CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

Precision Medicine in Type 2 Diabetes: Clinical Markers of Insulin Resistance Are Associated With Altered Short- and Long-term Glycemic Response to DPP-4 Inhibitor Therapy

John M. Dennis,[1] Beverley M. Shields,[2] Anita V. Hill,[2] Bridget A. Knight,[2] Timothy J. McDonald,[2,3] Lauren R. Rodgers,[1] Michael N. Weedon,[4] William E. Henley,[1] Naveed Sattar,[5] Rury R. Holman,[6] Ewan R. Pearson,[7] Andrew T. Hattersley,[2] and Angus G. Jones,[2] on behalf of the MASTERMIND Consortium

Diabetes Care 2018;41:705–712 | https://doi.org/10.2337/dc17-1827

OBJECTIVE

A precision approach to type 2 diabetes therapy would aim to target treatment according to patient characteristics. We examined if measures of insulin resistance and secretion were associated with glycemic response to dipeptidyl peptidase 4 (DPP-4) inhibitor therapy.

RESEARCH DESIGN AND METHODS

We evaluated whether markers of insulin resistance and insulin secretion were associated with 6-month glycemic response in a prospective study of noninsulin-treated participants starting DPP-4 inhibitor therapy (Predicting Response to Incretin Based Agents [PRIBA] study; *n* = 254), with replication for routinely available markers in U.K. electronic health care records (Clinical Practice Research Datalink [CPRD]; *n* = 23,001). In CPRD, we evaluated associations between baseline markers and 3-year durability of response. To test the specificity of findings, we repeated analyses for glucagon-like peptide 1 (GLP-1) receptor agonists (PRIBA, *n* = 339; CPRD, *n* = 4,464).

RESULTS

In PRIBA, markers of higher insulin resistance (higher fasting C-peptide [*P* = 0.03], HOMA2 insulin resistance [*P* = 0.01], and triglycerides [*P* < 0.01]) were associated with reduced 6-month HbA_{1c} response to DPP-4 inhibitors. In CPRD, higher triglycerides and BMI were associated with reduced HbA_{1c} response (both *P* < 0.01). A subgroup defined by obesity (BMI ≥30 kg/m^2) and high triglycerides (≥2.3 mmol/L) had reduced 6-month response in both data sets (PRIBA HbA_{1c} reduction 5.3 [95% CI 1.8, 8.6] mmol/mol [0.5%] [obese and high triglycerides] vs. 11.3 [8.4, 14.1] mmol/mol [1.0%] [nonobese and normal triglycerides]; *P* = 0.01). In CPRD, the obese, high-triglycerides subgroup also had less durable response (hazard ratio 1.28 [1.16, 1.41]; *P* < 0.001). There was no association between markers of insulin resistance and response to GLP-1 receptor agonists.

CONCLUSIONS

Markers of higher insulin resistance are consistently associated with reduced glycemic response to DPP-4 inhibitors. This finding provides a starting point for the application of a precision diabetes approach to DPP-4 inhibitor therapy.

[1]Health Statistics Group, University of Exeter Medical School, Exeter, U.K.
[2]National Institute for Health Research Exeter Clinical Research Facility, University of Exeter Medical School, Exeter, U.K.
[3]Blood Sciences, Royal Devon and Exeter Hospital, Exeter, U.K.
[4]Institute of Biomedical and Clinical Science, University of Exeter Medical School, Exeter, U.K.
[5]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, U.K.
[6]Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, U.K.
[7]Division of Molecular & Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee, U.K.

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

Received 31 August 2017 and accepted 28 December 2017.

Clinical trial reg. no. NCT01503112, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1827/-/DC1.

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at http://www.diabetesjournals.org/content/license.

abetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025

Type 2 diabetes is a heterogeneous condition characterized by varying degrees of reduced β-cell function and higher levels of insulin resistance. Most of the 400 million patients worldwide will at some point require glucose-lowering medication (1). Major international treatment guidelines recommend at least four oral treatment options after initial metformin has failed to achieve control, with choice between these informed predominantly by method of administration, overall side effect profile, and cost (2–5).

Individual response to glucose-lowering therapies in type 2 diabetes varies greatly. Identification of clinical phenotypic features or biomarkers robustly associated with glycemic response or other potentially beneficial effects (for example, reduced weight gain or side effects for each therapy) may allow treatment of patients with the agent that is most likely to be effective for them, an approach known as "precision" or "stratified" medicine (6,7). Although much research has focused on identifying genetic or novel biomarker predictors of response, precision diabetes is most likely to be cost effective and have clinical impact using simple inexpensive biomarkers or routinely available clinical phenotypic features (8,9).

Dipeptidyl peptidase 4 (DPP-4) inhibitors are common (20% of U.S. and 27% of U.K. second-line glucose-lowering prescriptions after metformin in 2013) (10,11), well-tolerated (12) oral therapy options recommended in all clinical guidelines (2–5). Beyond baseline HbA_{1c} and fasting glucose, it is unclear if other factors are associated with glycemic response to DPP-4 inhibitors (13,14). A major mechanism of action of DPP-4 inhibitors is potentiation of β-cell insulin secretion. We aimed to establish if measures of insulin secretion and insulin resistance were associated with short-term glycemic response and long-term durability of response in patients with type 2 diabetes starting DPP-4 inhibitor therapy.

RESEARCH DESIGN AND METHODS

We assessed whether clinical features and biomarkers associated with insulin secretion and insulin resistance were predictive of short-term 6-month glycemic response in analysis of a prospective study of patients starting DPP-4 inhibitor therapy as part of routine care (Predicting Response to Incretin Based Agents [PRIBA] study). To validate our findings, we tested the consistency of associations between routinely recorded factors associated with response in PRIBA in a retrospective analysis of a much larger group of patients from the U.K. Clinical Practice Research Datalink (CPRD), evaluating both 6-month glycemic response and long-term durability of response to 3 years.

Study Setting and Assessment

PRIBA Prospective Study

The PRIBA study was designed to test the hypothesis that those who have low insulin secretion, as measured by C-peptide, will have poor glycemic response to incretin-based treatments (https://clinicaltrials.gov/ct2/show/NCT01503112), with associations between glycemic response and other clinical features, islet autoantibodies and HOMA2 estimates of β-cell function, and insulin sensitivity evaluated in prespecified secondary analysis. Three hundred five participants due to start DPP-4 inhibitor therapy as part of their usual care were recruited from primary and secondary care across 17 National Institute for Health Research (NIHR) clinical research network centers in the U.K. from April 2011 to October 2013 as previously described (15).

At baseline (immediately prior to starting therapy), we measured HbA_{1c}, fasting glucose, clinical markers of insulin resistance and insulin secretion (fasting C-peptide and postmeal urine C-peptide creatinine ratio [UCPCR] [16,17], BMI, triglycerides, HDL-cholesterol [HDL-c] [18], sex hormone–binding globulin [SHBG], GAD, and IA2 islet autoantibodies), and other clinical characteristics (age at therapy, sex, duration of diabetes, estimated glomerular filtration rate [eGFR], ethnicity, LDL-cholesterol [LDL-c], and number of diabetes therapies). We calculated HOMA2-%B and HOMA2 estimates of insulin resistance (HOMA2-IR) from fasting glucose and C-peptide measures using the HOMA2 calculator available from http://www.dtu.ox.ac.uk/homacalculator/ (19). Laboratory analysis was conducted as previously reported (15). Participants were included in the analysis if they were not insulin treated and had at least 3 months' follow-up with >75% adherence to therapy and limited cotreatment change (see study profile in Supplementary Fig. 1*A*). Ethics approval was granted by the South West National Research Ethics Committee, and all participants gave written informed consent.

Retrospective Analysis of U.K. Primary Care Patients (CPRD Database)

CPRD is the world's largest longitudinal database of anonymized primary care electronic health records (20). We included 23,001 noninsulin-treated patients with type 2 diabetes with prescription records of starting a DPP-4 inhibitor for the first time from June 2007 to September 2016 and followed them up while they remained on DPP-4 inhibitor therapy without the addition or cessation of any other antihyperglycemic medication (see study profile in Supplementary Fig. 1*B*). We extracted baseline routine clinical characteristics (age at therapy, duration of diabetes, sex, and BMI) and biomarkers (HbA_{1c}, triglycerides, HDL-c, LDL-c, and eGFR), with baseline defined as the most recent record in the 3 months prior to the drug start date. Ethics approval was granted by the CPRD Independent Scientific Advisory Committee (ISAC 13_177R).

Outcomes

Short-term Glycemic Response (PRIBA and CPRD)

The primary outcome was the absolute change from baseline in HbA_{1c} 6 months after starting therapy, adjusting for baseline HbA_{1c}. When a 6-month HbA_{1c} was not available or eligible in the PRIBA study (Supplementary Fig. 1*A*), we used a 3-month HbA_{1c} measure, as previously described (15). In CPRD, a valid 6-month HbA_{1c} was defined as the closest HbA_{1c} to 6 months after the drug start date ±3 months for patients on unchanged antihyperglycemic therapy.

Durability of Glycemic Response (CPRD)

In CPRD, in which long-term follow-up data were available, we assessed durability of response as the time to glycemic failure up to 3 years in a complete case analysis of patients with baseline HbA_{1c} between 53 and 97 mmol/mol (7–11%) and at least 3 months on DPP-4 inhibitor therapy (n = 15,616). Glycemic failure was defined as *1*) two consecutive HbA_{1c} measurements >69 mmol/mol (8.5%) or *2*) a single HbA_{1c} measurement >69 mmol/mol (8.5%) followed by the addition of another antihyperglycemic therapy. To examine the sensitivity of results to this definition, we repeated the analysis using HbA_{1c} thresholds of *1*) 53 mmol/mol (7.5%) and *2*) the baseline HbA_{1c} level specific to each individual patient.

Downloaded from http://diabetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025

Statistical Analysis

Short-term Response (PRIBA and CPRD)

We examined associations between each standardized marker of insulin resistance and insulin secretion and 6-month HbA_{1c} response in a series of linear regression models adjusted for baseline HbA_{1c} and, in PRIBA, cotherapy change (13,20). Non-normally distributed variables were log-transformed. We conducted a complete case analysis for each marker, including all patients with valid data even if they had missing data for other markers. To evaluate model fit, we examined normality of residuals and linearity of associations for continuous variables. In both data sets, we tested the independence of initial associations for each marker of insulin resistance and insulin secretion with 6-month response in further multivariable analysis, controlling for baseline HbA_{1c} and other routinely recorded characteristics: age at therapy, duration of diabetes, sex, eGFR, LDL-c, ethnicity (CPRD only: white, nonwhite, and missing), and cotherapy change (PRIBA only; CPRD patients all on unchanged therapy).

To further assess the robustness of findings, we repeated the baseline adjusted analysis of 6-month response for males and females separately in both data sets and in PRIBA with additional adjustment for fasting glucose. In CPRD, we repeated the baseline adjusted analysis using 12-month response as the outcome in a distinct cohort of patients with a 12-month (closest ±3 months as for definition of 6-month response) HbA_{1c} record (n = 16,166).

Subgroup Analysis of Short-Term Response (PRIBA and CPRD)

Based on the initial results, we defined three patient subgroups by standard clinical cutoffs for obesity (BMI ≥30 kg/m^2) and high triglycerides (≥2.3 mmol/L) (21): group A, nonobese and normal triglycerides; group B, nonobese or normal triglycerides; and group C, obese and high triglycerides. We estimated the mean 6-month HbA_{1c} response for each subgroup using linear regression models adjusted for baseline HbA_{1c} and, in PRIBA, cotherapy change. We standardized baseline HbA_{1c} to the mean PRIBA baseline level of 74 mmol/mol (8.9%) for all subgroups in both data sets.

Durability of Response (CPRD)

For three subgroups defined by the same BMI and triglyceride thresholds, we compared mean durability in response to 3 years after starting therapy using a flexible parametric time to failure survival model. We included all patients with at least 3 months on therapy after starting a DPP-4 inhibitor with valid baseline records of all covariates (baseline HbA_{1c}, age at therapy, duration of diabetes, sex, and eGFR). The use of flexible parametric models allowed prediction of the probability of therapy failure over 3 years as well as hazard ratios (HRs) consistent with Cox proportional hazards regression (22). We tested continuous variables for nonlinearity and evaluated proportional hazards assumptions using Schoenfeld residuals. To estimate the probability of therapy failure for each subgroup, a predicted survival curve was calculated for each patient in the data set before the individual survival curves for all patients within a subgroup were averaged (23). Each curve was standardized to the mean CPRD values of other clinical covariates (baseline HbA_{1c} 72 mmol/mol [8.7%]; age at therapy 64 years; duration of diabetes 8 years; and eGFR 82 mL/min/1.73 m^2). Point estimates for the failure probability at 3 years by subgroup were calculated using the same approach.

Replication Analysis With Glucagon-like Peptide 1 Receptor Agonists (PRIBA and CPRD)

To test the specificity of findings for DPP-4 inhibitors, we repeated the analyses of short-term response and durability of response for noninsulin-treated subjects starting glucagon-like peptide 1 (GLP-1) receptor agonists, the other glucose-lowering drug evaluated in PRIBA (PRIBA, n = 339; CPRD, n = 4,464). We have previously reported the PRIBA primary analysis of predictors of glycemic response for the full PRIBA GLP-1 receptor agonist cohort, which included an additional 209 insulin-treated participants (14). All data extraction and analysis were conducted using Stata v14.0 (StataCorp, College Station, TX).

RESULTS

Patient Characteristics and Response to DPP-4 Inhibitor Therapy

Baseline characteristics and biomarker measures were similar for subjects starting DPP-4 inhibitors in both data sets (Table 1). In both cohorts, the majority of patients started sitagliptin. Two hundred fifty-four patients were included in PRIBA and 23,001 (for analysis of 6-month glycemic response) in CPRD (for study profiles, see Supplementary Fig. 1). Mean (SD) 6-month HbA_{1c} change was −8.3 (13.5) mmol/mol (−0.7% [1.2%]) in PRIBA and −7.6 (15.1) mmol/mol (−0.7% [1.4%]) in CPRD.

Higher Baseline Fasting C-Peptide and HOMA2-IR Are Associated With Reduced Glycemic Response to DPP-4 Inhibitors

In the PRIBA cohort, mean HbA_{1c} response was reduced by 1.67 mmol/mol for every 1 SD higher baseline fasting C-peptide (standardized β 1.67 [95% CI 0.17, 3.17] mmol/mol/SD; P = 0.03) (Fig. 1). We observed the same direction and similar size of effect for UCPCR (response reduction per SD higher 1.65 [95% CI −0.07, 3.37] mmol/mol; P = 0.06). Higher baseline HOMA2-IR was also associated with reduced response (response reduction per SD higher: 2.17 [95% CI 0.62, 3.72] mmol/mol; P = 0.01), but there was no evidence of an association between β-cell function (HOMA2-%B) and response (response reduction per SD higher 0.16 [95% CI −1.49, 1.81] mmol/mol; P = 0.85). Islet autoantibody prevalence was low (2.8% GAD or IA2 positive; response reduction for presence of autoantibodies: 5.6 [95% CI −3.6, 14.7] mmol/mol; P = 0.23).

Other Markers of Insulin Resistance Are Consistently Associated With Glycemic Response to DPP-4 Inhibitors in PRIBA and CPRD

In PRIBA, higher triglycerides was associated with reduced glycemic response (response reduction per SD increase 2.54 [95% CI 0.99, 4.08] mmol/mol; $P < 0.001$), with a consistent direction of association for higher BMI (response reduction per higher BMI 0.96 [95% CI −0.54, 2.46] mmol/mol; P = 0.21) and lower SHBG (response reduction per SD higher SHBG −1.19 [95% CI −2.81, 0.42] mmol/mol; P = 0.15) (Fig. 1 and Supplementary Table 1). In CPRD, higher triglycerides and BMI were associated with reduced HbA_{1c} response (Fig. 1 and Supplementary Table 1). HDL-c was not associated with response in either data set (P = 0.81 in PRIBA; P = 0.46 in CPRD).

Markers of Insulin Resistance Are Associated With Glycemic Response to DPP-4 Inhibitors Independently of Other Routine Clinical Characteristics

Results were consistent when *1*) stratifying by sex (Supplementary Table 1), *2*) controlling for baseline HbA_{1c}, age at therapy,

Downloaded from http://diabetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025

Table 1—Subject baseline characteristics

	PRIBA (*n* = 254)	CPRD (*n* = 23,001)
Characteristics		
Baseline HbA_{1c} (mmol/mol)	74 (12)	72 (15)
Baseline HbA_{1c} (%)	8.9 (1.1)	8.7 (1.3)
Age at therapy start (years)	63 (10)	64 (11)
Age at diagnosis (years)	54 (10)	56 (10)
Male sex, %	63	61
Duration of diabetes (years)	9 (6)	8 (5)
BMI	32 (29–37); 33 (6)	32 (28–36); 33 (6)
Ethnicity, %		
White	97	45
Nonwhite	3	6
Missing	0	49
Biomarkers		
Triglycerides (mmol/L)	1.7 (1.2–2.4); 1.8 (0.9)*	1.8 (1.3–2.6); 1.9 (1.0)*
HDL-c (mmol/L)	1.1 (0.9–1.3); 1.1 (0.3)*	1.1 (0.9–1.3); 1.1 (0.3)*
LDL-c (mmol/L)	1.9 (1.5–2.3); 1.9 (0.8)*	2.1 (1.6–2.6); 2.0 (0.8)*
SHBG (nmol/L)	27 (19–41); 27 (16)*	NA
Fasting C-peptide (pmol/L)	1,150 (820–1,460); 1,090 (480)*	NA
HOMA2-%B	54 (37–73); 51 (27)*	NA
HOMA2-IR	3.1 (2.3–4.2); 3.1 (1.5)*	NA
UCPCR (nmol/mmol)	3.4 (2.0–5.0); 3.0 (2.3)*	NA
eGFR (mL/min/1.73 m^2)	85 (70–98); 85 (24)	82 (66–97); 82 (23)
GAD or IA2 positive, %	3	NA
Therapy		
Number of concomitant therapies at therapy start, % of total		
0	3	6
1	35	51
2	57	42
3+	5	2
DPP-4 type, % of total		
Sitagliptin	87	72
Alogliptin	0	2
Linagliptin	4	10
Saxagliptin	6	12
Vildagliptin	2	4

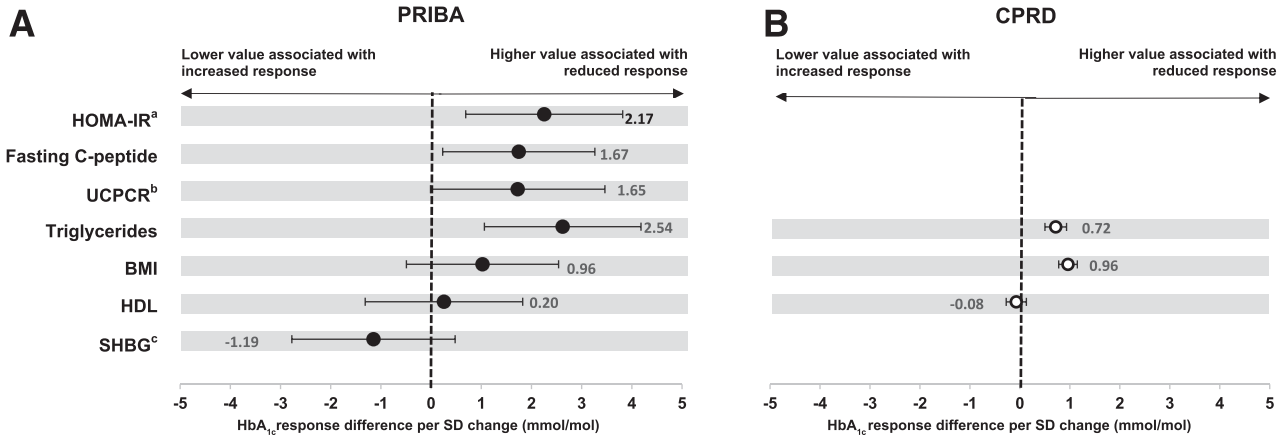
Data are median (interquartile range) or mean (SD) unless otherwise specified. NA, not available. *Log-transformed.

sex, duration of diabetes, eGFR, LDL-c, ethnicity (CPRD only), and cotherapy change (PRIBA only) in multivariable analysis of each data set (Supplementary Table 2), *3*) in PRIBA controlling for fasting glucose (Supplementary Table 3), and *4*) in CPRD with 12-month HbA_{1c} response as the outcome (Supplementary Table 4).

Standard Clinical Criteria of Obesity and High Triglycerides Can Identify Patients Likely to Have Markedly Reduced Glycemic Response to DPP-4 Inhibitors

Higher triglycerides were associated with reduced glycemic response independently of BMI in both data sets, and higher BMI was associated with reduced response independently of triglycerides in CPRD (Supplementary Table 5). To examine the potential clinical implication of this finding, we compared mean baseline HbA_{1c} adjusted response in three patient subgroups defined by standard clinical cutoffs for obesity (BMI ≥30 kg/m^2) and high triglycerides (≥2.3 mmol/L) (subgroup A: nonobese and normal triglycerides; subgroup B: nonobese or normal triglycerides; and subgroup C: obese and high triglycerides).

In PRIBA, we found mean 6-month baseline HbA_{1c} standardized glycemic response was halved for the obese and high triglycerides subgroup (subgroup C −5.2 [95% CI −1.8, −8.6] mmol/mol [−0.5% (95% CI −0.2, −0.8)]) compared with the nonobese and normal triglycerides subgroup (subgroup A −11.3 [95% CI −8.4, −14.1] mmol/mol [−1.0% (95% CI −0.8, −1.3)]) and was significantly reduced compared with intermediate subgroup B (−9.9 [95% CI −7.6, −12.2] mmol/mol [−0.9% (95% CI −0.7, −1.1)]) (Fig. 2*A*). Direction of effect was replicated in CPRD, albeit with smaller differences in mean response between subgroups (subgroup A mean baseline adjusted HbA_{1c} response −10.3 [95% CI −9.8, −10.7] mmol/mol



[a] HOMA2 measured insulin resistance [b] UCPCR = post meal urine C-peptide Creatinine ratio [c] SHBG = sex-hormone binding globulin

Figure 1—DPP-4 inhibitors: associations between markers of insulin resistance and HbA_{1c} response at 6 months. Circles (black, PRIBA in *A*; white, CPRD in *B*) denote the mean HbA_{1c} change (mmol/mol) at 6 months per 1 SD higher baseline value of each marker. Error bars denote 95% CI.

Downloaded from http://diabetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025

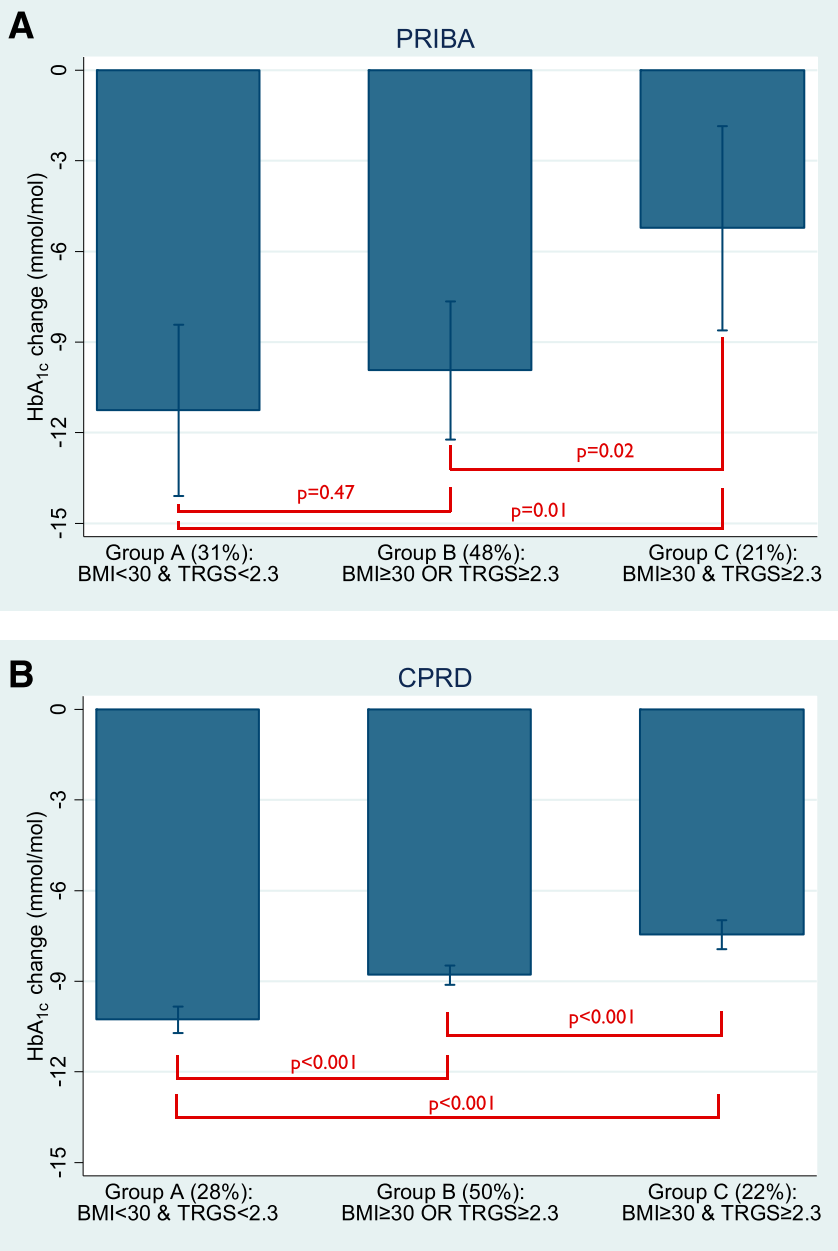


Figure 2—DPP-4 inhibitors: predicted mean absolute HbA_{1c} change from baseline at 6 months in PRIBA (*A*) and CPRD (*B*) across subgroups defined by the presence or absence of obesity (BMI ≥30 kg/m^2) and high triglycerides (TRGS) (≥2.3 mmol/L): subgroup A, nonobese and normal triglycerides; subgroup B, nonobese or normal triglycerides; and subgroup C, obese and high triglycerides. Baseline HbA_{1c} is standardized to the mean PRIBA baseline level of 74 mmol/mol (8.9%) for all subgroups. Error bars denote 95% CI.

[−0.9% (95% CI −0.9, −1.0)]; subgroup B −8.8 (95% CI −8.5, −9.1) mmol/mol [−0.8% (95% CI −0.8, −0.8)]; and subgroup C −7.5 (95% CI −7.0, −7.9) mmol/mol [−0.7% (95% CI −0.6, −0.7)]) (Fig. 2*B*).

Obesity and High Triglycerides Are Associated With Less Durable Glycemic Response to DPP-4 Inhibitors Over 3 Years

A total of 15,616 patients were followed up in this analysis for a mean time of 1.5 years. Over the 3-year study period, 3,514 (23%) patients had glycemic failure (confirmed HbA_{1c} ≥69 mmol/mol [8.5%]). We observed an increased relative risk of glycemic failure (reflecting a less durable response) in the same obesity- and high triglycerides–defined subgroups, standardizing for other clinical characteristics (HRs for glycemic failure: subgroup C, obese and high triglycerides vs. subgroup A, nonobese and normal triglycerides, 1.28 [95% CI 1.16, 1.41], $P < 0.001$; subgroup B, obese or high triglycerides vs. subgroup A, 1.17 [95% CI 1.08, 1.27], $P < 0.001$; and subgroup C vs. subgroup B, 1.09 [95% CI 1.01, 1.18], $P = 0.04$) (Supplementary Table 6). Consistent relative differences between subgroups were observed at HbA_{1c} failure thresholds of 7.5% and the baseline HbA_{1c} specific to each individual patient (Supplementary Tables 7 and 8). These results translated into significant differences between subgroups in the absolute probability of glycemic failure at 3 years (subgroup C: obese and high triglycerides, 39% [95% CI 37, 42]; subgroup B: obese or high triglycerides, 37% [95% CI 35, 38]; and subgroup A: nonobese and normal triglycerides, 32% [95% CI 31, 34]) (Supplementary Fig. 2).

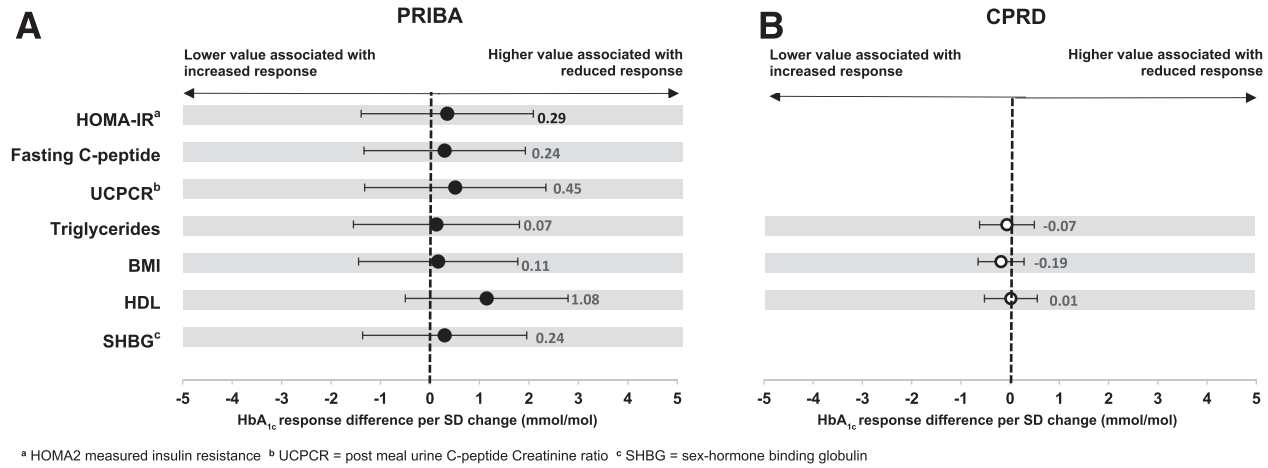
There Is No Evidence of an Association Between Markers of Insulin Resistance and Glycemic Response to GLP-1 Receptor Agonists

We found no evidence of an association between any marker of insulin resistance and 6-month glycemic response to GLP-1 receptor agonists in PRIBA (n = 339) or CPRD (n = 4,464) in continuous analysis (Fig. 3 and Supplementary Tables 8 and 9). There was also no evidence for a difference in response to GLP-1 receptor agonists across the obesity- and triglyceride-defined subgroups (all subgroup comparisons, $P > 0.40$) (Supplementary Table 10 and Supplementary Fig. 3), although there were few subjects in the nonobese, normal triglyceride subgroup starting GLP-1 receptor agonist therapy in both data sets (PRIBA, 2% and CPRD, 5%). Similarly, in CPRD, we found no evidence of an association between durability of glycemic response and BMI (HR per unit increase 1.01 [95% CI 1.00, 1.02]; $P = 0.29$) or triglyceride levels (HR per unit increase 0.99 [95% CI 0.95, 1.04]; $P = 0.80$) (Supplementary Table 11) or of a difference in durability of response across obesity- and triglyceride-defined subgroups (Supplementary Table 12 and Supplementary Fig. 4).

CONCLUSIONS

Our results show that markers of higher insulin resistance are consistently associated with reduced glycemic response to DPP-4 inhibitor therapy. In our U.K.-representative cohort, 22% of patients were obese with high triglycerides (≥2.3 mmol/L), and these patients had both

Downloaded from http://diabetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025



[a] HOMA2 measured insulin resistance [b] UCPCR = post meal urine C-peptide Creatinine ratio [c] SHBG = sex-hormone binding globulin

Figure 3—GLP-1 receptor agonists: associations between markers of insulin resistance and HbA_{1c} response at 6 months. Circles (black, PRIBA in *A*; white, CPRD in *B*) denote the mean HbA_{1c} change (mmol/mol) at 6 months per 1 SD higher baseline value of each marker. Error bars denote 95% CI.

markedly reduced short-term glycemic response and shorter durability of response on DPP-4 inhibitor treatment. With GLP-1 receptor agonists, we found no evidence of an association between markers of insulin response and either 6-month glycemic response or durability of response to 3 years. Findings were robustly demonstrated in a prospective study and validated in real-world data and provide a starting point for the application of a precision diabetes approach with DPP-4 inhibitor therapy.

Strengths of this study include that we have shown consistent findings across several clinical features and markers of insulin resistance in a prospective study and large data set of electronic health care records. We have shown that findings are robust with adjustment for baseline HbA_{1c} (13,24) and potential confounders and by definition of glycemic response, with similar associations for short-term (6- and 12-month) and long-term (3-year durability) glycemic outcomes. Our study is the first to identify characteristics associated with durability of response to DPP-4 inhibitor therapy, an area in which evidence is limited (25).

Limitations of this study include that we were only able to partially replicate our results from the PRIBA study cohort, as measures such as C-peptide were not available in our replication data set. Our effect size for triglycerides is notably smaller in our replication data set. It is possible this relates to differences in triglyceride measurement (we were unable to confirm if measured triglycerides were fasted in these real-world data), to increased error in electronic health care records in comparison with the prospective study (26), or to the effect of statistical chance in the smaller data set. The only long-term follow-up data we had to evaluate durability of glycemic response was from the routine primary care data set CPRD; further evaluation in a trial setting with greater follow-up than PRIBA would be of considerable interest. An additional important limitation is that this study has examined response to only two of the available therapies. Evidence is limited for other therapies, although a previous study found no evidence of a relationship between clinical insulin resistance or dyslipidemia markers and glycemic response with the sodium–glucose cotransporter 2 inhibitor dapagliflozin (27). High BMI and triglycerides have both been shown to be associated with modest increases in the rate of diabetes progression (28). Although this is unlikely to be relevant to our finding for 6-month glycemic response, this could influence our findings for treatment durability, and replication looking at other comparison therapies is therefore particularly important in this context. Although we have only examined relatively crude measures of insulin resistance, for clinical practice we consider it very unlikely that more complex measures would ever be feasible (29).

Existing studies of the association between insulin resistance and short-term glycemic response to DPP-4 inhibitors have not shown consistent findings and are constrained by methodological and reporting limitations, as recently reviewed by Bihan et al. (13). Meta-regression of study-level data has suggested reduced glycemic response in patients with higher BMI in one study (30), but no relationship in another analysis (31). These studies should be interpreted with some caution due to risk of ecological bias (32,33). A number of individual clinical trials of DPP-4 inhibitors have commented on consistency of glucose response across subgroups defined by baseline BMI or insulin resistance; reduced glycemic response with high HOMA2-IR was reported in two of seven studies and reduced response with high BMI in 6 of 36 studies, as reviewed in Bihan et al. (13). No studies reported an opposite direction of effect. These reports are very limited, with the vast majority providing no statistical comparison or details of what analysis was undertaken. An important issue for analysis of this nature is accounting for the influence of baseline HbA_{1c}, the strongest predictor of glycemic response, which may confound true associations, especially as baseline HbA_{1c} and insulin resistance are positively correlated (24,34, 35). There are limited data examining the relationship between triglycerides and response to DPP-4 inhibitors; however, one study stratified patients by baseline triglycerides (</>1.7 mmol/L) and found the odds of achieving an HbA_{1c} target of 53 mmol/mol (7%) were doubled in the low-triglyceride subgroup (odds ratio 2.2 [95% CI 1.0, 4.7]; $P = 0.04$) (36).

Although it is plausible that our finding of reduced glycemic response in those with high BMI or high triglycerides directly relates to insulin resistance through

Downloaded from http://diabetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025

reduced effect of drug-potentiated insulin secretion, this effect is not apparent in other drugs with effects on insulin secretion; for example, there is no relationship between obesity and response to sulfonylurea therapy or GLP-1 receptor agonists (15,37). An alternative explanation would be a direct effect of lipotoxicity, or indirect associations with other (unmeasured) factors important to DPP-4 inhibitor response. A direct mechanism for lipotoxicity in reducing response to incretin-based therapy has been previously suggested, with expression of GLP-1 receptors diminished in islets exposed to elevated fatty acid levels in animal models and β-cell response to GLP-1 restored following fatty acid reduction with fibrate pharmacotherapy; however, this mechanism would not explain the lack of an association between these features and GLP-1 receptor agonist response (38). It has also been shown that GLP-1 response is blunted in obese insulin-resistant patients with high liver fat and also blunted in patients with high fasting triglycerides (39,40); therefore, impaired GLP-1 secretion in obese insulin-resistant individuals represents a potential indirect mechanism that could also account for the lack of a similar relationship for injected GLP-1 receptor agonist therapy. Although the lack of association for HDL-c may be considered unexpected, we note HDL-c has a much weaker relationship with insulin resistance than either triglycerides or fasting insulin/C-peptide, which may explain this finding (18).

Our findings have potential implications for clinical practice, as both BMI and triglycerides are routinely available at no additional cost. Stratification of treatment based on these criteria may therefore be cost effective even with the more modest differences in treatment effect seen in our replication cohort. Although our own and previous research suggests these findings may be specific to DPP-4 inhibitors, further work examining the relationship between these and other factors and response to comparator drugs is needed. Our study design, emphasizing the importance of replication across data sets, provides an exemplar for such future analyses. In addition, although simple categorization by subgroup may provide a starting point for prediction of therapy response in type 2 diabetes, we anticipate a more sophisticated precision diabetes approach combining features into a multivariable response calculator will have greatest clinical utility, and this is an important area for future research (8,41).

In conclusion, our study shows simple markers of higher insulin resistance are consistently associated with reduced glycemic response to DPP-4 inhibitor therapy. This finding was robustly demonstrated in a prospective study, was validated in real-world data, and provides a starting point for the application of a precision diabetes approach to DPP-4 inhibitor therapy in type 2 diabetes.

Acknowledgments. The authors thank the staff of the NIHR Exeter Clinical Research Facility and NIHR Diabetes Research Network for assistance with conducting the study. The authors also thank the members of the PRIBA study group (see Supplementary Data for participating centers and members) and all cohort participants.

Funding. The PRIBA study was funded by a National Institute for Health Research (U.K.) Doctoral Research Fellowship (DRF-2010-03-72 to A.G.J.) and supported by the NIHR Clinical Research Network. The MASTERMIND Consortium is supported by the Medical Research Council (U.K.) (MR/N00633X/1). B.M.S., A.V.H., B.A.K., and A.T.H. are supported by the NIHR Exeter Clinical Research Facility. T.J.M. is an NIHR Chief Scientist Office Clinical Senior Lecturer. N.S. acknowledges support by Innovative Medicines Initiative Joint Undertaking under grant agreement 115372, the resources of which comprise financial contributions from the European Union's Seventh Framework Programme (FP7/2007–2013) and EFPIA (European Federation of Pharmaceutical Industries and Associations) companies' in-kind contribution. R.R.H. and A.T.H. are NIHR Senior Investigators. E.R.P. is a Wellcome Trust New Investigator (102820/Z/13/Z). A.T.H. is a Wellcome Trust Senior Investigator. A.G.J. is supported by an NIHR Clinician Scientist award.

The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR, or Department of Health. The funders had no role in any part of the study or in any decision about publication.

Duality of Interest. W.E.H. declares a grant from Quintiles. E.R.P. declares personal fees from Eli Lilly and Company, Novo Nordisk, and AstraZeneca. N.S. declares personal fees from Boehringer Ingelheim, Eli Lilly and Company, Novo Nordisk, and Janssen and a grant from AstraZeneca. R.R.H. declares research funding from Bayer, AstraZeneca, and Merck Sharp & Dohme and honoraria from Amgen, Bayer, Elcelyx, Janssen, Intarcia Therapeutics, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Servier. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.M.D. and A.G.J. designed the study and drafted the article. B.M.S., L.R.R., and M.N.W. extracted the CPRD data. A.V.H., B.A.K., T.J.M., and A.G.J. researched the data (PRIBA study). J.M.D., B.M.S., and A.G.J. analyzed the data with assistance from W.E.H. W.E.H., N.S., R.R.H., E.R.P., and A.T.H. discussed and contributed to study design and provided support for the analysis and interpretation of results. All authors critically revised the article and approved the final version. A.G.J. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the Diabetes UK Professional Conference, Manchester, U.K., 8–10 March 2017.

References

1. World Health Organization. Global report on diabetes [Internet], 2016. Available from http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf. Accessed 19 June 2017
2. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE guideline (NG28) [Internet], 2015. Available from https://www.nice.org.uk/guidance/ng28. Accessed 21 June 2017
3. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
4. American Diabetes Association. Pharmacologic approaches to glycemic treatment. Sec. 8. In *Standards of Medical Care in Diabetes–2017*. Diabetes Care 2017;40(Suppl. 1):S64–S74
5. Qaseem A, Barry MJ, Humphrey LL, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. Ann Intern Med 2017;166:279–290
6. Florez JC. Precision medicine in diabetes: is it time? Diabetes Care 2016;39:1085–1088
7. Marshall SM. Precision diabetes: a realistic outlook on a promising approach. Diabetologia 2017;60:766–768
8. Hattersley AT, Patel KA. Precision diabetes: learning from monogenic diabetes. Diabetologia 2017;60:769–777
9. Sattar N. Biomarkers for diabetes prediction, pathogenesis or pharmacotherapy guidance? Past, present and future possibilities. Diabet Med 2012;29:5–13
10. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: real-world evidence in patients newly diagnosed with type 2 diabetes. Diabetes Care 2017;41:69–78
11. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open 2016;6:e010210
12. Karagiannis T, Paschos P, Paletas K, Matthews DR, Tsapas A. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369
13. Bihan H, Ng WL, Magliano DJ, Shaw JE. Predictors of efficacy of GLP-1 agonists and DPP-4 inhibitors: a systematic review. Diabetes Res Clin Pract 2016;121:27–34
14. Esposito K, Chiodini P, Maiorino MI, et al. A nomogram to estimate the HbA1c response to different DPP-4 inhibitors in type 2 diabetes:

Downloaded from http://diabetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025

a systematic review and meta-analysis of 98 trials with 24 163 patients. BMJ Open 2015;5:e005892
15. Jones AG, McDonald TJ, Shields BM, et al.; PRIBA Study Group. Markers of β-cell failure predict poor glycemic response to GLP-1 receptor agonist therapy in type 2 diabetes. Diabetes Care 2016;39:250–257
16. Jones AG, Besser RE, McDonald TJ, et al. Urine C-peptide creatinine ratio is an alternative to stimulated serum C-peptide measurement in late-onset, insulin-treated diabetes. Diabet Med 2011;28:1034–1038
17. Besser RE, Ludvigsson J, Jones AG, et al. Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. Diabetes Care 2011;34:607–609
18. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 2003;139:802–809
19. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–1495
20. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–836
21. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–3421
22. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. Stata J 2009;9:265–290
23. Royston P, Lambert PC. *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model*. College Station, TX, Stata Press, 2011
24. Jones AG, Lonergan M, Henley WE, Pearson ER, Hattersley AT, Shields BM. Should studies of diabetes treatment stratification correct for baseline HbA1c? PLoS One 2016;11:e0152428
25. Esposito K, Chiodini P, Maiorino MI, Bellastella G, Capuano A, Giugliano D. Glycaemic durability with dipeptidyl peptidase-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of long-term randomised controlled trials. BMJ Open 2014;4:e005442
26. Ehrenstein V, Nielsen H, Pedersen AB, Johnsen SP, Pedersen L. Clinical epidemiology in the era of big data: new opportunities, familiar challenges. Clin Epidemiol 2017;9:245–250
27. Bujac S, Del Parigi A, Sugg J, et al. Patient characteristics are not associated with clinically important differential response to dapagliflozin: a staged analysis of phase 3 data. Diabetes Ther 2014;5:471–482
28. Zhou K, Donnelly LA, Morris AD, et al. Clinical and genetic determinants of progression of type 2 diabetes: a DIRECT study. Diabetes Care 2014;37:718–724
29. Ferrannini E, Mari A. How to measure insulin sensitivity. J Hypertens 1998;16:895–906
30. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia 2013;56:696–708
31. Monami M, Cremasco F, Lamanna C, Marchionni N, Mannucci E. Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials. Diabetes Metab Res Rev 2011;27:362–372
32. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002;21:1559–1573
33. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI; Anti-Lymphocyte Antibody Induction Therapy Study Group. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Stat Med 2002;21:371–387
34. Esposito K, Chiodini P, Capuano A, Maiorino MI, Bellastella G, Giugliano D. Baseline glycemic parameters predict the hemoglobin A1c response to DPP-4 inhibitors: meta-regression analysis of 78 randomized controlled trials with 20,053 patients. Endocrine 2014;46:43–51
35. Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. Diabetes Care 2006;29:2137–2139
36. Jamaluddin JL, Huri HZ, Vethakkan SR. Clinical and genetic predictors of dipeptidyl peptidase-4 inhibitor treatment response in type 2 diabetes mellitus. Pharmacogenomics 2016;17:867–881
37. Donnelly LA, Doney AS, Hattersley AT, Morris AD, Pearson ER. The effect of obesity on glycaemic response to metformin or sulphonylureas in type 2 diabetes. Diabet Med 2006;23:128–133
38. Kang ZF, Deng Y, Zhou Y, et al. Pharmacological reduction of NEFA restores the efficacy of incretin-based therapies through GLP-1 receptor signalling in the beta cell in mouse models of diabetes. Diabetologia 2013;56:423–433
39. Matikainen N, Bogl LH, Hakkarainen A, et al. GLP-1 responses are heritable and blunted in acquired obesity with high liver fat and insulin resistance. Diabetes Care 2014;37:242–251
40. Alssema M, Rijkelijkhuizen JM, Holst JJ, et al. Preserved GLP-1 and exaggerated GIP secretion in type 2 diabetes and relationships with triglycerides and ALT. Eur J Endocrinol 2013;169:421–430
41. Zeevi D, Korem T, Zmora N, et al. Personalized nutrition by prediction of glycemic responses. Cell 2015;163:1079–1094

Downloaded from http://diabetesjournals.org/care/article-pdf/41/4/705/549226/dc171827.pdf by guest on 20 April 2025