Review of clinical use of glucagon-like peptide-1 in the management of type 2 diabetes

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Abstract
Within the last decade, multiple new medications have been licensed for treating type 2 diabetes. These agents are vastly more expensive than their predecessors and usage requires review in practice.

This retrospective case series reviewed 55 patients to assess the effect of glucagon-like peptide-1 (GLP-1) mimetics as add-on to existing antidiabetic therapy, including insulin, in clinical practice. The primary outcome measures were change in HbA1c and weight. Analyses were also conducted to test the effect of: initial HbA1c; concomitant insulin use; GLP-1 prescribed; and duration of diabetes on the change in HbA1c and weight.

Mean BMI at initiation was 39.7kg/m2; duration of diabetes at initiation 8.2 years; duration of GLP-1 therapy at review 18.3 months. The mean changes in HbA1c (-15.9mmol/mol) and weight (-5.5kg) were both highly significant (p<0.0001). NICE targets for HbA1c and weight reductions were met in 34.5%. Significant negative correlations were found between initial HbA1c and subsequent change in HbA1c (p=0.0001) and between initial BMI and subsequent change in weight (p=0.04), whereas a significant positive correlation was observed between initial HbA1c and subsequent change in weight (p=0.01). No statistically significant changes in HbA1c or weight were observed in relation to: concomitant insulin use; GLP-1 prescribed; or duration of diabetes.

This study confirms GLP-1 agents provide clinically useful reductions in HbA1c and weight. Further work is required to assess their effect if used earlier. A practical and pragmatic approach to assessment of the effectiveness of GLP-1 has been proposed. Copyright © 2014 John Wiley & Sons.

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Introduction
The effects of the incretin agents, of which glucagon-like peptide-1 (GLP-1) is a member, have been known since the 1980s when it was discovered that plasma insulin levels increase by around three times on oral glucose administration than on intravenous.1 This ‘incretin effect’ results from the release of the insulin secretagogue GLP-1 from intestinal L-cells in postprandial concentrations three times that of fasting levels. Within type 2 diabetes, there is variable loss of this insulin secretory effect.2 Subsequently, synthetic analogues of GLP-1, the most potent incretin, have been licensed and are now commercially available for the treatment of type 2 diabetes.

The prevalence of diabetes (any type) within the Highlands of Scotland is 4.85% where there are known to be 13 190 patients with type 2, and its prevalence is increasing.3 Increased prevalence of type 2 diabetes and adoption of target-driven algorithms have resulted in larger numbers requiring more advanced treatments, ultimately leading to a greater cost of treatment. It is therefore essential that practitioners understand the effect the treatments they prescribe have on their patients. A number of clinical audits have been conducted in this regard.4–6 In all cases, this resulted in reductions in HbA1c and weight. The purpose of this study was to review the effectiveness of local prescribing of these agents. NICE treatment targets are an HbA1c drop of 11mmol/mol and a drop in weight of 3%.

Patients and methods
The setting for this retrospective case series was the South East area of NHS Highland comprising 18 GP practices with a total patient population of around 96 963. Each practice was invited to supply a list of patients prescribed a GLP-1 agonist (exenatide or liraglutide) within the last six months. The first letter was sent by email to each practice manager in October 2011; two reminders were
sent at monthly intervals to non-responders.

**Outcome variables and review**

Data collected for the purpose of the review included: date of birth; duration of diabetes; GLP-1 prescribed; date of initiation of GLP-1; concomitant medication including insulin if prescribed; HbA1c at initiation and review; BMI at initiation; weight at initiation and review; duration of GLP-1 therapy; and eGFR at review. The clinical details were collected from the SCI-DC system which is a database of all patients with a diagnosis of diabetes within Scotland and has access to all laboratory and clinical test results as well as links to primary care prescribing data.

**Statistical analyses**

Data were recorded in an SPSS database (version 21 SPSS, Carey Ltd). Pearson’s correlations and two-way ANOVA were performed using GraphPad Prism (Version 5, GraphPad Software, San Diego, CA, USA). Descriptive statistics, including frequency, percentage, mean and standard deviation, were used to profile the patients identified. Pearson’s correlation test was used to examine the correlation between initial HbA1c/initial weight and the subsequent change in HbA1c or weight. Two-way analysis of variance (ANOVA) was conducted to assess the between-group effectiveness of GLP-1 for reducing HbA1c and weight in three specific circumstances: concomitant insulin use (‘yes’ or ‘no’); GLP-1 prescribed (exenatide or liraglutide); and duration of diabetes (<10 years or ≥10 years). In all cases, a p-value of <0.05 was considered statistically significant.

**Results**

Of the 18 GP practices contacted, 14 responded with a list of type 2 patients currently prescribed GLP-1, resulting in a total of 69 patients. SCI-DC records were accessible for 55 patients. Data analysis has been completed on this cohort, of whom: 32 (58.2%) were female; 53 (96.4%) were on at least two other antidiabetic medications; 19 (34.5%) were on concomitant insulin; 35 (63.6%) had diabetes <10 years; 27 (49.1%) liraglutide vs 28 (50.9%) exenatide. See Table 1 for sample baseline characteristics.

The mean reduction between baseline and review for HbA1c was 15.9mmol/mol (95% CI 11.4–20.4; 2-tailed t-test p<0.0001) and the mean reduction in weight 5.5kg (95% CI 3.2–7.8; 2-tailed t-test p<0.0001); Figure 1. As a percentage of initial body weight the mean reduction was 4.6% (SD ±6.8).

Compared to NICE HbA1c and weight reduction targets of 11mmol/mol and 3% of initial body weight respectively, 34.5% (19) of patients met both targets while 83.6% (46) met both or either target. (Table 2.)

A highly significant correlation between the initial HbA1c and the subsequent change in HbA1c was observed (Pearson’s r=0.49; 95% CI 0.67 to -0.26; R²=0.24; p=0.0001), where the higher the initial HbA1c, the greater the drop in HbA1c. (See Figure 2.) Additionally, a significant correlation was seen between the initial HbA1c and subsequent change in weight (Pearson’s r=-0.34; 95% CI 0.08 to 0.55; R²=0.11; p=0.01), where the higher the initial HbA1c, the less likely the patient will be to lose weight. Similarly, a significant but weaker correlation was found between the initial BMI and the subsequent change in weight (Pearson’s r=-0.27; 95% CI -0.50 to -0.01; R²=0.06; p=0.04), where the higher the initial BMI the greater the drop in weight.

No significant between-group changes in HbA1c or weight were observed on any 2-way ANOVA conducted to assess the between-group effectiveness of GLP-1 for reducing HbA1c and weight in three specific circumstances: concomitant insulin use (‘yes’ or ‘no’); GLP-1 prescribed (exenatide or liraglutide); and duration of diabetes (<10 years or ≥10 years).

**Discussion**

**Summary of main findings**

This study of GLP-1 agonist effect has found highly significant decreases in HbA1c and weight when used in clinical practice. The mean change in HbA1c was found to be 15.9mmol/mol – greater than the 11mmol/mol drop

![Figure 1. GLP-1 effect on HbA1c (A) and weight (B). ***2-tailed t-tests demonstrated significant differences for both (A) and (B); (p<0.0001; n=55)](image)

![Table 1. Sample demographics (n=55)](table)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.6±11.2</td>
<td>27–74</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>8.2±5.0</td>
<td>1–26</td>
</tr>
<tr>
<td>BMI at initiation (kg/m²)</td>
<td>39.7±7.0</td>
<td>28.1–52.9</td>
</tr>
<tr>
<td>Duration on GLP-1 (months)</td>
<td>18.3±10.6</td>
<td>6–43</td>
</tr>
</tbody>
</table>

![Figure 2.](image)
advocated by NICE\textsuperscript{7,8} or the 5.5mmol/mol drop advocated by SIGN\textsuperscript{9} as a marker of treatment effect. The mean change in weight was 4.6\%, more than the 3\% drop advocated by NICE\textsuperscript{7,8} (no weight target was set by SIGN\textsuperscript{9}). Over a third of patients met the treatment targets for HbA\textsubscript{1c} and weight, while more than 80\% met one or other of the treatment targets.

Another indicator for the appropriate use of GLP-1 in clinical practice was the elevated mean BMI at initiation which was 39.7kg/m\textsuperscript{2}, greater than the 30kg/m\textsuperscript{2} set by SIGN\textsuperscript{9} or the 35kg/m\textsuperscript{2} set by NICE\textsuperscript{7,8}. The results from this study have shown that those with a higher initial BMI are likely to lose more weight.

These clinical data support the existing published evidence that higher HbA\textsubscript{1c} at initiation of GLP-1 treatment results in a larger drop of HbA\textsubscript{1c}. The inverse was found to be true for HbA\textsubscript{1c} at initiation and change in weight, where those with a higher initial HbA\textsubscript{1c} were less likely to lose as much weight as those with a lower HbA\textsubscript{1c}. The concomitant use of insulin at initiation had no significant effect on the anticipated HbA\textsubscript{1c} or weight decrease with GLP-1 treatment.

Beta-cell insulin secretory function is more likely to be impaired in those who have had diabetes for longer, arbitrarily those known to have type 2 diabetes for more than 10 years, and therefore the effects of GLP-1 would be weakened. No evidence of this association was found in this study and could be evidence of careful selection of patients for GLP-1 therapy by the specialist team.

No statistically significant differences were found between HbA\textsubscript{1c} or weight reductions of liraglutide versus exenatide.

**Limitations of this work**
The primary limitation of this work is the sample size. However, as highly statistically significant decreases in HbA\textsubscript{1c} and weight have been observed, it strongly suggests that these associations are accurate. Consideration must be given as to the sample size for the lack of effect when looking at: sub-analyses for the groups of patients with concomitant insulin use; type of GLP-1 prescribed; and duration of diabetes <10 years vs \( \geq 10 \) years. To elicit differences in these groups would require a larger sample size, and for those groups to be matched.

**Comparison with the findings from other literature**
The results of this study can be contrasted with the results of a recently published audit \( n=81 \) of incretin mimetic activity: mean duration of GLP-1 therapy 18.3 vs 18.6 months; mean \( \Delta \)HbA\textsubscript{1c} -15.9 vs -7.5mmol/mol; mean \( \Delta \)weight -5.5 vs -3.6kg.\textsuperscript{10} These differences may be explained by the mean duration of diabetes at initiation of the GLP-1. Patients included in this study were found to have been started on GLP-1 at a much earlier stage in their disease (mean 8.2 years), compared to the audit completed by Dhesi \textit{et al.}\textsuperscript{10} (mean 15.3 years duration of diabetes after mean follow up of 18.6 months).

When compared with the results of the Association of British Clinical Diabetologists audit\textsuperscript{5} \( n=4857 \), where 39.6\% of patients were on insulin and GLP-1 treatment, the results of our study also found no association with weight reduction. However, no significant reduction in HbA\textsubscript{1c} was observed – likely as a result of the sample size.

**Implications for practice**
While overall the clinical effect of GLP-1 in this study was encouraging,
there were still just over a third of patients who met the NICE targets for HbA1c and weight reduction at six months. There still exists a question about how best to review patients with regard to HbA1c and weight reduction targets: principally GLP-1 agents are licensed for glycaemic control, not weight loss and thus there should be a means of assessing the efficacy of these agents within these terms. A decision tool was developed locally to support this review process (see Figure 3). Therefore, all patients with a drop in HbA1c to the 11 mmol/mol target would be continued on the agent, regardless of the weight change. Patients not meeting the HbA1c target would have their weight assessed: those with some degree of weight loss would be continued on the GLP-1 agent with subsequent follow up and ‘further review’ for continued efficacy. Patients falling into the amber ‘further review’ category would continue on the treatment for another six months before subsequent review of efficacy; patients in the green category should continue, and those in red, stop treatment.

**Conclusion**

This study of the clinical effect of GLP-1 agents has confirmed clinically significant decreases in HbA1c and weight in patients with type 2 diabetes. Further work is required to assess whether these agents would be more beneficial if used earlier, or what effect they can have on the amelioration of weight gain in concomitant prescription with insulin, sulphonylurea and thiazolidinedione regimens. A practical and pragmatic approach to assessment of the effectiveness of GLP-1 has been proposed.

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**Declaration of interests**

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**References**