The metabolic and psychological effects of an insulin regimen change

Phillip Pickstock

Article points

1. Rapid- and long-acting insulin analogues represent a major advance in diabetes care.
2. New insulin analogues have several advantages over traditional insulin preparations.
3. Patients reported enhanced wellbeing after a regimen change to insulin glargine plus regular human insulin or a rapid-acting insulin analogue.
4. Regardless of the bolus insulin used, there was a significant improvement in HbA_{1c} levels after the regimen change.
5. Better glycaemic control could contribute to enhanced wellbeing.

Key words

- Insulin analogues
- Regimen change
- Psychological wellbeing

The last few years have seen several new developments in the treatment and management of diabetes, including new insulin formulations and delivery methods, simpler blood sugar tests and people with diabetes taking greater responsibility for the management of their condition (Naess and Eriksen, 2002). Among the new treatment regimens that have emerged, the development of rapid- and long-acting insulin analogues using recombinant DNA technology represents a major advance in the treatment of diabetes (Barrio Castellanos, 2005). Insulin analogues can replicate endogenous basal and bolus (mealtime) insulin secretion 'with unprecedented accuracy' and reduce HbA_{1c} levels (Barnett, 2002). Further therapeutic developments in the pipeline include trials of inhaled insulin as a non-invasive alternative to injected insulin (Amiel and Alberti, 2004). In this article Phillip Pickstock describes a retrospective questionnaire analysis assessing the effect of an insulin regimen change on treatment satisfaction and general wellbeing.

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The basal–bolus insulin regimen is the most common one for people with type 1 diabetes. It involves long-acting (basal) insulin, which is injected at night, and an additional bolus injection of short-acting insulin before each meal. People with type 2 diabetes who have deteriorating glycaemic control may also follow a basal–bolus regimen. Before the advent of insulin analogues, the use of regular human insulin as the bolus component was widespread; its major disadvantage is that it causes a peak in plasma insulin concentration 1–2 hours after injection, unlike the short-lived prandial response seen in people without diabetes (Kumar and Clark, 1998). The rapid-acting insulin analogues (insulins lispro [Humalog; Eli Lilly], aspart [NovoRapid; Novo Nordisk] and glulisine [Apidra; Sanofi-Aventis]) are absorbed more swiftly from subcutaneous tissue, are active for a shorter time and restrict postprandial glucose fluctuations much more than regular human insulin (Rosenstock et al, 2000); they also reduce the number of episodes of severe hypoglycaemia (Owens et al, 2001; Dailey et al, 2004). In addition, the rapid-acting insulin analogues offer convenience as well as clinical benefits – they are injected immediately before a meal rather than 30–45 minutes in advance (Lepore et al, 2000).

The long-acting basal insulin analogue glargine (Lantus; Sanofi-Aventis), compared with regular short-acting insulin, helps achieve better HbA_{1c} levels, improves fasting plasma glucose levels and postprandial glucose control, and reduces the risk of nocturnal hypoglycaemia (Pieber et al, 2000;

Yki-Jarvinen et al, 2000). In addition, insulin glargine has a stable metabolic profile that more closely mimics the action of endogenous insulin (Naess et al, 2004). Metabolic activity reaches a plateau 4 hours after its administration, remaining constant for 30 hours, whereas the time–action profile of traditional Neutral Protamine Hagedorn (NPH) insulin shows a pronounced peak after 4–6 hours followed by a decline (Heinemann et al, 2000). In addition, insulin glargine's constant and peakless profile allows its flexible administration – whereas traditional insulins must be injected at bedtime – and it has a lower inter-subject variability than short-acting insulins, making accurate dosing and titration easier (Lepore et al, 2000).

Another long-acting insulin analogue, detemir (Levemir; Novo Nordisk), was released in the UK in June 2004 after the clinical phase of the author's study had been conducted (Naess and Eriksen, 2002). Insulin detemir is currently licensed as part of a basal–bolus insulin regimen only (Novo Nordisk, 2005). Preliminary data suggest detemir, given twice daily, is associated with a reduced risk of nocturnal hypoglycaemia and weight gain compared with NPH in people with type 1 diabetes (Hermansen et al, 2001; Vague et al, 2003; Home et al, 2004).

An alternative regimen to basal–bolus for people with type 2 diabetes is twice-daily pre-mixed insulin in which traditional short- or rapid-acting insulin and intermediate-acting basal insulin are combined in one syringe. Modern pre-mixes manufactured using rapid-acting insulin analogues offer better postprandial control and are therefore replacing the traditional products (Garber, 2006). Despite their convenience for older people and people with visual impairment (Coscelli et al, 1992; McCormack and McElduff, 2004), such mixes do not closely match the profile of endogenous insulin and studies comparing them with a basal insulin and oral antidiabetic agent (OAD) combination have produced mixed findings (Janka et al, 2005). One study found more participants achieved glycaemic targets on a twice-daily pre-mix using biphasic insulin aspart (NovoMix 30; Novo Nordisk) than with once-daily glargine plus OADs (Raskin et al, 2005), although the number of minor hypoglycaemic episodes, weight gain and insulin doses were greater in the pre-mix group. Another study found that more individuals achieved target HbA_{1c} levels with insulin glargine plus OADs than those on 30% regular/70% human NPH insulin. Participants on glargine plus OADs had fewer confirmed hypoglycaemic events than patients on 30/70 (Janka et al, 2005).

Management of wellbeing in diabetes care

Research has shown that people with diabetes report lower psychological wellbeing than those without reported disease (Naess et al, 2004); therefore, the maintenance or improvement of psychological outcomes is an important goal of diabetes care (Witthaus et al, 2001). As hyperglycaemia is associated with a greater incidence of vascular complications, improved glycaemic control could contribute to improved psychological wellbeing and vice versa, but a positive correlation cannot be assumed (Witthaus et al, 2001). Van der Does et al (1996) found higher HbA_{1c} levels were significantly associated with higher symptom scores (which were obtained using a health outcome measures instrument specific to diabetes, developed by Grootenhuis and colleagues [1994]), worse mood and worse general wellbeing. Other, more controversial, findings found low levels of HbA_{1c} related to low wellbeing (Naess et al, 1995).

Modern treatment regimens could improve psychological wellbeing; other contributory factors could include environmental factors, such as the changes in attitude towards people with chronic conditions and less stigmatisation, and the increase or reduction of complications (Naess and Eriksen, 2002). Naess and Eriksen (2002) are currently working to establish whether improved methods of diabetes control lead to improved psychological wellbeing and reduced co-morbidity.

Witthaus et al (2001) assessed treatment satisfaction and psychological wellbeing in 517 people with type 1 diabetes who were randomised to treatment with insulin glargine once daily, or NPH once or twice daily, depending on their previous regimen, with regular human insulin as the bolus component. Participants were asked to complete the Diabetes Treatment Satisfaction

Page points

1. Research has shown that people with diabetes report lower psychological wellbeing than those without reported disease; therefore, the maintenance or improvement of psychological outcomes is an important goal of diabetes care.
2. Modern treatment regimens may improve psychological wellbeing, although other contributory factors could include environmental factors, such as the changes in attitude towards people with chronic conditions and less stigmatisation, and the increase or reduction of complications.

Table 1. Sample from the retrospective questionnaire. Participants were invited to circle more than one word if appropriate.

The questionnaire asked people to circle one or more words/phrases which they related to with regard to their previous insulin regimen and the new one:

- miserable
- sad
- depressed
- anxious
- unwell
- under the weather
- OK
- good
- happy
- healthy
- energetic
- fit

They were also asked to circle the following words/phrases with respect to their hypoglycaemic episodes:

- more frequent
- more of a problem
- the same
- less frequent
- no longer a problem

They were also asked to circle the following words/phrases with respect to how they found testing their blood glucose:

- worse
- more difficult
- the same
- better
- easier

Questionnaire and the Wellbeing Questionnaire during clinic visits at baseline and at weeks 8, 20 or 28. Treatment satisfaction improved with insulin glargine but deteriorated slightly with NPH. There was greater satisfaction with insulin glargine, regardless of previous regimen or injection device, and most emphasis was on treatment satisfaction items for 'convenience' and 'desire to continue treatment'. Overall psychological wellbeing improved in both treatment groups.

Similar increases in treatment satisfaction have been reported from unblinded trials comparing insulin lispro with regular human insulin (Kotsanos et al, 1997). Indeed, those who reverted to regular insulin from lispro had marked reductions in treatment satisfaction, although these did not affect differences in responses concerning insulin glargine and NPH (Witthaus et al, 2001). Trials combining insulin glargine with a rapid-acting analogue may demonstrate improvement in treatment outcomes.

The Burton upon Trent experience

In the author's hospital a total of 30 patients with long-standing type 1 diabetes and suspected poor glycaemic control – owing to their need for six or more specialist nurse interventions over the previous 2 years – were recruited and their glycaemic control was confirmed by HbA_{1c} measurement before being switched from their existing regimens (twice-daily pre-mixes [using traditional 'non-analogue' insulins], or basal–bolus with ultralente or NPH) to a basal–bolus regimen using glargine as the basal insulin. There was no intentional randomisation and inclusion was determined solely on the participants' previous need for specialist nurse intervention. If patients were already on a basal–bolus regimen, their rapid-acting insulin component was left unchanged. Those switching from twice-daily pre-mixes were prescribed insulin aspart as their bolus insulin. Therefore, all patients received insulin glargine plus either regular human insulin (Actrapid, Novo Nordisk) or one of two rapid-acting insulin analogues (lispro or aspart) available in the UK at the time of the study. At routine follow-up consultations, a number of patients commented on an improvement in their general wellbeing, prompting the author, in collaboration with consultant diabetologists Jonathan Benn and Andrew Willis, to devise a postal questionnaire. The questionnaire was designed to retrospectively establish patients' perceived wellbeing before and after their regimen change.

A further 70 patients (giving N=100) were recruited from routine clinic appointments because of their poor glycaemic control or other management issues such as significant hypoglycaemic events. As before, participants were switched from existing regimens (either basal–bolus or twice-daily pre-mixes using traditional 'non-analogue' insulins) to insulin glargine which was added to their existing rapid-acting component: either regular human insulin soluble insulin or a rapid-acting insulin analogue. Of the 100 patients surveyed, 95 had type 1 diabetes (64 of whom were males) and five had type 2 diabetes (three of whom were males). The average age was 45.4 years, average duration of diabetes was 23.3 years and the mean HbA_{1c} level was 9.21 %.

The postal questionnaire was designed and sent out between 3 and 6 months after the regimen change. The questionnaire asked patients to rate their perceived wellbeing before and after the regimen change by circling the most appropriate words from a list describing positive and negative emotional states (*Table 1*). The questionnaire also asked about the frequency of hypoglycaemic episodes and whether management of blood glucose levels was any easier after the regimen change (*Table 1*). HbA_{1c} levels after the regimen switch were measured at the individuals' next clinic appointment between 3 and 6 months later.

The author's diabetes centre manager, the consultant physician and the research manager were consulted regarding ethical approval. It was decided that ethical approval was not necessary as the clinical decision to change treatment regimens was made before the decision to conduct the study. The additional members of the group all required regimen changes due to poor glycaemic control. No randomisation of patients took place; the study was effectively a retrospective internal audit so it was felt that there were no ethical issues.

Results

Comparison of clinic-measured HbA_{1c} levels before and after the regimen change

A total of 79 participants had their HbA_{1c} measurements taken before and after the regimen change (21 non-attendees), including 66 who switched from a basal–bolus regimen with traditional basal insulin (NPH or ultralente) and 13 formerly on twice-daily traditional insulin pre-mixes. Under the new basal–bolus regimen, with insulin glargine (basal) plus either an insulin analogue (insulins aspart or lispro) or regular human insulin (bolus), 42 patients received regular human insulin and 37 received either insulin aspart (n=28) or lispro (n=9). There was a significant improvement in HbA_{1c} levels after the regimen change (P<0.001) regardless of previous regimen or bolus component (*Tables 2 and 3*).

There was a greater average reduction in HbA_{1c} among those switching from twice-daily insulin pre-mixes than those switching from basal–bolus regimens (1.29% compared with 0.96%; P<0.001), despite lower baseline HbA_{1c} levels in the insulin pre-mix group. Those receiving bolus insulin analogues also experienced a greater average reduction in HbA_{1c} than those receiving regular human insulin (1.16% vs. 0.89%).

Questionnaire analysis

All of the 100 participants were sent the questionnaire; 75 individuals returned it.

Comparison of wellbeing before and after the regimen change

Respondents' frequency of negative words was 115 and that of positive words was 35, which represents their perceived wellbeing before changing from their old regimen to a basal–bolus regimen with insulin glargine (basal) plus either an insulin analogue (insulins aspart or lispro) or regular human insulin as the bolus component (*Table 4*). After the regimen change, patients selected eight negative words and 131 positive words (*Table 5*). Comparison of the before and after estimates of wellbeing revealed that the regimen change resulted in a reduction in negative word selection of 93% (P<0.001) and an increase in positive word selection of 274% (P<0.001).

Table 2. HbA_{1c} levels before and after the regimen change.

	Number of patients	HbA_{1c} value before change	HbA_{1c} value after change	Change	*P*-value
Previous regimen	79	9.21%	8.2%	-1.02%	<0.001
Basal–bolus	66	9.32%	8.36%	-0.96%	<0.001
Twice-daily insulin pre-mixes	13	8.71%	7.42%	-1.29%	<0.001

Table 3. Comparison between regular human insulin (RHI) and short-acting insulin analogues as the bolus component.

Bolus component	Number of patients	HbA_{1c} value before change	HbA_{1c} value after change	Change	*P*-value
RHI	42	9.1%	8.21%	-0.89%	<0.001
Analogues	37	9.35%	8.19%	-1.16%	<0.001

Hypoglycaemia and managing blood glucose levels

Patients were invited to circle words (more than one if appropriate) that described their perception of their episodes of hypoglycaemia and the management of their blood glucose levels. Out of 75 respondents, the majority felt their hypoglycaemic events were 'less frequent' (n=40) or 'no longer a problem' (n=22), while nine felt they were the same and six reported more frequent events (*Table 6*).

Responses (n=72) to the question about managing blood glucose indicate that the majority of patients felt glycaemic control was better (n=69) or easier (n=63) to achieve after the regimen change, even including those whose glycaemic

Table 4. Wellbeing scores before the regimen change (number of responders=61).

Positive comment	Frequency each comment cited
OK	15
Good	4
Happy	4
Healthy	5
Energetic	2
Fit	5
Total number of positive comments made	*35*
Negative comment	**Frequency each comment cited**
Miserable	18
Sad	5
Depressed	13
Anxious	27
Unwell	22
Under the weather	30
Total number of negative comments made	*115*

Table 5. Wellbeing scores after the regimen change (number of responders=61).

Positive comment	Frequency each comment cited
OK	19
Good	34
Happy	27
Healthy	20
Energetic	16
Fit	15
Total number of positive comments made	*131*
Negative comment	**Frequency each comment cited**
Miserable	1
Sad	0
Depressed	1
Anxious	4
Unwell	1
Under the weather	1
Total number of negative comments made	*8*

Table 6. Hypoglycaemic events.

Number of respondents	More frequent	More of a problem	The same	Less frequent	No longer a problem
75	6	0	9	40	22

Table 7. Management of blood glucose (including HbA_{1c} levels).

Number of respondents	Worse	More difficult	The same	Better	Easier
72	0	0	13	69	63

control deteriorated (n=5; mean increase in HbA_{1c}=0.28%; data not shown). Management of glycaemic control remained the same as before for 13 patients; none reported deterioration in the management of their blood glucose (*Table 7*).

Findings

There was a significant improvement in HbA_{1c} after the regimen change, regardless of whether a rapid-acting insulin analogue or regular human insulin was used as the bolus insulin. These results, along with the perceived reduction in hypoglycaemic events, agree with previous findings that insulin glargine effectively enables the achievement of glycaemic control and reduces hypoglycaemic events (Pieber et al, 2000; Riddle et al, 2003).

The increase in self-reported wellbeing after the regimen change suggests that better glycaemic control could contribute to an improvement in wellbeing. Many other variables may also influence wellbeing, including those related to diabetes (such as perceived reduction in hypoglycaemic episodes, easier management of diabetes and perceived flexibility of dosing) and those unrelated to diabetes (such as changing life circumstances). It must be noted that both wellbeing estimates were recorded at the same time after the regimen change; therefore, the pre-change wellbeing estimate was recorded retrospectively. This could compromise patient recall and, therefore, accuracy, so these findings should be interpreted with caution. It should also be noted that the survey questionnaire was devised at Queen's Hospital and has not been scientifically validated. Further research using validated questionnaires is required to establish whether or not there is a relationship between improved glycaemic control, enhanced wellbeing and an insulin regimen change to a long-acting insulin analogue.

Implications of these findings for primary care practitioners

Fear of hypoglycaemic events is a major barrier to insulin initiation, for both patients and healthcare professionals, particularly in primary care, where prescribers are more likely to have limited experience. It is reassuring for prescribers that long-acting insulin analogues offer equivalent glycaemic control with a reduced risk of hypoglycaemia compared with NPH (Riddle et al, 2003; Chapman and Perry, 2005).

Physicians may find insulin glargine is especially helpful for patients who work shifts, where work patterns may be irregular, because its 24-hour action profile means it can be administered at any time of the day, as long as it is the same time each day (Riddle et al, 2003). Traditionally, long-acting insulin had to be administered at bedtime, but for shift workers who retire at 2200 hours one week and 0800 hours the next, for example, changing injection time to correspond with a variable bedtime can compromise glycaemic control. One of the author's patients now administers insulin glargine at 1400 hours – the time he gets up when on night shift and a convenient time to inject when he works day shifts. In the author's experience, patients on older long-acting insulins

who alter their injection times may experience hyperglycaemic and hypoglycaemic episodes that they cannot adjust for. Insulin detemir does not afford this same flexibility because a once-daily dose (insulin detemir is sometimes administered twice daily) must be administered with the evening meal or at bedtime (RxList, 2006).

Conclusion

A regimen change from traditional insulin therapy to a basal–bolus approach using a long-acting insulin analogue plus a regular human insulin or rapid-acting insulin analogue bolus in people with diabetes and with poor glycaemic control improved HbA_{1c} and enhanced self-reported wellbeing in this study population. ■

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