vascular disease
Number	20[a]	3[b]	11	14	12
Age (years)	51.3 ± 15.4	59.0	51.5 ± 11.3	52.9 ± 10.4	63.1 ± 7.6
Duration of diabetes (years)	32.6 ± 9.1	41.7	37.8 ± 5.8	39.3 ± 4.8	46.0 ± 8.2
Glycosylated Haemoglobin (HbA_1) (%)		12.0	13.4 ± 1.9	13.1 ± 1.7	12.1 ± 1.4

[a] Data expressed as mean ± SD. [b] Standard deviations were not calculated for this small group

Table 2. The relationship of initial acute insulin sensitivity classified as normal Glucose Assimilation Index (GAI) $= 0.082\,mmol \cdot l^{-1} \cdot min^{-1}$ or greater) or low ($GAI < 0.082\,mmol \cdot l^{-1} \cdot min^{-1}$) and death from both vascular and non-vascular causes, and vascular disease status after 18 years, in 51 long-term Type 1 (insulin-dependent) diabetic patients

Patient outcome[a]	Initial insulin sensitivity	
	Normal	Low
Death from vascular disease	4	16
Vascular disease status		
Severe	2	1
Moderate	7	4
Minimal	8	4
Death from non-vascular causes	3	2
Total	24	27

[a] Data presented as number of patients

close ($n = 0.92$) [12]. As in previous reports based on a determined normal range, GAI was classified as normal if it was $0.082\,mmol \cdot l^{-1} \cdot min^{-1}$ or greater. This divided the subjects into two groups of approximately equal size.

The 25 individuals who had died were classified as: death due to vascular disease (atherosclerosis, including myocardial infarction; ischaemic heart disease and/or microangiopathy including renal failure, usually with hypertension; severe neuropathy, both peripheral and autonomic and retinopathy) or death due to non-vascular disease, where a clearly unrelated disease was responsible. The 26 survivors were classified, as in previous reports [11, 12], as having severe, moderate or minimal vascular disease due to both atherosclerotic and microangiopathic disease. Those with severe disease had either previous severe myocardial infarction or cerebral thrombosis with or without proliferative retinopathy, neuropathy, renal impairment and hypertension. All were partially at least incapacitated. In those with moderate disease there was evidence of retinopathy, both background and proliferative, treated by photo-coagulation; peripheral neuropathy with at most slight impairment of peripheral sensation in the feet and absent ankle reflexes; normal renal function; normal ECG with the exception of 3 patients with hypertension that was adequately controlled. Peripheral vascular disease was present in 2 patients with 2 of 4 pedal pulses absent, but both were leading active normal lives. Those with minimal disease had, at most, a few microaneurysms on retinal examination, including angiography; absent ankle reflexes but no other manifestation of neuropathy; normal renal function; no excess proteinuria; normal blood pressure ($\leq 150/90$); and no evidence of cardiac or peripheral vascular disease.

Statistical analysis

Data was analysed by Student's t-test, by contingency table analysis using chi-squared tests and by linear logistic regression using GLIM [14].

Results

In 1984, 20 of the original 51 individuals had died from vascular disease. The cause of death was primarily atherosclerotic disease in 15 patients (12 with myocardial infarction, 3 with cerebral thrombosis), but 6 of those 15 patients had severe microangiopathic disease as well. Five patients died primarily from microangiopathy and 3 in end-stage renal failure. Five died from non-vascular causes (acute myeloid leukaemia, septicaemia, multiple sclerosis, fractured skull after hypoglycaemia, chronic tuberculous fibrotic lung disease); these individuals were excluded from some of the analyses. The 26 survivors were classified as having severe vascular disease ($n = 3$), moderate vascular disease ($n = 11$) or minimal disease ($n = 12$) by the criteria above. The mean age and duration of diabetes in these groups is shown in Table 1. Those with minimal vascular disease were significantly both older ($p < 0.01$) and had longer duration of diabetes ($p < 0.02$) than those survivors with moderate vascular disease, or with either moderate or severe disease. The 20 patients who died from vascular disease were both younger and had shorter diabetes duration than those with minimal disease ($p < 0.02$). Age of onset was not related to outcome.

The acute hypoglycaemic potency of insulin was reproducible over the period of follow-up when the separate determinations at each review were compared (GAI 1966 versus GAI 1972, $r = 0.61$, $p < 0.001$; GAI 1966 versus GAI 1984, $r = 0.59$, $p < 0.01$; GAI 1972 versus GAI 1984, $r = 0.65$, $p < 0.01$.

The relation of initial insulin sensitivity to outcome in 1984 for the whole series followed for 18 years or to death from vascular disease is shown in Table 2. There is a significant association between initial acute insulin sensitivity below the lower limit of normal (GAI $0.082\,mmol \cdot l^{-1} \cdot min^{-1}$) and death from vascular disease irrespective of whether individuals dying from

non-vascular causes are included ($p < 0.01$). When the latter five individuals are excluded the association is stronger, and there is a significant trend in the association between low GAI and severity of vascular disease: minimal, moderate, severe or deceased ($p < 0.02$). Hypertension (systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 95 mmHg) is also significantly associated with death from vascular disease ($p < 0.01$), but this association is no longer significant once GAI status has been taken into account. Neither age, sex, duration of diabetes, age of onset, body mass index, diastolic blood pressure or plasma cholesterol were associated with death from vascular disease at the 18 year follow-up. Further, none of these factors significantly altered the association of GAI status with death from vascular disease.

Atherosclerotic disease was the major cause of death and of severe vascular disease, and in both 1966 and 1972 there was a closer relationship of low GAI to atherosclerotic disease than microangiopathy. As those with initial severe atherosclerotic disease had all died by the 7-year follow-up, we considered the relation of acute insulin sensitivity to outcome at 18 years in the 42 individuals who were initially classified as having moderate or minimal atherosclerosis. Initial reduced acute insulin sensitivity (GAI 0.082 $mmol \cdot l^{-1} \cdot min^{-1}$) was associated with a bad prognosis of death from atherosclerotic disease ($p < 0.01$), and this association was not modified by any of the other measured variables. Angiopathic disease showed a similar trend, which was not significant.

In 1972 we found that initial low GAI had a bad prognosis after seven years [12]. The individuals who survived to 1972 were analysed according to their status in 1984. Death was significantly associated with both GAI status ($p < 0.001$) and hypertension ($p < 0.01$) as measured in 1972. Multivariate analysis showed that, although age was not a univariate predictor of death, when GAI, hypertension and age were included in a logistic regression model they were all significantly ($p < 0.05$) associated with death. Further, the association with GAI status, as judged by the odds ratio estimate, increased after adjustment for age and hypertension. When analysis was restricted to deaths from vascular disease, associations were stronger; i.e., although by 1972 the survivors were older and those with initial severe vascular disease had died, acute insulin insensitivity remained a strong and independent predictor of death at 12-year follow-up.

The mean glycosylated haemoglobin (HbA_1) values of the surviving 26 individuals are shown in Table 1. HbA_1 ranged from 9.8% to 16.5%. Although the mean value of the group with minimal vascular disease was lower than the other groups, there was no significant difference between those with severe or moderate disease and those with minimal vascular disease. Initial body weight in all subjects was within normal limits (body mass index 19.4–26.2). Body weight did not change appreciably in any individual over the 18-year follow-up, and was not related to GAI. Plasma cholesterol and triglycerides were not related to atherosclerosis or microangiopathy, either initially or subsequently. Initial and final insulin dose was related (1966 vs 1984, $r = 0.76$, $p < 0.001$), but mean insulin dose in the 26 survivors decreased from 49 units in 1966 to 40 units in 1984. Insulin was given as one injection per day in 17 and as two injections in 9 of the 26 survivors using Isophane and soluble insulin (10), Lente (5), Semi-Lente (6), soluble alone (3) and Protamine zinc (2).

Discussion

The 51 individuals with Type 1 diabetes followed in this series had all had diabetes for at least 15 years at the time of their initial investigation. It is thus perhaps not surprising that there is an inverse relationship between age and duration of diabetes, and the occurrence of vascular disease, in this series. Of the 46 individuals followed either for 18 years or until their death from vascular disease, 12 (24%) had only minimal clinical features of either atherosclerotic or microangiopathic vascular disease, and were both significantly older and had longer diabetes duration than those who had died or had severe or moderate disease. Twelve of 26 (46%) of those who had minimal disease at the initial examination were essentially unchanged at the 18-year review after an average of 46 years of diabetes. This pattern of development of vascular complications is similar to that reported by Knowles et al. [8].

Our previous findings [11, 12] that normal acute insulin sensitivity is associated with a good vascular prognosis, and reduced hypoglycaemic potency of intravenous insulin with a poor prognosis in the group of Type 1 diabetic patients studied, has been confirmed in this reported of an 18-year follow-up. When vascular disease was considered as clinical atherosclerosis and microangiopathy separately, the association of reduced acute insulin sensitivity with a poor prognosis was significant with atherosclerosis but not microangiopathy. In turn, atherosclerotic disease was the major cause of either death or severe vascular disease. The only other parameter that was significantly related to outcome and progression of vascular disease in this series was hypertension; however, once GAI has been taken into account, hypertension is no longer significant. In this group of non-obese Type 1 diabetic patients we found no relationship between either acute insulin sensitivity or vascular disease and body mass index, age, duration of diabetes, plasma cholesterol, triglycerides, growth hormone or insulin antibody level, or insulin dose [11–13]. Unfortunately, smoking habits were inadaequately recorded initially and could not be assessed. When the survivors of the 7-year follow-up were reassessed, GAI remained an independent predictor. The small numbers of individuals in the study and the con-

sistently significant associations of survival with GAI suggest that acute insulin insensitivity is a strong and independent predictor of vascular death in this series.

In 1966 a clinical assessment of control of diabetes did not show a significant association of good control with less vascular disease [11]. Glucose control of the 26 survivors was not ideal, and in only 3 survivors was $HbA_1 < 11\%$ compared to the upper limit of normal (9%) used for the assay. In the majority, little attempt had been made to alter control over the period of follow-up unless there was a major problem such as recurrent hypoglycaemia; it is therefore likely that the final assessment by HbA_1 was representative of the patients' control over the whole period. This was not related to vascular status in the 26 survivors, as shown in Table 1.

Previous studies of very long-term insulin-dependent diabetes have not clearly defined factors associated with freedom from vascular disease [2, 8, 15-18]. This report suggests that a reduced acute hypoglycaemic potency of intravenous insulin is a factor associated with the development and progression of vascular disease, particularly atherosclerosis in insulin-dependent diabetes, and that this crude index of insulin sensitivity is reproducible. However, we cannot from our data determine whether there is a cause and effect relationship or whether some other factor is responsible for both decreased insulin sensitivity and increased vascular disease, particularly atherosclerosis.

Our finding that acute insulin sensitivity is reduced in many patients with Type 1 diabetes [13] has been confirmed by recent studies with glucose and insulin clamp techniques [19-23]. Similarly, the lack of relationship between acute insulin sensitivity, insulin dose and insulin antibody titre in individuals who were not clinically insulin resistant [24] has also been recently confirmed. Waldhäusl et al. [23] found no significant difference in insulin sensitivity in diabetic patients with high and low plasma insulin binding capacity. Gardner et al. [25] showed no relationship between the duration of action of subcutaneous crystalline insulin and circulating insulin antibodies. The possibility that reduced acute insulin sensitivity could be related to obesity, inactivity or very high diet fat content has been considered [13]. In the present series a criteria of selection was normal body weight; within that limit there was no relationship between body mass index and insulin sensitivity. Diets were prescribed in an era when fat content was not restricted, but a carbohydrate intake of 150 g and commonly over 200 g a day were standard. One individual who initially had a low acute insulin sensitivity (GAI) was placed on a low fat/high carbohydrate diet to correct hypercholesterolaemia without any subsequent change in acute insulin sensitivity. Physical activity was not quantitated, but there was no clinical suggestion that it was related to acute insulin sensitivity in this group.

Several studies of insulin resistance in insulin-dependent diabetes using clamp techniques have shown an improvement after a period of intense insulin treatment and normoglycaemia. These include studies in newly-diagnosed [22] and longer-term Type 1 diabetic patients [20, 21, 23], but in none of these reports did insulin resistance completely resolve and sensitivity return to the level of normal controls. Some investigators concluded that the cause is a peripheral post-receptor defect as the suppression of the raised hepatic glucose output by insulin was normal [21, 22]. The present investigation has shown association between reduced acute insulin sensitivity and mortality in a group of long-term insulin-dependent diabetic patients. This association appeared unrelated to other risk factors and more closely correlated with clinical atherosclerosis than microangiopathy. Although it is possible that there is not a direct cause and effect relationship in the present findings, they do emphasize the importance of insulin action in this context. The definition of the causes and extent of the demonstrated abnormalities in acute insulin effects in individuals with insulin-dependent diabetes is an urgent priority which we believe could be important in the prevention of the long-term vascular complications of diabetes.

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