Contact frequency determines outcome of basal insulin initiation trials in type 2 diabetes

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Abstract
Aims/hypothesis The aim of the present study was to investigate whether predetermined contact frequency with the study team and endpoint insulin dose are associated with study outcomes in basal insulin initiation trials in type 2 diabetes.

Methods A systematic Medline search was performed. Using data from the selected studies, contact frequency was plotted against HbA1c reduction and endpoint insulin dose. The importance of face-to-face vs telephone contact was also analysed. Insulin dose was plotted against HbA1c reduction, hypoglycaemia rate and weight gain. To investigate non-specific study effects, the relationship between contact frequency and HbA1c was also assessed in dipeptidyl peptidase-4 (DPP-4) inhibitor trials.

Results The reduction in HbA1c was highly correlated with contact frequency and endpoint insulin dose ($r^2=0.751$, $p<0.001$ and $r^2=0.433$, $p=0.008$, respectively). However, after adjusting for contact frequency, the relationship between insulin dose and HbA1c reduction was no longer significant ($p=0.270$). The frequency of both clinical and telephone contacts were independent predictors of HbA1c improvement ($p=0.010$ and $p<0.001$, respectively). We found no dose–response relationship between end-of-study insulin dose and hypoglycaemia or weight gain. In DPP-4 inhibitor studies, contact frequency was not positively associated with HbA1c.

Conclusions/interpretation The frequency of contact with the study team is highly correlated with the improvement in HbA1c achieved in basal insulin initiation trials in type 2 diabetic patients. This has important implications for trial design and interpretation, as well as for clinical care.

Keywords Basal insulin preparations · Glycaemic control · Insulin initiation · Insulin therapy · Type 2 diabetes

Abbreviations DPP-4 · Dipeptidyl peptidase-4
RCT · Randomised controlled trial
SMBG · Self-monitoring of blood glucose

Introduction
In type 2 diabetes basal insulin preparations are advocated for the initiation of insulin therapy [1]. Insulin initiation using insulin detemir (NN304) [B29Lys(ε-tetradecanoyl),desB30 human insulin] or insulin glargine (A21Gly,B31Arg,B32Arg human insulin) has been examined in a number of Phase 3 and 4 clinical studies [2–8], comparing either analogue with NPH insulin or with each other [6] for their ability to decrease HbA1c levels. However, in addition to the merits of the insulin preparation under investigation, factors related to the design of the trials may affect this and other study endpoints. Therefore, we explored whether frequency of contact with the study team as per study protocol and endpoint insulin dose are associated with study outcomes in randomised controlled trials (RCTs) comparing insulin initiation with one basal insulin vs another in insulin-naive participants with type 2 diabetes.

Methods

Medline was searched using the terms ‘detemir’, ‘glargine’, ‘neutral protamine hagedorn’, ‘NPH’, ‘neutral protamine lispro’, ‘NPL’, ‘type 2 diabetes’, ‘non-insulin dependent diabetes mellitus’ and ‘NIDDM’. In order to take the current more stringent glycaemic goals and the relatively
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recent use of insulin titration algorithms into account, the
search was limited to studies published between April
1999 and April 2009. All English-language RCTs with a
duration ≥ 24 weeks comparing insulin initiation with a
basal insulin vs another basal insulin in insulin-naive type 2
diabetic participants were included. Studies investigating
combination therapy with rapid-acting insulin and those
that had differences across treatment arms in additional
glucose-lowering interventions (e.g. oral agents), titration
algorithms and/or contact frequency were excluded.

The search yielded 417 papers, including 112 RCTs, of
which ten met our criteria [2–11]. Using these, associations
between the frequency of contact as per protocol and the
study outcomes reduction in HbA1c and endpoint daily
insulin dose were explored by plotting the contact frequency
(clinical and telephone contacts combined and standardised
to the number of contacts per year) against the two outcome
measures. To examine the relative importance of clinical vs
telephone contact, we standardised both to the number of
contacts per year and performed a multivariable linear
regression analysis. Similarly, endpoint insulin dose, related
to the study design factors titration frequency and titration
target, was plotted against the study outcomes HbA1c
reduction, hypoglycaemia rate and weight gain. For all
associations, we performed weighted least squares regression
using treatment group size as the weight variable.

Of the ten included studies, two were excluded from all
analyses as they did not report contact frequency, endpoint
insulin dose as U kg⁻¹ day⁻¹ or endpoint weight [2, 11].
One more study did not mention the frequency of contact
[9]. Three more studies did not report insulin dose as
U kg⁻¹ day⁻¹ but for two this could be calculated [3, 4]. For
another three studies the change in HbA1c was calculated
[5, 7, 8]. Concerning hypoglycaemia, the studies used
different variable definitions. We used event rates rather than
numbers of participants affected to account for the effect
of study duration on hypoglycaemia frequency. We defined
hypoglycaemia as an event confirmed by a low glucose
measurement, as this definition maximised the number of
studies that could be included in the analysis [4–7, 9]. All
in all, 15 treatment groups were analysed for the
associations between contact frequency and HbA1c, dose and
HbA1c, and dose and weight gain; 13 were analysed for the
association between contact frequency and dose, and ten
for the association between dose and hypoglycaemia.

In addition to the efficacy of the study insulin and certain
features of the study design, improvements in HbA1c during
trial participation may result from non-specific study effects
[12, 13]. To investigate these non-specific study benefits,
we also determined the relationship between contact
frequency and HbA1c reduction in studies examining the
initiation of dipeptidyl peptidase-4 (DPP-4) inhibitors. Both
study populations chose to start a new intervention in the
setting of a clinical trial, so presumably all were equally
motivated to improve their diabetes management. However,
in contrast with the continuous dose titration during the
insulin trials, fixed dosages were used throughout the
DPP-4 studies. We included the trials that were recently
meta-analysed in a Cochrane systematic review and that
compared DPP-4 inhibitor monotherapy with placebo or a
single oral glucose-lowering agent [14]. After exclusion of
one study because of lack of contact frequency data, we
analysed 14 studies comprising 29 DPP-4 inhibitor treat-
ment groups.

Results

Figure 1a shows that the improvement in HbA1c achieved
in studies of basal insulin initiation in patients with type 2
diabetes was highly correlated with the predetermined
frequency of contact with the study team (r² = 0.751,
p < 0.001). Multivariable analysis of the standardised num-
ers of clinical visits and telephone contacts showed a strong
association with HbA1c reduction (adjusted r² value 0.754).
Both frequencies were independent predictors of HbA1c
improvement (p = 0.010 and p < 0.001 for clinical and
telephone contacts, respectively). The regression equation
was: HbA1c reduction = 0.282 + (0.033 × number of clinical
contacts per year) + (0.055 × number of telephone contacts
per year). In the DPP-4 studies, however, higher contact
frequency was not, and, if anything, negatively associated
with greater improvement in glycaemic control (r² = 0.233,
standardised β = −0.483, p = 0.008) (Fig. 1f).

In the insulin trials, we also found significant relationships
between contact frequency and insulin dose at study endpoint
(r² = 0.366, p = 0.028) (Fig. 1b), and between endpoint insulin
dose and HbA1c reduction (r² = 0.433, p = 0.008) (Fig. 1c).
The effect of increasing insulin doses on the occurrence of
hypoglycaemia was not apparent in insulin-naive patients
(r² = 0.011, p = 0.774), and we found no evidence for a dose–
response relationship between insulin dose and weight gain
(r² = 0.076, p = 0.320) (Fig. 1d, e). Finally, to determine
whether contact frequency and insulin dose were also
independently associated with improvement in glycaemic
control, we performed a multivariable regression analysis.
The adjusted r² value of this model was 0.718, and while
contact frequency remained an independent predictor of
HbA1c reduction (p = 0.003), insulin dose did not (p = 0.270).

Discussion

Our main finding was that, while there were significant
dose–response relationships between the predetermined
frequency of contact and endpoint insulin dose and the
improvement in glycaemic control achieved during RCTs investigating basal insulin initiation in type 2 diabetic patients, only contact frequency was an independent predictor of HbA1c reduction. The frequency of both clinical visits and telephone contacts showed a significant relationship with HbA1c improvement, but a higher frequency of telephone contact may be particularly beneficial. In studies examining the start of DPP-4 inhibitors we did not find a positive association between contact frequency and HbA1c improvement.

Assuming that the non-specific study effects of the insulin and DPP-4 trials were comparable, the lack of a logical association between contact frequency and HbA1c improvement in the latter studies suggests that the benefit of frequent patient contact found in the insulin trials is primarily related to the frequency of insulin dose titration. This is supported not only by Fig. 1b, which shows a significant relationship between contact frequency and insulin doses used at study endpoint, but also by the multivariable analysis of the frequencies of clinical and telephone contacts. The higher coefficient for telephone contacts suggests that these may be more beneficial than clinical visits, presumably due to their focus on dose titration (compared with the performance of many study-related procedures during clinical visits).

However, it cannot be ruled out that the non-specific study benefits did indeed differ between the two types of trials. In type 1 diabetes, the improvement in glycaemic control after trial participation itself was found to be mediated by increased self-monitoring of blood glucose (SMBG) and a more active coping style [13]. In contrast with the insulin initiation trials, SMBG was not performed in the DPP-4 studies. Additionally, it is possible that patients failing on oral therapy and requiring insulin are more ‘ready for change’ and more motivated to do well than those (merely) starting on another tablet. However, regardless of whether the benefit of regular patient contact is primarily related to titration frequency or to non-specific study effects, our analyses demonstrate that predetermined contact frequency is a major determinant of the HbA1c improvement achieved in insulin initiation trials. In addition to the obvious consequences for the design and interpretation of clinical trials comparing different insulin preparations, our findings have important implications for patient care, in as far as providing frequent contact after starting insulin therapy may be very effective in improving glycaemic control.

Fig. 1 Relationships between (a) the frequency of contact with the study team as per study protocol and mean reduction in HbA1c level (15 treatment groups, $r^2=0.751$, standardised $\beta=0.866$, $p<0.001$), and (b) the frequency of contact and mean end-of-study daily insulin dose (13 treatment groups, $r^2=0.366$, standardised $\beta=0.605$, $p=0.028$). Relationships between mean endpoint daily insulin dose and (c) mean reduction in HbA1c level (15 treatment groups, $r^2=0.433$, standardised $\beta=0.658$, $p=0.008$), (d) rate of hypoglycaemia confirmed by a low glucose measurement per patient-year (ten treatment groups, $r^2=0.011$, standardised $\beta=-0.104$, $p=0.774$) and (e) mean weight gain (15 treatment groups, $r^2=0.076$, standardised $\beta=-0.276$, $p=0.320$). RCTs comparing insulin initiation with a basal insulin vs another basal insulin in insulin-naive participants with type 2 diabetes were analysed. f Relationship between the predetermined frequency of contact and mean reduction in HbA1c level in clinical studies investigating initiation of DPP-4 inhibitor treatment (29 treatment groups, $r^2=0.233$, standardised $\beta=-0.483$, $p=0.008$). The size of the symbols reflects treatment group size.
We found no relationship between daily insulin dose and hypoglycaemia event rate, but this may reflect the low a priori risk of hypoglycaemia of the study populations. These type 2 diabetic participants had just started insulin treatment, so were presumably protected against hypoglycaemia by residual endogenous insulin secretion. An alternative possible explanation for the observed lack of a relationship is that participants on higher daily doses after titration have similar rates of hypoglycaemia to those in whom titration is stopped at lower insulin doses. In this case, the graph could suggest that perceived risk of hypoglycaemia is the signal to stop insulin dose titration. The lack of association between insulin dose and weight gain suggests that the weight increase commonly seen after initiation of insulin therapy is related to reductions in glucosuria and/or increased energy intake, rather than to the number of insulin injections or the daily insulin dose [15].

In conclusion, the frequency of contact with the study team is highly correlated with the improvement in glycaemic control achieved after basal insulin initiation in type 2 diabetes. Our analyses indicate that when comparing the outcomes of different clinical trials, their design should also be considered. Our findings also have implications for trial design and patient care. Frequent contact and dose titration may facilitate successful insulin initiation.

Duality of interest S. G. H. A. Swinnen is employed by the Department of Internal Medicine of the Academic Medical Centre, partly through funding from Novo Nordisk and sanofi-aventis for the conduct of clinical trials. J. H. DeVries has received honoraria for consultancy work as well as research funding from Novo Nordisk and sanofi-aventis.

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