Home Blood Glucose Levels, Glycosylated Haemoglobin and Serum C-Peptide Levels in Diabetics Receiving Different Insulin Regimens

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There is increasing evidence that the incidence of complications of diabetes mellitus is related to the degree of sustained hyperglycaemia[1,2]. It is thus widely held that the management of diabetes should be aimed at maintaining blood glucose levels as near normal as possible[3]. However, until the recent advent of home monitoring of blood glucose levels[4], it was difficult to assess the quality of diabetic control and its relation to the various insulin regimens available.

In the present investigation we have used home filter paper capillary blood sampling to assess diabetic control, and have altered insulin dosage to try to achieve blood glucose levels within the normal range. We have then analysed the relationship between total daily insulin dose, the best mean glucose levels obtained and the pattern of overnight glycaemia in patients treated with different insulin regimens. Glycosylated haemoglobin levels have been found to be proportional to hyperglycaemia in the preceding 6 to 10 weeks[5,6] and we have measured this repeatedly to assess the effect of home monitoring of blood glucose on diabetic control.

There is conflicting evidence about the contribution of endogenous insulin secretion to blood glucose control in insulin-dependent diabetics[7-10]. We have assessed this by measuring fasting serum C-peptide levels in a proportion of the patients studied, as most insulin-dependent diabetics show little C-peptide response to stimulation tests[11].

Patients and Methods

Patients

One hundred and forty-two adult insulin-requiring patients from three diabetic clinics in Bristol were studied, all of whom provided capillary blood glucose profiles on several occasions. All of them understood the reasons for home monitoring of their diabetes and willingly took part. Of the patients, 35 were receiving insulin because of previous unsatisfactory response to diet and sulphonylureas, 5 were diagnosed during pregnancy, and the remaining 102 had presented with hyperglycaemia and ketosis and had been treated with insulin from the time of diagnosis. Insulin treatment regimens were: twice daily soluble and isophane (32); twice daily Actrapid and Monotard (26); twice daily Leoneutral and Leoretard (26); twice daily Actrapid and Semitard (22); once daily Monotard or Monotard and Actrapid (25); and once daily IZS Lente (11). Of the patients receiving twice daily insulins, 12 provided a sufficient number of blood samples to allow assessment of their overnight diabetic control only.

Forty of the patients receiving twice daily mixed short and intermediate acting insulins were studied for 12 months or more, glycosylated haemoglobin levels being measured at the start of the study and repeated at least once after 12 months of home blood glucose monitoring.

Fasting serum C-peptide levels were measured in 51 of the ketosis-prone patients receiving twice daily insulin injections.

Methods

Glucose levels were measured by the method previously described[12] on capillary blood samples taken by the diabetics at home and spotted on to strips of filter paper. Blood samples were requested before and two hours after each of the three main meals, between 11 p.m. and 12 midnight and, if possible, between 2 a.m. and 4 a.m.

The results of the 24-hour blood glucose profiles were discussed with each patient and the existing insulin treatment adjusted as appropriate. Home monitoring was repeated at least twice after each change of treatment.

Percentage glycosylated haemoglobin was measured by a commercial application of small column techniques (Quick-Sep, Isolab) at 22.5°C. The normal range was 5.5-7.0 per cent, the coefficient of variation 3.5 per cent. Samples were washed and incubated in glucose-free saline

for 12 hours before assay to dissociate rapidly glycosylated haemoglobin[13].

Serum C-peptide was measured by the method of Heding[14] after precipitation of insulin antibodies with polyethylene glycol[15]. The lower limit of detection of C-peptide was found to be 0.05 pmol/ml, and a value of twice this, or 0.1 pmol/ml, was taken as the limit above which significant endogenous insulin secretion was considered to be present.

Results

Several patients experienced symptomatic or biochemical (blood glucose less than 2 mmol/litre) hypoglycaemia during the course of the investigation. We have, however, restricted our analysis to the results of the day in which each diabetic achieved his lowest mean blood glucose level in the absence of any such hypoglycaemia.

A positive correlation was found between the mean of the best 24-hour blood glucose profiles and insulin dose (u/kg) in the 36 patients treated with once daily insulin (Fig. 1), and the 94 receiving twice daily insulin injections

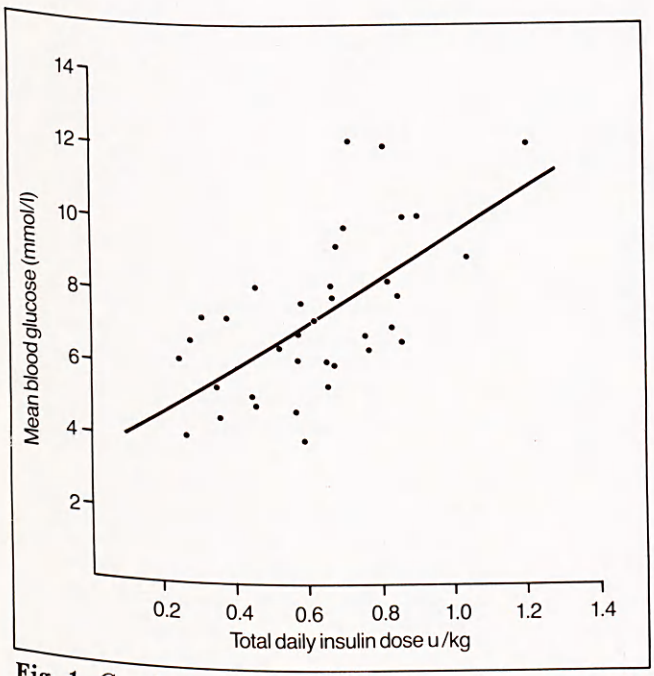


Fig. 1. *Correlation of best mean blood glucose levels during 24 hours with total daily insulin dose in 36 diabetics on once-daily insulin injections. $r = 0.65$. $P < 0.0001$.*

(Fig. 2). The slope of the regression line for the former group was significantly steeper than in the latter (6.0 mmol/u/kg and 3.2 mmol/u/kg respectively, $P<0.05$). The mean blood glucose level was less than 8 mmol/litre in all patients on once daily insulin in a dosage of less than 0.6 u/kg and in the majority of patients on a twice daily insulin dosage of less than 1.0 u/kg.

Our assessment of the effectiveness of the different insulin regimens in controlling overnight hyperglycaemia is shown in Fig. 3. The results from the 84 patients receiving twice daily soluble and isophane insulin or the

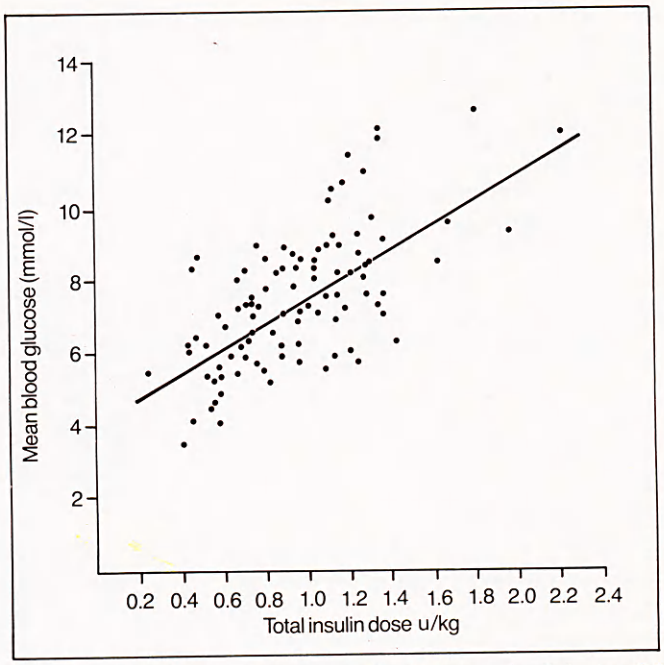
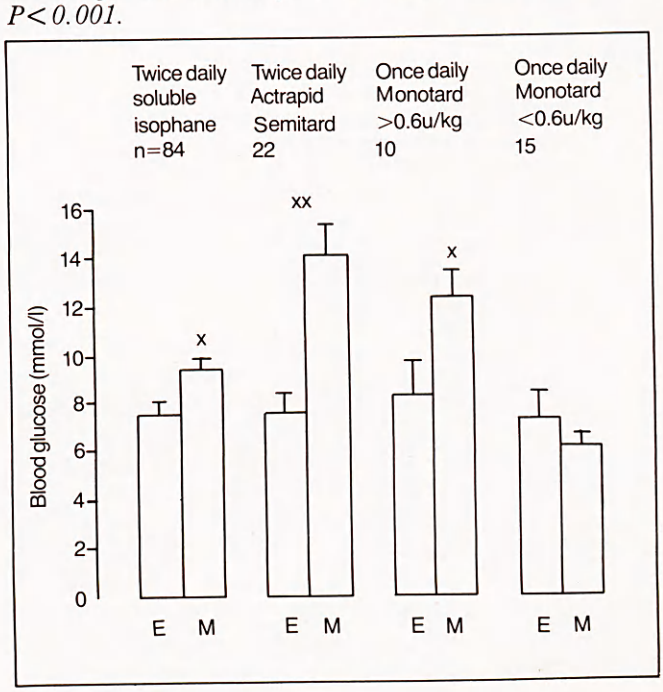


Fig. 2. *Correlation of best mean blood glucose level during 24 hours with total daily insulin dose in 94 diabetics on twice-daily insulin injections. $r = 0.63$. $P < 0.0001$.*

equivalent in more highly purified insulins (Actrapid and Monotard, Leoneutral and Leoretard) have been analysed together because no significant differences were found between these regimens. The means of both late evening (11 p.m.—12 midnight) and fasting morning blood glucose levels were below 10 mmol/litre, although

Fig. 3. *Comparison of mean late evening and mean morning fasting blood glucose levels during the same 24 hours in diabetics on different insulin regimens. E—evening—11 p.m. to midnight. M—morning—7-8 a.m. X—$P<0.01$. XX—$P<0.001$.*



the morning blood glucose level was significantly higher than that in the evening. In contrast, only two of the 22 patients treated with Actrapid and Semitard twice daily had morning blood glucose levels of less than 10 mmol/litre, although the majority of their late evening blood glucose levels was below this figure.

Twenty-five patients were treated with once daily Monotard or Monotard and Actrapid insulin. In those whose dose was less than 0.6 u/kg, the means of their morning and evening blood glucose were consistently less than 10 mmol/litre. In contrast, however, only one of the eight patients receiving more than 0.6 u/kg daily had a morning fasting blood glucose level of less than 10 mmol/litre.

In the 40 patients who were studied for more than one year, glycosylated haemoglobin fell from 11.2 ± 2.1 per cent to 9.8 ± 1.5 per cent (mean $\pm$ SD) between the beginning and the end of the year ($P < 0.01$).

Figure 4 shows the relationship between diabetic control, insulin dose, and fasting serum C-peptide levels.

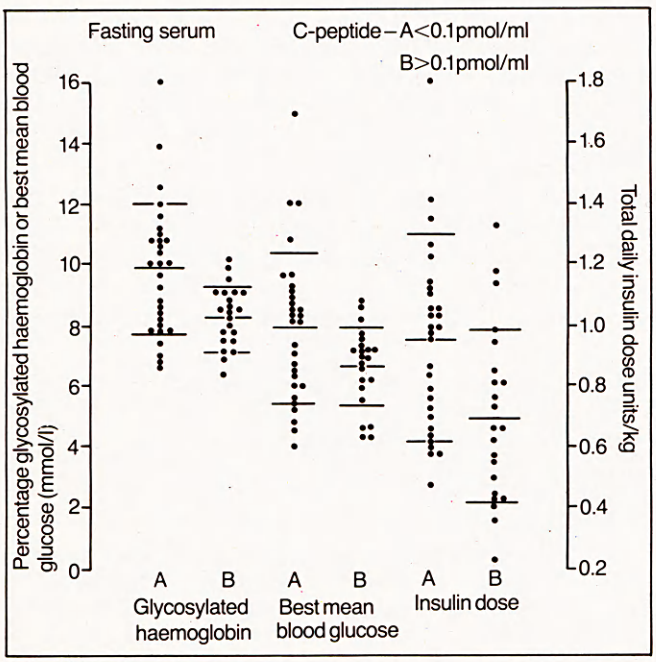


Fig. 4. *Best mean blood glucose levels, glycosylated haemoglobin levels, and total daily insulin dose in patients with fasting serum C-peptide levels of < 0.1 pmol/ml (A) and > 0.1 pmol/ml (B).*

Using an unpaired 't' test, patients who retained endogenous insulin secretion (> 0.1 pmol/ml) had significantly lower glycosylated haemoglobin levels, best mean blood glucose levels and total daily insulin dose (all at $P < 0.01$). Nevertheless, there was considerable overlap between the groups, and many patients with low levels of fasting serum C-peptide achieved good diabetic control with small doses of insulin.

Discussion

The results of the present study show that once daily insulin treatment of insulin-requiring diabetics may provide satisfactory control so long as the total daily insulin dosage is below 0.6 u/kg, but that, with larger doses, diabetic control is likely to be unacceptable.

Patients on both once and twice daily insulin showed a positive correlation between mean blood glucose levels and insulin dosage. Comparisons of the regression lines in Figs 1 and 2 show that, even with identical total daily insulin doses, patients receiving insulin twice daily were more likely to achieve lower mean blood glucose levels than those on one injection a day.

The maintenance of effective insulin treatment during the night is clearly of critical importance with regard to diabetic control. In the sub-group of patients treated with Actrapid and Semitard, the Semitard did not, on the whole, act for long enough, which might lead to insulin over-treatment[16]. Patients receiving once daily Monotard in a dosage of less than 0.6 u/kg achieved acceptable overnight control of their blood sugar, but this was not the case in patients on larger doses.

Three insulin injections daily have been recommended by some workers[17]. Nevertheless, in the present study of patients without symptomatic or biochemical hypoglycaemia, 90 per cent of all those receiving twice daily mixed short and intermediate acting insulin achieved mean blood glucose levels of less than 10 mmol/litre and 80 per cent of those on doses less than 1.0 u/kg had mean blood glucose levels of less than 8 mmol/litre. Thus it would seem that many patients can achieve these degrees of control of their diabetes on conventional twice daily insulin treatment[18].

Several groups have shown that retention of endogenous insulin secretion is associated with better blood glucose control in insulin-dependent diabetics[7-9], though others have not shown this to be so[10]. The association of low insulin requirements with a lower morbidity and mortality from diabetes mellitus may result from preservation of endogenous insulin secretion and lower blood glucose levels in such diabetics[19,20]. There were significantly lower mean glycosylated haemoglobin, best mean blood glucose levels, and total daily insulin dose in our patients with significant fasting serum C-peptide levels compared to those without. Nevertheless, there was considerable overlap between the results of the two groups.

It is clear that factors other than endogenous insulin secretion can influence control of the blood glucose in insulin-dependent diabetics and that some of these factors can be influenced by management, for example by split doses of insulin.

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Carcinoembryonic Antigen and Smoking

Papers from Australia[1,2] and from the UK[3] have shown an association between raised carcinoembryonic antigen (CEA) and smoking. The study of healthy males by Clarke *et al.*[3] has been added to the 100 already reported. The results confirm the previous findings.

The mean CEA (ng/ml) was 8.16 for 48 non-smokers, 9.15 for 26 ex-smokers, 10.58 for 29 cigar/pipe smokers and 12.68 for 30 cigarette smokers. No non-smokers had a CEA level at or above 15 ng/ml, but this level was reached or exceeded in 4 ex-smokers, 5 cigar/pipe smokers and 12 cigarette smokers.

Of the 133 subjects, 68 were reassessed after 2 to 4 years. The mean CEA had increased by 2.38 in 30 non-smokers, 4.15 in ex-smokers, 4.29 in 12 cigar/pipe smokers and 6.06 in 13 cigarette smokers. These higher levels were unrelated to age, but may be partly accounted for by a change in 1979 of the laboratory carrying out the tests. However, the rise is greater in smokers, particularly of cigarettes, and ex-smokers than in non-smokers.

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