Association of British Clinical Diabetologists

Sandwell and West Birmingham Hospitals NHS
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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 variability in treatment response and higher cost compared with other antidiabetes therapies.[2–5]
- 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,[6–8] 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.[9,10]
- The aim of this study was to investigate the relationship between beta-cell function, as assessed by UCPCR, and glycaemic 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 glycaemic 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 (HbA_{1c}) change were evaluated using both non-parametric and parametric statistical methods.
- Multilinear regression models assessed the association between pre-treatment and on-treatment logarithm-transformed UCPCR (log UCPCR) and HbA_{1c} reduction at 32 weeks.
- HbA_{1c} change was assessed with increasing quartiles of pre-treatment UCPCR.
- Data are presented as mean ± standard deviation (SD) unless otherwise stated.

Results

- Overall, mean baseline HbA_{1c} was 9.3%, body mass index (BMI) was 38.2 kg/m^2, 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 HbA_{1c} reduction of –0.9% (±1.5) ($p<0.001$).
  - On-treatment subjects achieved a mean (SD) HbA_{1c} reduction of –1.4% (±1.3) ($p<0.001$).
- HbA_{1c} change was not found to be associated with age, duration of diabetes, estimated glomerular filtration rate, baseline weight, BMI, length of time taken between individual's HbA_{1c} measurements, gender, ethnicity, number of background oral antidiabetes drugs or concurrent insulin treatment.
- HbA_{1c} changes from baseline across quartiles of pre-treatment UCPCR are shown in Table 1.

Table 1: HbA_{1c} changes across quartiles of pre-treatment UCPCR.

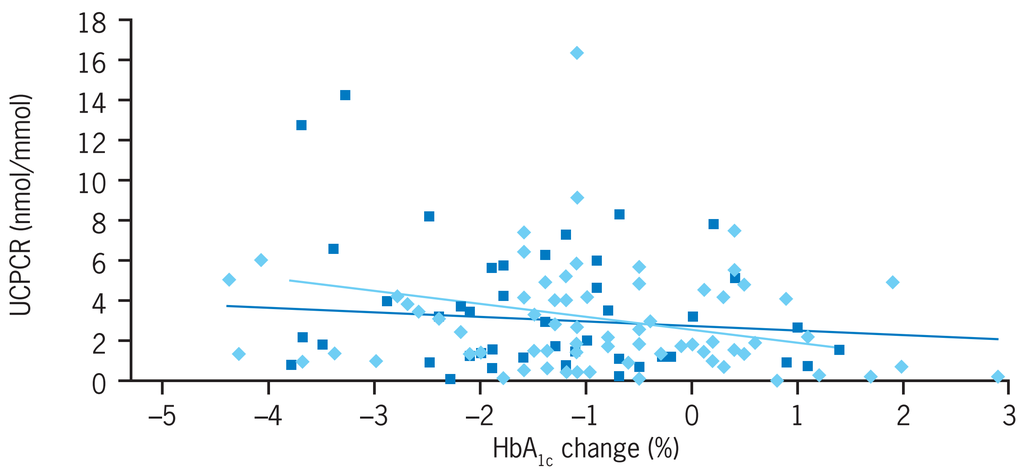
	Q1	Q2	Q3	Q4
n	17	18	18	17
UCPCR range (nmol/mmol)	<0.02–0.94	0.96–1.87	1.89–4.19	4.17–16.37
HbA_{1c} reduction (unadjusted)†				
%	–0.3 ± 1.6	–1.1 ± 1.4	–1.0 ± 1.2	–1.1 ± 1.6
mmol/mol	–3 ± 17	–12 ± 15	–11 ±13	–12 ± 17
p-value	0.52	0.003	0.002	0.016
HbA_{1c} reduction (adjusted)‡				
%	–0.5 ± 0.3	–0.8 ±0.3	–1.2 ± 0.3	–1.0 ± 0.3
mmol/mol	–5 ± 3	–9 ± 3	–13 ± 3	–11 ± 3

HbA_{1c} reduction shown: mean (±SD) (unadjusted) and least squares (LS) mean (±SEM) after adjusting for baseline HbA_{1c}. †p=0.27, ‡p=0.41 for effect across quartile groups. SEM, standard error of mean; UCPCR, urinary C-peptide creatinine ratio.

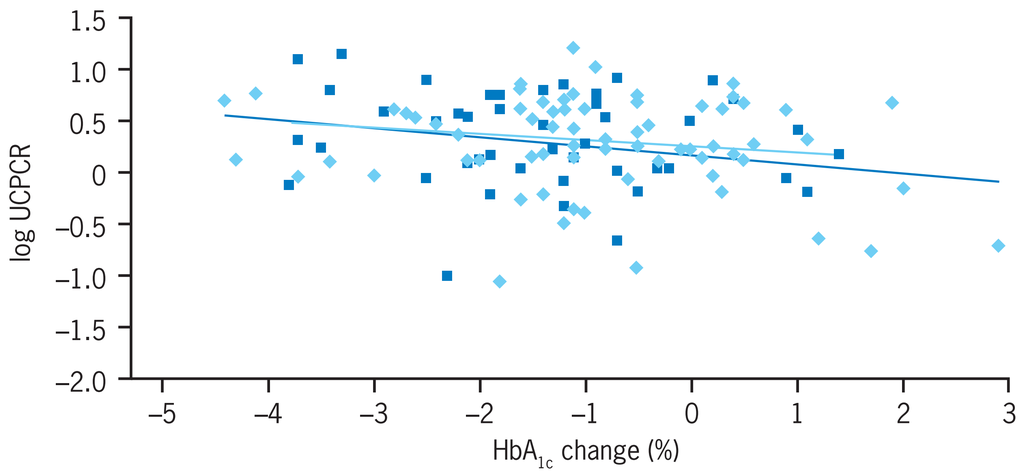
- No significant association between pre-treatment or on-treatment UCPCR and change in HbA_{1c} with liraglutide was found using non-parametric statistical analysis (Figure 1a).
- The association between UCPCR and change in HbA_{1c} improved after UCPCR was logarithm-transformed (log UCPCR) (Figure 1b).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

Figure 1: Scatterplot to show association between UCPCR and change in HbA_{1c}.

(a) UCPCR and HbA_{1c} change with liraglutide treatment at 32 weeks.



(b) log UCPCR and HbA_{1c} change with liraglutide treatment at 32 weeks.



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.

Where EVERYONE Matters

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