Markers of β-Cell Failure Predict Poor Glycemic Response to GLP-1 Receptor Agonist Therapy in Type 2 Diabetes

*Angus G. Jones,[1] Timothy J. McDonald,[1] Beverley M. Shields,[1] Anita V. Hill,[1] Christopher J. Hyde,[2] Bridget A. Knight,[1] and Andrew T. Hattersley,[1] for the PRIBA Study Group**

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OBJECTIVE

To assess whether clinical characteristics and simple biomarkers of β-cell failure are associated with individual variation in glycemic response to GLP-1 receptor agonist (GLP-1RA) therapy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We prospectively studied 620 participants with type 2 diabetes and HbA_{1c} ≥58 mmol/mol (7.5%) commencing GLP-1RA therapy as part of their usual diabetes care and assessed response to therapy over 6 months. We assessed the association between baseline clinical measurements associated with β-cell failure and glycemic response (primary outcome HbA_{1c} change 0–6 months) with change in weight (0–6 months) as a secondary outcome using linear regression and ANOVA with adjustment for baseline HbA_{1c} and cotreatment change.

RESULTS

Reduced glycemic response to GLP-1RAs was associated with longer duration of diabetes, insulin cotreatment, lower fasting C-peptide, lower postmeal urine C-peptide–to–creatinine ratio, and positive GAD or IA2 islet autoantibodies ($P \leq 0.01$ for all). Participants with positive autoantibodies or severe insulin deficiency (fasting C-peptide ≤0.25 nmol/L) had markedly reduced glycemic response to GLP-1RA therapy (autoantibodies, mean HbA_{1c} change −5.2 vs. −15.2 mmol/mol [−0.5 vs. −1.4%], $P = 0.005$; C-peptide <0.25 nmol/L, mean change −2.1 vs. −15.3 mmol/mol [−0.2 vs. −1.4%], $P = 0.002$). These markers were predominantly present in insulin-treated participants and were not associated with weight change.

CONCLUSIONS

Clinical markers of low β-cell function are associated with reduced glycemic response to GLP-1RA therapy. C-peptide and islet autoantibodies represent potential biomarkers for the stratification of GLP-1RA therapy in insulin-treated diabetes.

The glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) are effective glucose-lowering therapies commonly prescribed for patients with type 2 diabetes, typically as second- or third-line agents in combination with metformin and/or other oral therapy or in combination with insulin (1–3). These treatments are associated with weight loss and have a low risk of hypoglycemia in comparison with older therapies (4). However, in the absence of a clear difference in effectiveness and

[1]National Institute for Health Research Exeter Clinical Research Facility, University of Exeter Medical School and Royal Devon and Exeter National Health Service Foundation Trust, Exeter, U.K.
[2]Institute of Health Research, University of Exeter Medical School, Exeter, U.K.

Corresponding author: Angus G. Jones, angus.jones@exeter.ac.uk.

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**A list of members of the PRIBA Study Group is available in the Supplementary Data.*

long-term outcome, the choice of second- and third-line therapy in type 2 diabetes remains a subject of considerable debate (2,5).

The glycemic response to GLP-1RAs is highly variable, with some individuals achieving very marked response but others achieving no improvement in HbA_{1c} (3,6,7). While some of this variability will relate to lifestyle change, medication adherence, and measurement imprecision, it is likely that there will also be biological mechanisms contributing to this treatment response variation. Type 2 diabetes is a highly heterogeneous disease likely with different pathologies (8), and biomarker predictors of response to glucose-lowering therapies have been identified (9). Identifying clinical features or biomarkers predictive of response may help target treatment to those most likely to benefit; this would be particularly beneficial for the incretin therapies given their relatively high cost and frequency of short-term side effects (10).

A major mechanism of action of GLP-1RAs is potentiation of β-cell insulin secretion (4). We hypothesized that patients with more marked β-cell failure will be unable to substantially increase insulin secretion in response to GLP-1RAs and therefore will have reduced glycemic response.

We aimed to determine whether clinical characteristics and simple biomarkers associated with β-cell failure are associated with glycemic response to GLP-1RAs in patients with a clinical diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study hypothesis and outcomes were pre-specified and registered with ClinicalTrials.gov (https://clinicaltrials.gov/show/NCT01503112).

Study Setting and Participants

We prospectively studied 620 participants with a clinical diagnosis of type 2 diabetes, HbA_{1c} ≥58 mmol/mol (7.5%), and estimated glomerular filtration rate >30 mL/min/1.73 m^2 commencing GLP-1RA therapy as part of their usual diabetes care and assessed response to therapy over 6 months. Participants were identified from National Health Service primary and secondary care and recruited at 17 participating sites in England between April 2011 and October 2013. Ethics approval was granted by the South West National Research Ethics committee, and all participants gave written informed consent.

Assessment

At baseline, prior to commencing treatment, we assessed HbA_{1c} and clinical markers of β-cell failure (fasting C-peptide [11], post–largest home meal urine C-peptide–to–creatinine ratio [UCPCR] (12), GAD and IA2 autoantibodies [13], diabetes duration, and insulin cotreatment [14]). At 3 months (10–14 weeks) and 6 months (22–26 weeks) after commencing GLP-1RA therapy, we assessed HbA_{1c} and adherence (self-reported over the 2 weeks prior to HbA_{1c} measurement). Concurrent treatment was recorded at all visits.

The primary outcome measure was change in HbA_{1c} in the first 6 months of GLP-1RA therapy. Change in weight (baseline to 6 months) was assessed as a secondary outcome.

To minimize confounding by adherence or treatment change, we excluded a follow-up visit from analysis where participants had stopped therapy ≥7 days prior to HbA_{1c} assessment, had <75% self-reported adherence, had commenced any additional glucose-lowering therapies, or had stopped one or more concurrent oral hypoglycemic agent (OHA). Treatment response was based on the most recent eligible HbA_{1c}, with the 3-month result used if the 6-month result did not meet the above criteria. Analysis of weight change was restricted to those who met the above criteria at 6 months (n = 443, weight at 3 months was not assessed).

Statistical Analysis

Continuous Analysis

We assessed the relationship between baseline clinical markers of β-cell function and treatment response (HbA_{1c} change post–GLP-1RA therapy) using least squares linear regression with adjustment for baseline HbA_{1c} and cotreatment change (discontinuation of OHA and % change in insulin dose). Results were not adjusted for OHA dose change owing to lack of association with response (P = 0.3).

For determination of whether biomarkers added to knowledge of insulin treatment status, this analysis was repeated in subgroups defined by presence or absence of insulin cotreatment, with the inclusion of HOMA estimates of β-cell function (HOMA2%B) in non–insulin-treated participants. For determination of independence of autoantibody status and fasting C-peptide, this model was repeated with both C-peptide and autoantibody status as covariates. We assessed the relationship between clinical markers of β-cell function and weight loss post–GLP-1RA therapy using the same model with weight change (6 months − baseline) as the outcome variable.

Categorical Analysis

We assessed differences in adjusted mean change in HbA_{1c}, weight, and insulin dose across subgroups defined by autoantibody and C-peptide status using univariate ANOVA with baseline HbA_{1c} and treatment change as covariates. Fasting C-peptide subgroups were defined using previously reported thresholds for insulin requirement/type 1 diabetes (≤0.25 nmol/L) and absence of "clinically significant" endogenous insulin secretion (≤0.08 nmol/L) (15).

Additional Analysis

Differences in HbA_{1c} change at 3 and 6 months' follow-up were assessed with the related-samples t test, with analysis restricted to those on treatment at both visits with >75% adherence and no change in glucose-lowering cotreatments.

Statistical analysis was performed using Stata Statistical Software: Release 13 (StataCorp, College Station, TX).

Laboratory Analysis

HbA_{1c} and fasting glucose were measured in recruitment centers' local laboratories (all are accredited National Health Service blood science laboratories). HbA_{1c} measurement was standardized to the International Federation of Clinical Chemistry and Laboratory Medicine reference method procedure, and all repeated measurements within the same individual were analyzed within the same laboratory. C-peptide (blood and urine), urine creatinine (for UCPCR), and GAD/IA2 autoantibodies were measured in the Blood Sciences Department at the Royal Devon and Exeter Hospital, Exeter, U.K. C-peptide was measured using the E170 immuno-analyzer from Roche Diagnostics (Manheim, Germany). GAD and IA2 were measured using commercial ELISA assays (RSR Limited, Cardiff, U.K.) and a Dynex DSX automated ELISA system (Launch

Diagnostics, Longfield, U.K.) and were considered positive if ≥97.5th centile of 500 adult control subjects (GAD >11 World Health Organization units/mL, IA2 >15 World Health Organization units/mL) as previously reported (16).

HOMA2%B and HOMA estimates of insulin sensitivity (HOMA2%S) were calculated in non–insulin-treated participants from fasting glucose and C-peptide using the HOMA2 calculator available from http://www.dtu.ox.ac.uk/homacalculator/ and are reported in Supplementary Data.

RESULTS

Participant Characteristics and Response to Therapy

Participant characteristics are shown in Table 1, and participant flow is detailed in Fig. 1. Mean (SD) reduction in HbA_{1c} and weight was 14.9 (17.2) mmol/mol (1.4 [1.6]%) and 4.5 (5.6) kg. A total of 546 participants met criteria for inclusion in analysis (analysis on treatment HbA_{1c} at 6 months n = 443 and at 3 months n = 103). HbA_{1c} change at 3 and 6 months posttreatment was not different (mean change −15.7 vs. −15.1 mmol/mol, respectively, P = 0.2). Of participants, 64% were treated with liraglutide, 27% exenatide twice daily, and 9% exenatide once weekly.

Markers of Low Insulin Secretion Are Associated With Reduced Glycemic Response to GLP-1RAs

Markers of reduced insulin secretion were consistently associated with reduced glycemic response to GLP-1RA therapy (Table 2). Less response was seen in those with lower C-peptide, lower UCPCR, positive GAD or IA2 islet autoantibodies, longer duration of diabetes, and insulin cotreatment ($P \leq 0.01$ for all). A 1 nmol/L decrease in fasting C-peptide was associated with 3.2 mmol/mol (0.3%) less HbA_{1c} reduction post–GLP-1RA therapy (Supplementary Fig. 1); the presence of insulin cotreatment or islet autoantibodies was associated with an 8.5 and 10.0 mmol/mol (0.8 and 0.9%) reduction in glycemic response, respectively.

Baseline measurements associated with glycemic response were not associated with change in weight ($P > 0.2$ for all).

Participants With Severe Insulin Deficiency Had Markedly Reduced Glycemic Response to GLP-1RA Therapy

Participants with C-peptide <0.25 nmol/L (a previously reported threshold for insulin requirement and type 1 diabetes [15]) had markedly reduced glycemic response (Fig. 2*A*) (mean adjusted HbA_{1c} change −2.1 [95% CI −10.2, 6.0] vs. −15.3 [−16.5, −14.0] mmol/mol [−0.2 vs. −1.4%], P = 0.002). Prevalence of C-peptide ≤0.25 nmol/L was low, with this characteristic predominantly found in insulin-treated participants (6.1% and 0.3% of insulin and non-insulin-treated participants, respectively).

A lower C-peptide threshold of ≤0.08 nmol/L (absence of "clinically significant" endogenous insulin [15]) identified fewer participants (3.4% of those insulin treated) with more marked lack of response to therapy (adjusted mean change 3.7 mmol/mol [95% CI −6.6, 14.0] vs. −15.2 mmol/mol [−16.4, −14.0] [0.3 vs. −1.4%], P = 0.0004).

Table 1—Participant baseline characteristics

Characteristics	Mean (SD) or %
HbA_{1c} (mmol/mol)	83 (17)
HbA_{1c} (%)	9.7 (1.6)
Fasting glucose (mmol/L)	11.9 (3.7)
% male	54
% insulin treated	38
Age (years)	56 (10.4)
Duration of diabetes (years)	10.0 (6.6)
BMI (kg/m^2)	39.7 (7.5)
Fasting C-peptide (nmol/L) (n = 532)	1.2 (0.6)
UCPCR (nmol/mmol) (N = 496)	3.6 (3.1)
Islet autoantibody positive (GAD/IA2) (N = 520)	3.7% (GAD only 3.1%, GAD and IA2 0.6%, IA2 only 0%)

N = 546 except where otherwise specified.

Presence of Raised GAD and/or IA2 Islet Autoantibodies Is Independently Associated With Reduced Response to GLP-1RA Therapy

Glycemic response to GLP-1RA was also markedly lower in those who were GAD or IA2 antibody positive (adjusted mean HbA_{1c} change −4.6 mmol/mol [95% CI −10.3, 1.1] vs. −15.5 mmol/mol [−16.8, −14.2] [−0.4 vs. −1.4%], P = 0.0003) (Fig. 2*B*). The relationship between autoantibody status and response was not fully explained by differences in fasting insulin secretion: after adjustment for fasting C-peptide, autoantibodies were associated with an 8.1 mmol/mol (0.7%) reduction in glycemic response to GLP-1RA (P = 0.02). Eight percent of insulin-treated participants and 0.9% of non–insulin-treated participants were GAD or IA2 positive.

When analysis was restricted to autoantibody-negative participants, diabetes duration, insulin cotreatment, and fasting C-peptide remained associated with glycemic response (Supplementary Table 1).

Biomarkers of β-Cell Failure Remained Associated With Glycemic Response in Patients Receiving Insulin Treatment

Insulin treatment was strongly associated with other markers of β-cell failure, with longer diabetes duration, lower C-peptide–based measures, and higher proportion of positive autoantibodies seen in insulin-treated patients (P < 0.001 for all) (Supplementary Table 2). In those treated with insulin, C-peptide–based measures and autoantibodies remained predictive of glycemic response (Supplementary Table 3): a 1 nmol/L decrease in fasting C-peptide was associated with a 4.3 mmol/mol (0.4%) reduction in glycemic response (P = 0.01), and positive autoantibodies were associated with an 8.1 mmol/mol (0.7%) reduction in response (P = 0.03). However, these characteristics were not associated with response in non–insulin-treated participants (P for all >0.18) (Supplementary Table 4).

Insulin-Treated Patients With Low C-Peptide or Positive Autoantibodies Have Reduced Response to GLP-1RA Therapy

Eleven percent of insulin-treated participants had either positive autoantibodies or low C-peptide (≤0.25 nmol/L).

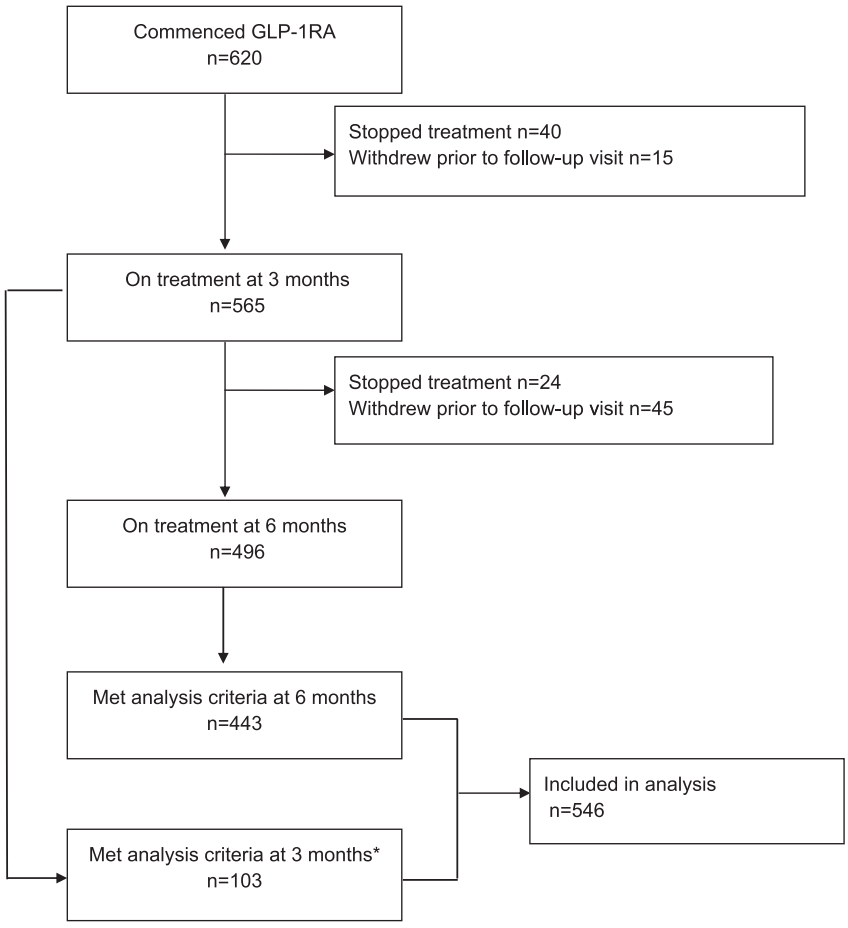

Figure 1—Study profile.

These participants had mean change in HbA_{1c} after GLP-1RA therapy of −2.3 mmol/mol (95% CI −8.4, 3.7) (−0.2%) compared with −10.9 mmol/mol (−12.9, −8.8) (−1.0%) in other insulin-treated participants (Fig. 3). Antibody-positive/low C-peptide participants also had less reduction in insulin dose (17% vs. 40%, $P = 0.006$); however, weight loss was similar (weight change at 6 months −4.2 vs. −5.0 kg, $P = 0.05$) (Fig. 3). The clinical characteristics of insulin-treated participants with and without low C-peptide and/or positive autoantibodies were similar: mean BMI 36.6 vs. 39.7 kg/m^2 ($P = 0.07$), age at diagnosis 42.2 vs. 44.3 years ($P = 0.4$), diabetes duration 14.5 vs. 12.8 years ($P = 0.3$), and time to insulin 5.8 vs. 5.9 years ($P = 0.9$).

CONCLUSIONS

This study demonstrates that markers of β-cell failure are associated with reduced glycemic response to GLP-1 receptor analogs. Insulin-treated patients and those who have positive islet autoantibodies and/or low C-peptide have markedly reduced glycemic response to this treatment. Participants with these markers of β-cell failure had reduced glycemic response without additional weight loss, suggesting that they will derive less overall benefit from GLP-1RA treatment.

Our finding that markers of β-cell failure are associated with reduced response to GLP-1RA therapy is consistent with findings of previous studies. Research in smaller cohorts has suggested that those with lower blood C-peptide have less insulin secretion in response to GLP-1RA (17) and are less able to replace insulin with a GLP-1RA (18,19) and that low home postmeal urine C-peptide–to–creatinine ratio is associated with reduced glycemic response to liraglutide (20). Previous research demonstrating reduced response to GLP-1RA in those receiving insulin cotreatment or with longer diabetes duration is also consistent with our findings (3,21). In contrast, one study has demonstrated increased HbA_{1c} reduction in insulin-treated patients with longer duration of diabetes, a finding principally driven by increased response to placebo in the short-duration comparator group (22).

To our knowledge, this is the first study to assess the relationship between islet autoantibodies and response to GLP-1RA therapy. The independence of autoantibody and C-peptide testing in our study may suggest that the mechanism, as well as the severity, of underlying β-cell failure is important to treatment response.

Table 2—The relationship between baseline markers of β-cell function and HbA_{1c} changes after GLP-1RA therapy

	Association with HbA_{1c} change (mmol/mol)			
Baseline characteristic	Regression coefficient (95% CI)*	Standardized regression coefficient (95% CI)**	*T* statistic***	Significance (*P*)
Diabetes duration (years)	0.27 (0.08, 0.46)	0.10 (0.03, 0.18)	2.7	0.006
Insulin cotreatment	8.5 (5.3, 11.7)	—	5.2	<0.001
Fasting C-peptide (nmol/L)	−3.2 (−5.2, −1.2)	−0.12 (−0.19, −0.04)	−3.1	0.002
UCPCR (nmol/mmol)	−0.56 (−1.0, −0.12)	−0.10 (−0.18, −0.02)	−2.5	0.01
Autoantibody (GAD/IA2) positive	10.0 (3.1, 16.8)	—	2.8	0.005

*A negative regression coefficient denotes a greater HbA_{1c} reduction with a higher baseline value or presence of dichotomous state. **Number of SDs difference in HbA_{1c} change post–GLP-1RA for a 1-SD increase in baseline value. ***Regression coefficient/SE.

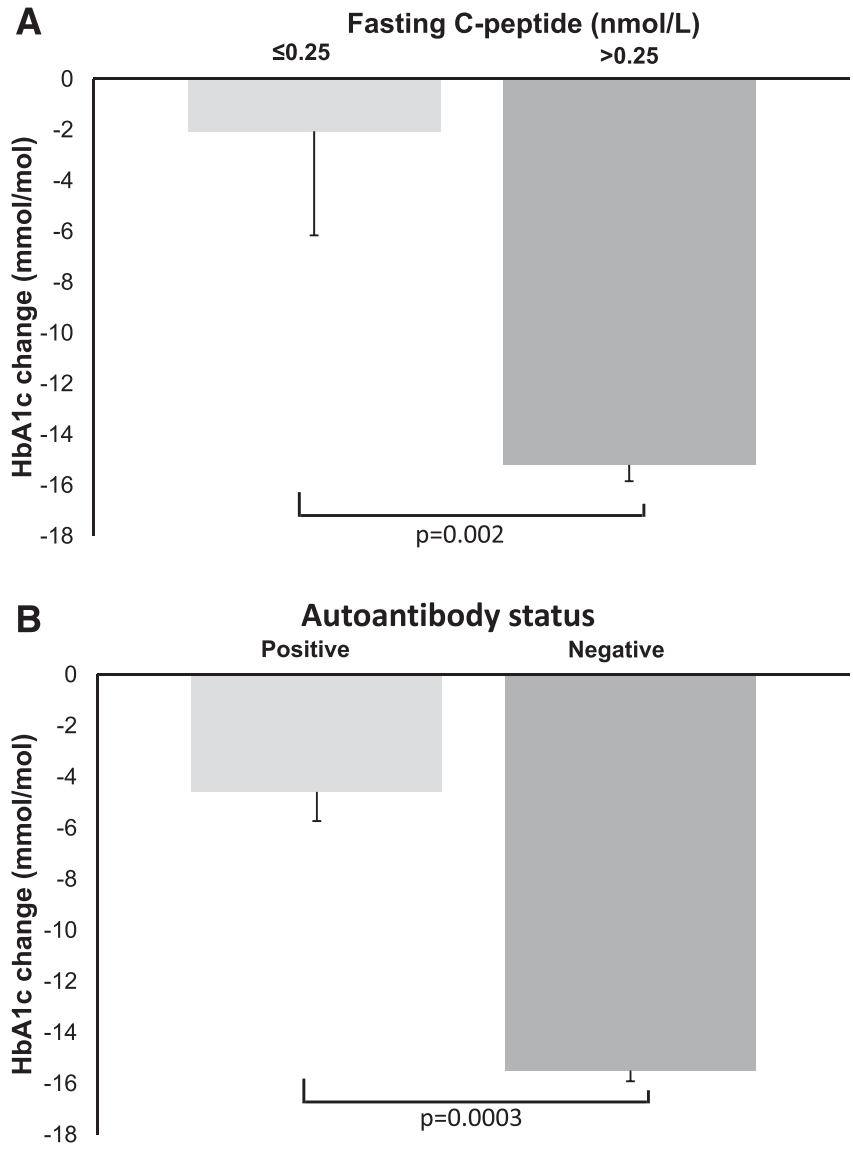

Figure 2—HbA_{1c} change post–GLP-1RA therapy in those with and without severe insulin deficiency (C-peptide ≤0.25 nmol/L; *n* = 13 of 516) (*A*) and positive GAD and/or IA2 antibodies (*n* = 19 of 501) (*B*). Bar represents mean change, and error bars represent SE.

Further studies with more robust assessment of stimulated insulin secretion would be needed to test this hypothesis.

The lack of glycemic response seen in this cohort where β-cell failure is marked is consistent with potentiation of β-cell insulin secretion being the major mechanism of glucose lowering by GLP-1RAs. These agents have additional non–β-cell-dependent glucose-lowering effects on gastric emptying and suppression of glucagon; however, the relative contributions of these actions to glucose lowering remain unclear (23,24). While acute administration of GLP-1 markedly reduces meal-induced glucagon secretion, gastric emptying, and postprandial glucose even in C-peptide–negative type 1 diabetes (25), chronic treatment with GLP-1RAs appears to have only a small effect on plasma glucagon (26–30) and may have little effect on gastric emptying (31,32). This finding is consistent with poor glycemic effect of ongoing administration of GLP-1RAs in type 1 diabetes randomized controlled trials, where there appears to be a small reduction in insulin dose without improvement in glycemia (33,34).

Strengths and Weaknesses

A strength of this study is that we have prospectively examined a large number of participants in a real-world setting with detailed assessment at both baseline and follow-up. Our finding that many different markers of reduced β-cell function are consistently associated with reduced GLP-1RA response suggests that this is a robust finding.

Limitations of this study include that our major assessment of β-cell function is fasting blood or post–home meal urine C-peptide. These are affected by concurrent glucose, insulin sensitivity, and C-peptide clearance and therefore represent relatively crude indicators of underlying β-cell function (15). Physiological assessment of β-cell function would ideally involve measures after a standardized stimulus alongside correction for insulin sensitivity (35); however, these measures would not be feasible for clinical practice. β-Cell function and insulin sensitivity are inversely related (36,37). A role for β-cell failure (rather than insulin sensitivity) in reduced GLP-1RA glycemic response is supported by the direction of association (better insulin sensitivity being an unlikely cause of reduced treatment response) and finding associations for factors predominantly associated with β-cell failure (autoantibodies [13], absolute insulin deficiency, insulin cotreatment, and diabetes duration [14]). In addition, characteristics associated with insulin resistance (BMI, triglycerides, HDL, sex hormone–binding globulin, and HOMA2%S [38,39]) were not associated with glycemic response in this cohort ($P > 0.6$ for all) (Supplementary Table 5).

An additional potential limitation of fasting C-peptide measurement in a cohort including insulin-treated patients is the potential suppression of fasting C-peptide if concurrent insulin results in low fasting glucose (40). However, study participants had high fasting glucose at the time of C-peptide assessment, and the difference between those treated with and without insulin was small (mean fasting glucose 11.2 and 12.4 mmol/L, respectively).

Clinical Implications

The main clinical implications of this study are for use of GLP-1RA therapy in insulin-treated patients. Our study confirms that overall less glycemic response should be expected in those who are insulin treated. Where insulin-treated patients are known to be antibody positive or have low C-peptide, our results suggest that these patients are

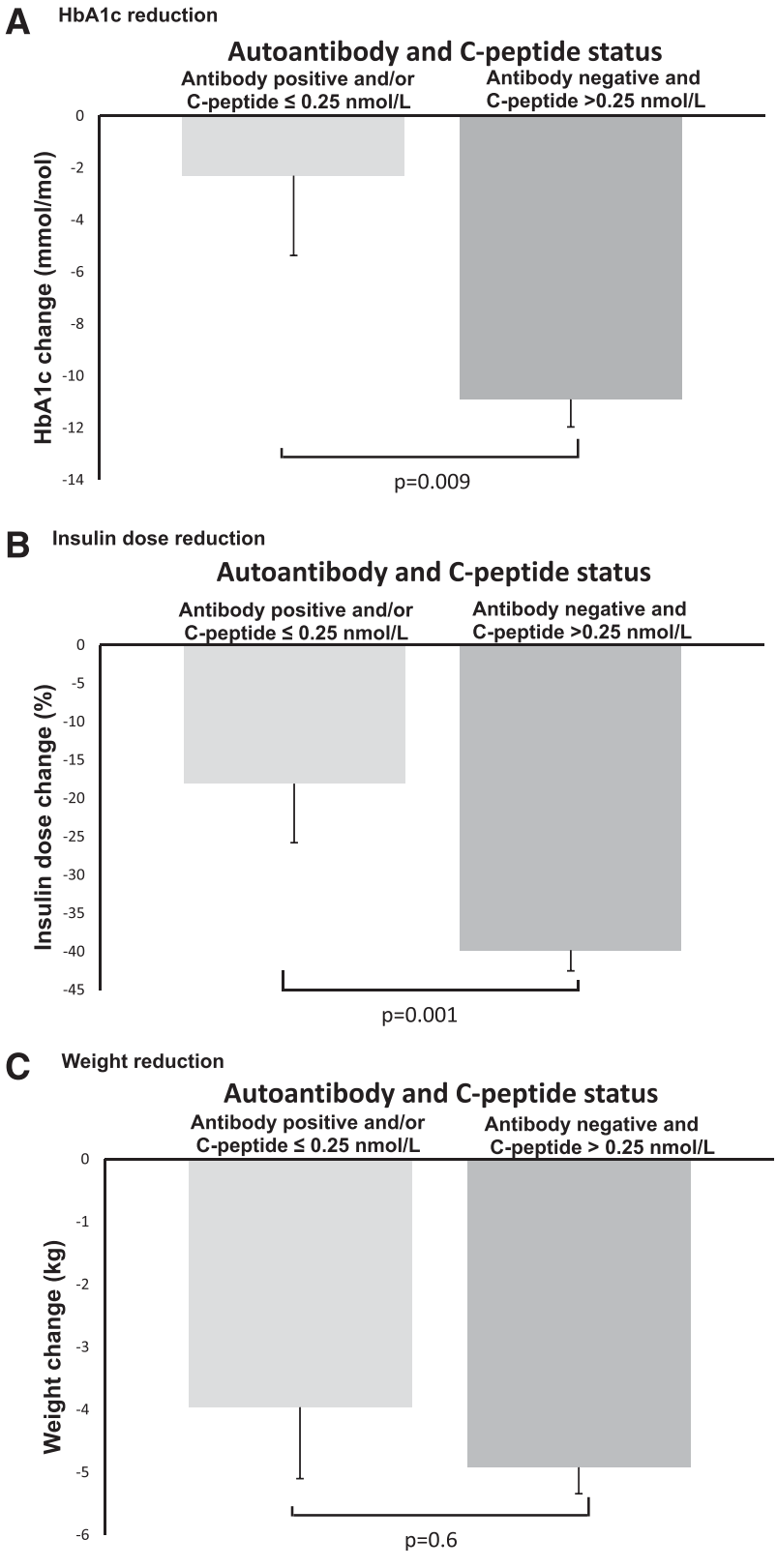

Figure 3—Treatment response to GLP-1RA therapy in insulin-treated participants by autoantibody and C-peptide status. Analysis adjusted for baseline HbA_{1c} and cotreatment change. Bar represents mean change, and error bars represent SE. Antibody positive and/or low C-peptide, $n = 22$; remaining participants, $n = 176$. *A*: HbA_{1c} reduction. *B*: Insulin dose reduction. *C*: Weight reduction.

unlikely to receive glycemic benefit from GLP-1RA therapy. This would be consistent with existing guidelines, which do not recommend GLP-1RA therapy for type 1 diabetes. When the antibody and C-peptide status is not known, the cost of testing needs to be balanced against an empirical trial of therapy; further larger studies to confirm the effect size and prevalence of these features would be needed to determine whether testing for this reason would be cost-effective.

Our results show that a significant proportion of insulin-treated patients receiving these treatments in the U.K. have islet autoantibodies and/or low C-peptide, despite having a clinical diagnosis of type 2 diabetes. These patients could not be identified by their clinical features. This may relate to the obese (and relatively young) nature of our cohort, as U.K. guidelines restrict these treatments to the obese (1). Differentiating type 1 and type 2 diabetes is particularly difficult in younger obese individuals. Both the clinical presentation and course of autoimmune diabetes can be very different from classical type 1 diabetes in the obese (41).

Our study does not support the measurement of antibodies and C-peptide in non–insulin-treated patients, as prevalence of low C-peptide and positive autoantibodies was very low in this group and an association with response was not seen.

Unanswered Questions and Future Research

Our findings of reduced response in those with positive autoantibodies and severe insulin deficiency need replication, as they are driven by a marked difference in response in a relatively small number of participants. This would ideally be in the setting of a randomized trial targeting insulin-treated patients who are more likely to have these characteristics. Further research is also needed to assess whether insulin-treated patients with high antibody titers and/or absolute insulin deficiency have reduced response to all noninsulin glucose-lowering cotherapies. This is an important question given the increasing difficulties distinguishing type 1 and 2 diabetes as obesity becomes more prevalent and the lack of glycemic effect of noninsulin treatments in type 1 diabetes

randomized controlled trials to date (33,34,42–44), which may relate to loss of endogenous insulin secretion even where a treatment's mechanism of action appears unrelated (45).

Summary

In summary, markers of reduced insulin secretion are associated with less glycemic response to GLP-1RA therapy. C-peptide and autoantibodies represent potential biomarkers for the stratification of glucose-lowering treatment in insulin-treated diabetes.

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