An RCT into calculating insulin start dose in type 2 diabetes

There is an increasing incidence of diabetes in the UK and indeed throughout the world, and this has been described as a ‘diabetic epidemic’ (Wild et al, 2004). Many people with type 2 diabetes need insulin added into their treatment regimen to be able to achieve and maintain their glycated haemoglobin (HbA1c) below the seven per cent level. This is something that will increasingly need to be done at the primary care level to tackle the increased number of people who reach this stage in their diabetes.

This element of diabetes care would be encouraged if there was a framework to support GPs and practice nurses to take on insulin therapy as a step on the treatment ladder for people with type 2 diabetes.

Background
There are a large number of studies that compare one type of insulin with another, or insulin with or without differing oral hypoglycaemic agents. We only found one study that compared methods of calculating the insulin starting dose in type 2 diabetes (Taylor et al, 2000). Our randomised controlled trial investigated two methods of insulin initiation in type 2 diabetes.

The UK Prospective Diabetes Study (UKPDS, 1998) showed that intensive treatment for type 2 diabetes significantly reduced microvascular complications (Stratton et al, 2000). It highlighted the progressive nature of type 2 diabetes and the inevitable need for insulin therapy as the disease progresses. Since the publication of the results of the UKPDS study (1998), insulin therapy is being used earlier and more frequently in the treatment of type 2 diabetes (Holmwood and Philips, 1999).

The UKPDS did not, however, examine different methods of changing people from oral hypoglycaemic agents to insulin. A previous questionnaire study of diabetes specialist nurses and diabetologists (Jarvis et al, 2000) showed there was no consistent practice when starting insulin therapy.

**TABLE 1. BASELINE DEMOGRAPHIC CHARACTERISTICS OF THE TWO GROUPS**

<table>
<thead>
<tr>
<th></th>
<th>Conventional (C)</th>
<th>Calculated (CALC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>South Asian</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–40</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>41–50</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>51–60</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>61–70</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>More than 71</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Weight (mean; +/-1SD)</td>
<td>79.3kg (16.2)</td>
<td>85.9kg (18.9)</td>
</tr>
<tr>
<td>Body mass index (mean; +/-1SD)</td>
<td>28.8 (5.5)</td>
<td>30.7 (7.1)</td>
</tr>
<tr>
<td>HbA1c (mean; +/-1SD)</td>
<td>9.8% (1.4)</td>
<td>9.2% (1.2)</td>
</tr>
<tr>
<td>Male: female</td>
<td>16:14</td>
<td>18:12</td>
</tr>
</tbody>
</table>

The outcomes that were compared were glycated haemoglobin levels (HbA1c), hypoglycaemia, weight gain, insulin dose, quality of life, treatment satisfaction, blood pressure, and frequency of DSN contact.

**Results** HbA1c levels values were reduced significantly in the CALC group during the first three months after starting insulin (p=0.0001) and improved by one per cent overall during 12 months (p=0.03). No difference was found in rates of hypoglycaemia, blood pressure, quality of life, and treatment satisfaction. Weight gain was seen in both groups but was significantly higher in the CALC group. People in the CALC group needed significantly less DSN time (p=0.01).

**Conclusions** HbA1c target values were achieved more quickly and with less DSN contact using the CALC method. The difference in weight gain with the CALC method needs further investigation.
insulin; doses, type of insulin, and frequency of follow-up differed greatly. The usual insulin doses prescribed when starting insulin treatment were small, often 20 units daily. The most conventional dose used at the time of the study was 10 units twice a day of isophane insulin. This was the starting dose in the conventional (C) arm of the randomised controlled trial.

Insulin was first used to treat people with type 1 diabetes, and this is where ideas on dosage originated. People with type 2 diabetes are generally older, overweight and have more insulin resistance than those with type 1 diabetes. This means that daily insulin requirements for people with type 2 diabetes may be much larger than for people with type 1 diabetes. In most instances small starting doses used for type 2 diabetes will be much lower than the daily requirement needed to achieve and maintain glycaemia. For example, a person with type 2 diabetes may need in excess of 100 units of insulin a day and may only start on 20 units a day. This is a large difference. Patients can find the size of the increase worrying and blood glucose levels can initially get worse at first if tablet therapy is stopped.

In many centres once insulin treatment has been started diabetes specialist nurses (DSNs) follow up and support the individual until the next appointment with the clinician. One of the aims during this time is for the DSN to ensure that injection skills have been adequately learnt, and another is to teach how to alter insulin doses to achieve target glycaemia. HbA1c levels of below seven per cent.

Many nurses work to protocols to advise on adjustments of insulin therapy. These protocols may be based on a 10 per cent increase or decrease rule—the nurse advises the patient that they may like to consider an increase or decrease of insulin by 10 per cent of the current dose. For example, if a patient was taking 20 units of insulin a day the nurse could increase the dose by two units. Other protocols state the number of units (usually 2–4) that may be changed when giving advice. Both of these adjustments of dose could be described as conventional. These small adjustments were derived for the person with type 1 diabetes and are often effective (Diabetes Control and Complications Trial (DCCT), 1998). They are less effective for a person with type 2 diabetes who may require much more insulin, and advising an increase of the starting dose by 10 per cent may prolong the time taken to achieve the required daily dose.

However, there is a dose measurement tool to initiate insulin for people with type 2 diabetes that calculates an individual’s starting and adjustment dose. This was developed by Holman and Turner (1985) and used in the UKPDS. It calculates 80 per cent of the required daily dose by using the individual patient’s height, weight, and fasting blood glucose. The calculation gives a total daily dose of insulin and the proportions used as basal and meal-time (prandial) insulin.

We performed a study to compare the two methods (C and CALC) to find the optimum daily insulin amounts needed for the transition from tablet to insulin therapy for people with type 2 diabetes.

**Methods**

This study was a pragmatic, 12-month, prospective, randomised controlled trial, analysed by ‘intention to treat’. Patients were randomised to receive either ‘C’ (10 units of isophane insulin twice daily with soluble insulin added subsequently as necessary) or ‘CALC’ (a calculated dose isophane insulin twice a day with a calculated dose of soluble insulin added at a later date as necessary, before meals). In both groups the soluble insulin was added to control high glucose values after meals. The CALC daily amount of insulin was derived from height, weight, and fasting plasma glucose.

A slide rule devised by Holman and Turner (1985) was used to calculate the appropriate dosage, which is based on a mathematical calculation. Patients were randomised in the same way as in the UKPDS, with patients allocated to either the calculated or conventional group by opening an envelope as they arrived at the clinic, 30 patients randomised to each group. Due to the study design, neither patients nor DSN could be blind to the randomisation. Patients were supported by one of four DSNs. C group was advised using the 10 per cent rule, and CALC group were advised using a slide rule based on the formula.

Follow-up by a clinician was done at three, six and 12 months, with extra interim visits if required. Patients were followed up by the DSN by telephone or in a nurse clinic at least weekly or more often depending on need. All patients were seen by a diabetes specialist dietitian at some point during the follow-up period.

Effectiveness was measured by looking at the primary outcomes of HbA1c levels and hypoglycaemia. HbA1c was performed using a DCA 2000tm (DCCT calibrated) benchtop analyser, with appropriate internal and external quality assurance. Hypoglycaemia was graded into mild, moderate and severe; mild was a self-treated event, moderate was an event requiring the assistance of another (excluding separate episode), and severe was an event resulting in a seizure or coma.

Secondary outcomes were also compared, particularly weight change, insulin dose, quality of life, treatment satisfaction, and frequency of DSN contact.

Quality of life was assessed using the diabetes quality

<table>
<thead>
<tr>
<th>TABLE 2. HbA1c RESULTS IN THE TWO GROUPS AT SCREENING, THREE, SIX, AND 12 MONTHS</th>
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<tr>
<td></td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Screening</td>
</tr>
<tr>
<td>3 months</td>
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<tr>
<td>6 months</td>
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<tr>
<td>12 months</td>
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**REFERENCES**


This article has been double-blind peer-reviewed.

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of life (DQOL) questionnaire that was developed for use in the DCCT (DCCT, 1988). Treatment satisfaction was measured using the diabetes treatment satisfaction questionnaire developed by Bradley (1993).

Data was collected by the research follow and was documented on the electronic shared care record and therefore included the DSN, dietitian, and medical follow-up records.

Patients
Patients gave written consent. The study was approved by the local ethical committee. Patients were recruited from outpatient clinics and nurse-led clinics. All patients had type 2 diabetes with a diabetes diagnosis of more than two years and were on maximum tolerated doses of oral hypoglycaemic agents. All patients were over 30 and had an HbA1c result at the recruitment clinic of more than 7.5 per cent. Patients were recruited over 12 months and were excluded from the study if they had type 1 diabetes or if they were pregnant.

Statistics
Power calculations were performed (Altman, 1991) to determine sample size, using the expected difference in HbA1c derived from the UKPDS and in-house results for the variants of HbA1c. Differences between groups were evaluated using appropriate parametric or non-parametric tests. Significance was defined as p<0.05. Results are expressed as means (+/-1 standard deviation).

Results
Sixty patients were recruited into the study; 51 patients completed the trial, four dropped out (two from each group) and five patients died (one from C and four from CALC – not significant, p=0.133).

There were no significant differences in baseline characteristics between groups (Table 1).

HbA1c levels
HbA1c was measured at screening, three, six, and 12 months. The C group began with higher HbA1c results: 9.8 per cent (+/-1.42) compared with the CALC group 9.2 per cent (+/-1.2) p=0.07. Table 2 shows the subsequent HbA1c results, with significant difference occurring at three months when C was 9.1 per cent (+/-1.5 per cent) and CALC 7.5 per cent (+/-1.2 per cent) (p=0.0001). At six and 12 months the values remained lower in CALC but the differences were not significant. HbA1c results were also analysed by examining percentage reduction in HbA1c that confirmed a significant reduction at three months p=0.007. Mean updated HbA1c during the study was significantly different with one per cent less in the CALC group (7.2 per cent) compared with the C group (8.2 per cent), 2p=0.003.

Hypoglycaemia
All episodes except two were mild, with one moderate episode occurring in each group. At six weeks there were three people who reported mild episodes in the C group compared with nine people in the CALC group (p=0.0001). At three, six and 12 months there was no significant difference between the two groups (Table 3). Those who reported hypoglycaemia had no difference between groups.

Weight
The CALC group started the trial with a higher mean body mass index (BMI) (30.7; +/-7.1) than the C group (28.8; +/-5.5), (not significant). The CALC mean weight was 85.9kg (+/-18.9) whereas C weighed 79.3 kg (+/-16.2), p=0.15. Weight gain was seen in both groups. Over the 12 months C gained 6.8kg (+/-3.1) and CALC gained 10.4kg (+/-8.6) p=0.03, Mann-Whitney. One outlier in CALC gained 35kg. Weights are shown in Table 4.

Insulin dose
The starting isophane insulin dose for C was 20 units/day of insulin. The mean initial starting dose for CALC was 35.6 units/day (+/-16.6) p=0.0001, in some patients a mixture of both isophane and soluble insulin.
At six weeks the mean insulin dose following increases made by the DSN were 47.3 units/day (+/-25.3) for C, compared with 77.8 units/day for CALC (+/-44.7), p=0.003. At three months the CALC mean daily dose was 88.1 units/day (+/-54.8) compared with 63.7 units/day for C, p= 0.053. The C insulin doses then increased gradually at six and 12 months with the difference remaining insignificant (Table 5).

Quality of life
In both groups there was improvement in quality of life and treatment satisfaction between baseline and 12 months. At baseline, quality of life in the CALC was less than in C (p=0.0065), this persisted at six weeks (p=0.005) but there was no significant difference at three, six, and 12 months (p=0.09).

There was no difference in treatment satisfaction throughout the trial. Satisfaction scores did not drop below five for any group throughout the trial (six was the highest available score) and no deterioration in scores was seen in either group.

Patient contact:
CALC patients (14.7; +/-3.9) needed less total contact than C patients (18.0; +/-4.9) p=0.01, this included clinic visits, telephone contacts, and home visits. The CALC group also needed significantly less telephone contact (8.2; +/-3.7 v 11.04; +/-4.8) p=0.02. Contact for home visits and preplanned nurse and clinician clinics showed no significance between groups (Table 6).

Discussion
In this study oral hypoglycaemic agents (OHA) were discontinued when insulin was started, because this was the most common method used at the time of the study. Also, the type of hypoglycaemic agent varied among the patients recruited into the study and may have influenced the outcomes of the study.

At the time the study was formulated, there was little evidence in favour of combined OHA and insulin. Now that metformin and insulin have shown an advantageous effect in minimising weight in those patients who can tolerate it, and sulphonylureas with insulin in UKPDS, the most common method used at the time of the study. Also, the type of hypoglycaemic agent varied among the patients recruited into the study and may have influenced the outcomes of the study.

Another explanation for the weight gain may have been a possible difference in attitude of the DSNs. These nurses had previously started insulin at the lower doses, possible reason for this discrepancy is that the Holman and Turner (1985) method was derived from a white population. The CALC method can be used to increase the dose if found to be inadequate – calculation is performed again using the current fasting blood glucose.

The calculation of insulin requirements using a simple formula allows more rapid control of glycaemia, with fewer unpredicted educator contacts, with treatment satisfaction and quality of life similar to that of a conventional approach.

The disadvantages were that there was more weight gain in the CALC group, and hypoglycaemia was increased in the CALC group, particularly in the first three months. The hypoglycaemia was mild except for one instance of moderate severity in each group, the overall exposure to high levels of HbA1c was significantly improved in the CALC group.

The patients included in the study were representative of the local population, which has a high proportion of South Asian people. The ages reflect the broad age range of people with type 2 diabetes.

As expected, BMI in both groups was high but there were non-significant differences in initial weight in both groups that may have partly influenced results. Patients in both groups increased in weight significantly – a result that has been shown previously with insulin treatment (UKPDS, 1998).

In our study we removed the OHAS and this may have affected weight gain, it is known that initial weight is one determining factor for weight gain, so that the non-significant difference in weight at onset of the study may have been important (Taylor et al, 2000). We examined weight gain between the groups using ANOVA (analysis of variance between groups) with starting weight as a covariate. There was no significant difference in weight gain between the groups.

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Another explanation for the weight gain may have been a possible difference in attitude of the DSNs. These nurses had previously started insulin at the lower doses.

### Table 5. Insulin Dose Between Groups with Time

<table>
<thead>
<tr>
<th></th>
<th>Conventional (C) mean (units/day +/-1SD)</th>
<th>Calculated (CALC) mean (units/day +/-1SD)</th>
<th>p value separate variance t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>20</td>
<td>35.6 (16.6)</td>
<td>0.054</td>
</tr>
<tr>
<td>6 weeks</td>
<td>47.3 (25.3)</td>
<td>77.8 (44.7)</td>
<td>0.0032</td>
</tr>
<tr>
<td>3 months</td>
<td>63.7 (28.6)</td>
<td>88.1 (54.8)</td>
<td>0.053</td>
</tr>
<tr>
<td>6 months</td>
<td>73.5 (28.6)</td>
<td>79.6 (44.75)</td>
<td>0.57</td>
</tr>
<tr>
<td>12 months</td>
<td>77.5 (30.6)</td>
<td>82.25 (46.02)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**REFERENCES**


as in group C. The larger doses in CALC may have increased the nurses’ fear of causing hypoglycaemia, and they may have placed a greater emphasis on snacking and carbohydrate intake. CALC patients may also have felt hungrier from the larger initial doses of insulin.

We believe that DSN anxiety about the size of the starting dose is the likely explanation for the weight gain in CALC, as after the study was completed and CALC became the norm, audit revealed that there was no excess weight gain (Byard et al, 2002).

The unfamiliarity of the CALC techniques may also account for the significant difference found in the initial lower quality of life scores in CALC patients. This was measured just after randomisation and the DSNs may have unwillingly passed on their concerns about a new method of working.

Members of the CALC group began the trial with a poorer quality of life score than the C group. The start of insulin was not delayed if patients chose to take part in the study – hence the quality of life tests were performed after randomisation and first injection.

As we speculated previously, the results may have been affected by the attitude of the nurse – or may have been related to discomfort from injecting a larger dose of insulin – but could otherwise have occurred due to chance. These possibilities do require further investigation by a prospective psychological analysis. By 12 months there was no difference found in quality of life and treatment satisfaction between the two groups. Both quality of life and treatment satisfaction improved in the two groups during the trial.

The initial differences in hypoglycaemia did not reach significance, and probably reflected the level of glycaemic control; the lower the HbA1c the more the chance of hypoglycaemia. This was supported by the remarkable similarity in the rates of hypoglycaemia between the two groups when their HbA1c levels were not different.

Patients included in the study were representative of the local population and the age ranges reflect the broad age range of type 2 diabetes. As expected, BMI and HbA1c in both groups were high on recruitment into the study. There were five deaths during the two-year study period of recruitment and follow-up.

The study was not powered to detect differences in mortality but the differences between the groups were not significant. The five died at different time intervals during the 12-month follow-up and causes of death were acute left ventricular failure, myocardial infarction, cardiac arrest, cancer, and one died overseas of unknown causes. The deaths did not correlate to weight gain.

This finding reflects the increased mortality of late-stage diabetes. A population-based study undertaken in Leicestershire (Croxson et al, 1994) showed that in people with known diabetes, over the age of 65 years, 52 per cent had died within four years.

This compared with 11 per cent of the non-diabetic population of a similar age. Insulin therapy is often feared by both patients and health professionals and initiation of insulin is often delayed by both parties. The high HbA1c levels at recruitment confirm this to be the case in this study population.

The amount of follow-up needed by the CALC group was less than that needed by the C group. This was particularly true of telephone contact (which was the most frequent form of contact). This difference has cost savings in terms of staffing issues. Less time spent advising patients about increasing the insulin dose should allow the DSN to spend more time educating patients about the lifestyle implications of insulin therapy, including self-adjustment of insulin. Less contact time may also mean that more DSN time can be allocated to group education (Pieber et al, 1995).

The level of glycaemic control and the rate at which this is achieved should be individually agreed with the patient. Some of the things that would influence this include age, living arrangements, and pre-proliferative or proliferative retinopathy. Retinopathy can be made worse by improved glycaemic control in the short term but can be improved in the long term, so therefore is not seen as a reason to delay starting insulin (UKPDS, 1998).

CALC methodology provides a suitable framework for nurses to use to start and adjust insulin appropriately, particularly if the person with diabetes is performing home blood glucose monitoring or the practice nurse is using fasting blood glucose to assess the need for adjustment of insulin dose. It is a technique that should allow safe use of insulin in primary care.

**Conclusion**

We have shown that the use of a formula that includes height, weight, and fasting glucose (measured directly or indirectly) is more effective in achieving acceptable control, than the classical methods. It does so without affecting rates of hypoglycaemia, quality of life or treatment satisfaction. Weight gain increased when the amount of follow-up was expressed as number of contacts.

**TABLE 6. DIFFERENCES IN PATIENT FOLLOW-UP EXPRESSED AS NUMBER OF CONTACTS**

<table>
<thead>
<tr>
<th></th>
<th>Conventional mean; +/-1SD</th>
<th>Calculated mean; +/-1SD</th>
<th>P value separate variance t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total contact</td>
<td>18.0 (4.9)</td>
<td>14.7 (3.9)</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Telephone contact</td>
<td>11.04 (4.8)</td>
<td>8.2 (3.7)</td>
<td>p=0.02</td>
</tr>
<tr>
<td>Home visit</td>
<td>0.1 (0.4)</td>
<td>0.2 (0.5)</td>
<td>p=0.45</td>
</tr>
<tr>
<td>Nurse-led clinic</td>
<td>1.4 (1.4)</td>
<td>1.3 (1.2)</td>
<td>p=0.8</td>
</tr>
<tr>
<td>Clinician clinic</td>
<td>5.2 (0.6)</td>
<td>5.0 (0.8)</td>
<td>p=0.4</td>
</tr>
</tbody>
</table>