The association between postprandial urinary C-peptide creatinine ratio (UCPCR) and the treatment response to liraglutide: a multicentre observational study


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Introduction

• Liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), is used to manage hyperglycaemia in adults with type 2 diabetes (T2D).
• Activation of the GLP-1 receptor increases insulin secretion, reduces hyperglucagonaemia, slows short-term gastric emptying and suppresses appetite.1
• These desirable effects of GLP-1RAs for T2D therapy are balanced against an anecdotal evidence for GLP-1RAs to be useful where beta-cell function is severely compromised, such as in type 1 diabetes.
• There is suggestion that the efficacy of GLP-1RAs is dependent on adequate beta-cell function, although this has not been formally tested.2,3
• Currently, no clinical or biochemical marker has been developed that can predict response to GLP-1RA treatment.
• Despite evidence that GLP-1RAs improve indices of beta-cell function,4,5 there is a paucity of evidence for GLP-1RAs to be useful where beta-cell function is severely compromised, such as in type 1 diabetes.
• There is suggestion that the efficacy of GLP-1RAs is dependent on adequate beta-cell function, although this has not been formally tested.
• C-peptide is produced by cleavage of proinsulin to insulin, and its stability in the body makes it easily measurable.
• A single-sample urinary C-peptide creatinine ratio (UCPCR) correlates well with serum C-peptide, and its utility as biological marker of beta-cell function has been suggested.6-10
• The aim of this study was to investigate the relationship between beta-cell function, as assessed by UCPCR, and glycemic response to liraglutide in subjects with T2D.

Methods

• Ten diabetes centres based in the UK participated in the study.
• Single, outpatient UCPCR samples were taken 2 hours after the largest meal of the day from non-insulin- or insulin-treated adults with T2D prescribed liraglutide 1.2 mg – UCPCR levels and glycemic responses to liraglutide after 32 weeks’ treatment were compared.
• The study consisted of two arms:
  – In the pre-treatment arm, subjects provided a single urine sample for UCPCR within a week before they initiated liraglutide.
  – In the on-treatment arm, subjects provided a urine sample between 20–32 weeks of liraglutide treatment.
• Univariate correlations of UCPCR and glycosylated haemoglobin (HbA1c) change were evaluated using both non-parametric and parametric statistical methods.
• Multilinear regression models assessed the association between pre-treatment and on-treatment UCPCR levels and HbA1c change at 32 weeks.
• Data are presented as mean ± standard deviation (SD) unless otherwise stated.

Results

• Overall, mean baseline HbA1c was 9.3%, body mass index (BMI) was 38.2 kg/m², and 39.7% (n=46/116) subjects were receiving insulin.
• At a median of 24 weeks after initiation of liraglutide therapy:
  – Pre-treatment subjects achieved a HbA1c reduction of –0.9% (±1.5) (p<0.001).
  – On-treatment subjects achieved a mean (SD) HbA1c reduction of –1.4% (±1.2) (p<0.001).
• HbA1c change was found not to be associated with age, duration of diabetes, estimated glomerular filtration rate, baseline BMI, length of time taken between individual’s HbA1c measurements, gender, ethnicity, number of background oral antidiabetes drugs or concurrent insulin treatment.2-5
• HbA1c changes from baseline across quartiles of pre-treatment UCPCR are shown in Table 1.

Table 1: HbA1c changes across quartiles of pre-treatment UCPCR.

<table>
<thead>
<tr>
<th>UCPCR range (mmol/mmol)</th>
<th>n</th>
<th>Q1 (–0.3 ± 1.6)</th>
<th>Q2 (–2.0 ± 0.8)</th>
<th>Q3 (–1.0 ± 1.2)</th>
<th>Q4 (–1.4 ± 1.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c reduction (unadjusted)†</td>
<td>%</td>
<td>-0.3 ± 1.6</td>
<td>-2.0 ± 0.8</td>
<td>-1.0 ± 1.2</td>
<td>-1.4 ± 1.6</td>
</tr>
<tr>
<td>mmol/mol</td>
<td></td>
<td>0.52</td>
<td>0.003</td>
<td>0.002</td>
<td>0.016</td>
</tr>
<tr>
<td>HbA1c reduction (adjusted)</td>
<td>%</td>
<td>-0.5 ± 0.3</td>
<td>-0.8 ± 0.3</td>
<td>-1.2 ± 0.3</td>
<td>-1.0 ± 0.3</td>
</tr>
<tr>
<td>mmol/mol</td>
<td></td>
<td>-5 ± 3</td>
<td>-9 ± 3</td>
<td>-12 ± 3</td>
<td>-11 ± 3</td>
</tr>
</tbody>
</table>

HbA1c reduction shown: mean (±SD) (unadjusted) and least squares (LS) mean (±SEM) after adjusting for baseline HbA1c. †p≤0.05; ‡p=0.41 for effect across quartile groups. SEM, standard error of mean; UCPCR, urinary C-peptide creatinine ratio.

• No significant association between pre-treatment or on-treatment UCPCR and change in HbA1c with liraglutide was found using non-parametric statistical analysis (Figure 1a).
• The association between UCPCR and change in HbA1c improved after UCPCR was logarithm-transformed (log UCPCR) (Figure 1b). After inputting baseline HbA1c, multilinear regression analysis revealed a significant association between pre-treatment and on-treatment log UCPCRs and HbA1c change (p=0.048 and p=0.040, respectively).

Discussion

• These findings suggest that response to liraglutide treatment correlates with the patients’ postprandial UCPCR prior to initiation of liraglutide and levels achieved after liraglutide treatment.
• It may be hypothesised that patients’ response to liraglutide is dependent on endogenous beta-cell function.