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ORIGINAL RESEARCH

Reduced Weight Gain with Pioglitazone vs Vildagliptin in *CREBRF* rs373863828 A-allele Carriers: Insights from the WORTH Trial

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Background/Objectives: This subgroup analysis of a randomised, open-label, two-period crossover trial in Aotearoa New Zealand (February 2019 to March 2020) assessed whether the glucose-lowering effects of vildagliptin, vs pioglitazone varied by the *CREBRF* (p.Arg457Gln) rs373863828 genotype.

Methods: Adults with type 2 diabetes and HbA1c > 58 mmol/mol (>7.5%) received either pioglitazone (30 mg) or vildagliptin (50 mg) for 16 weeks, then switched medications for another 16 weeks. Differences in HbA1c between treatments (pioglitazone vs vildagliptin) were tested for an interaction with *CREBRF* rs373863828 A-allele carrier status and controlling for baseline HbA1c using linear mixed models. Secondary endpoints included weight, systolic blood pressure, and diabetes treatment satisfaction.

Results: Participants with the AA/AG genotype had a higher baseline weight than those with the GG genotype (121.4 kg vs 106.6 kg, respectively; $p<0.01$). No significant difference in achieved HbA1c was found based on A-allele carrier status (0.43 mmol/mol; 95% CI −4.83, 5.69; $p=0.87$). Among Māori and Pacific participants with the A-allele, a smaller weight difference was observed after pioglitazone vs vildagliptin compared to those with the GG genotype (interaction effect −1.66 kg; 95% CI −3.27, −0.05; $p=0.04$).

Conclusion: *CREBRF* rs373863828 A-allele carriers show a similar HbA1c-lowering response to pioglitazone vs vildagliptin compared to non-carriers but exhibit less weight gain with pioglitazone, despite having significantly higher baseline weights.

Keywords: pioglitazone, vildagliptin, CREBRF, pharmacogenetics, precision medicine, stratified drug response

Introduction

There are a range of medications that may be used for glucose-lowering on an additive basis for the treatment of type 2 diabetes (T2D). Identifying baseline factors that contribute to varying glucose-lowering responses to different medications is essential for guiding precision medicine in the treatment of T2D.[1] Achieving glycaemic control remains the primary therapeutic goal, but considering weight-related outcomes is also important, as weight loss improves glycaemic control and mitigates diabetes-related complications.[2] Therefore, weight gain, alongside cost and patient preferences, is equally important to consider in the glycaemic treatment algorithm.[3]

In individuals with T2D, thiazolidinediones generally yield greater glucose-lowering effects compared to dipeptidyl peptidase-4 inhibitors (DPP4i).[4] Body mass index (BMI) appears to be a predictor of glucose-lowering response to each

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of these medications, as those with higher BMI often experience a greater glucose-lowering response with thiazolidinediones (insulin sensitiser).[5] Conversely, those with normal BMI and triglyceride levels, indicating less insulin resistance, tend to have a greater glucose-lowering response to DPP4i (insulin secretagogue).[6] BMI has been validated as a key stratification marker for predicting glucose-lowering response to these two classes of medications.[7]

Genetic variants have also been identified as predictors of differential response to these two medications. For example, polymorphisms in genes such as *PPARG* and *CYP2C8* influence responses to thiazolidinediones. The *CYP2C8*3* variant in Scottish patients was associated with reduced HbA1c lowering (−0.21%, p=0.01) and less weight gain (−0.93 kg, p=0.02) with rosiglitazone treatment.[8] Similarly, variants in *GLP1RA* and *DPP4* genes have been associated with altered responses to gliptins.[9–12]

A missense variant (rs373863828, p.Arg457Gln) in the *CREBRF* gene, encoding for the CREB3 regulatory factor, is uniquely found in individuals of Māori and Pacific ancestry. This variant is associated with elevated BMI[13,14] and height,[15] yet paradoxically a lower odds ratio for T2D[13,14] and gestational diabetes,[16] reduced myostatin levels[17] and enhanced insulin secretion capacity.[18] Given Māori and Pacific people face disproportionately high rates of T2D and its complications in Aotearoa New Zealand (NZ),[19] understanding the pharmacogenetic implications of this variant contribute to precision medicine initiatives that could appropriately intervene.[20]

Pioglitazone, a thiazolidinedione, exerts its glucose-lowering effects by activating *PPARG*, which enhances peripheral insulin sensitivity and reduces hepatic gluconeogenesis.[21] Conversely, vildagliptin, a DPP4i, improves glycaemic control by increasing insulin secretion via inhibiting the DPP4 enzyme responsible for degrading incretin hormones (eg, glucagon-like peptide-1).[22] The *CREBRF* variant, which has been associated with enhanced insulin secretion,[18] may interact differently with these two classes of antidiabetic medications. For example, the variant's role in insulin secretion may complement the action of vildagliptin. Therefore, investigating these potential pharmacogenetic interactions could aid in optimising T2D treatments for those carrying this variant.

Our previous findings from the Which One is Right Here (WORTH) trial showed no significant difference in glucose-lowering effects between pioglitazone and vildagliptin when considering Māori andPacific ethnicity.[23] However, pioglitazone demonstrated a more favourable response among participants with obesity and/or elevated triglycerides.[23] In this pre-specified sub-study, we aimed to assess whether the difference in glucose-lowering between pioglitazone and vildagliptin varied depending on the *CREBRF* (p.Arg457Gln) rs373863828 genotype.[24] We hypothesised that variant carriers with T2D would respond less well to pioglitazone, which promotes insulin sensitivity, compared to vildagliptin, relative to non-carriers.

Materials and Methods

Research Design and Methods

This study employed a multicentre, randomised, two-period, two-treatment, crossover trial with an open-label design. The primary endpoint, HbA1c, reflects the 8–12 weeks of glycaemia of each 16-week treatment period, minimising the potential for carry-over effects from the initial treatment. Secondary endpoints included measurements such as body weight, blood pressure (in mmHg), frequency of adverse effects, total Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores, and changes in DTSQ scores.[24]

The trial took place across nine sites in Aotearoa NZ, covering both urban areas (Auckland and Waikato) and rural regions (Te Tai Tokerau [Northland] and Te Taiarāwhiti [East Coast]). The trial aimed for at least 40% participation from individuals of Māori and/or Pacific ancestry. During the baseline visit, participants self-reported their ethnicity, selecting from the following options: Māori, Pacific, NZ European, Other European, Indian, Other Asian, or Other (with specification). If participants identified as Māori or Pacific, these classifications were prioritised, even if they were also selected under "Other". The trial was registered with www.anzctr.org.au (identifier ACTRN12618001907235). The study complied with the Declaration of Helsinki and received ethical approval from the NZ Health and Disability Ethics Committee, as previously published.[24]

Genotyping

The *CREBRF* rs373863828 genotyping was performed by Grafton Clinical Genomics (GCG, Auckland, NZ) using the iPLEX® assay and MassARRAY® system (Agena Bioscience, San Diego, CA, USA). This system allows for high-throughput and accurate genotyping through mass spectrometry.[25] DNA extraction from whole blood samples was carried out using the DNeasy Blood and Tissue kit (Qiagen, Hilden, Germany). The genomic DNA (gDNA) was then amplified from the gDNA sample using custom designed primers for the rs373863828 variant. The sample DNA and PCR cocktail mixes were manually dispensed individually into the PCR plate. The amplified DNA was subjected to the iPLEX® assay to produce allele-specific extension products of different masses depending on the sequence analysed, which was subsequently analysed using mass spectrometry to identify the presence of the A or G alleles. Genotypes were called using the MassARRAY Typer Analyzer software, which analyses the mass spectrometry data and categorises the samples into AA, AG, or GG genotypes.

Study Participants

The key eligibility criteria included patients aged between 18 and 80 years who had been on stable doses of metformin and/or sulfonylurea for more than three months and had not previously used medications from the DPP4i, thiazolidinedione, or insulin classes.[23,24] Among the 189 Māori and/or Pacific participants with T2D in this trial, genotype information for the *CREBRF* rs373863828 variant was available for 166 individuals. Of these, 36 were carriers (AA/AG) of the minor A-allele (36/166, 21.7%). Among the Māori and Pacific participants (n=189), there were 92 females with a mean age (± standard deviation [SD]) of 56.2 ± 10.9 years and a mean BMI of 38.0 ± 7.9 kg/m^2 (Table 1). All participants provided written informed consent. The CONSORT flow diagram has been published in previous work done in the WORTH trial.[23]

Table 1 Baseline Demographics and Clinical Characteristics

Characteristic	Māori and/or Pacific
Age (years)	56.2 (10.9)
Sex	
Female	92 (48.7%)
Male	97 (51.3%)
Genotype	
AA/AG	36 (19.0%)
GG	130 (68.8%)
Missing	23 (12.2%)
Duration of diabetes (years)	8.4 (6.4)
Current smoker	36 (19.0%)
Baseline diabetes medication	
Metformin	186 (98.4%)
Sulfonylureas	120 (63.5%)
*Other	7 (3.7%)
BMI (kg/m^2)	38.0 (7.9)
Mean BP systolic (mmHg)	131.4 (15.6)
Mean BP diastolic (mmHg)	80.7 (8.8)
Fasting Glucose (mmol/L)	10.5 (3.1)
Fasting TG (mmol/L)	2.1 (1.7)
Creatinine (umol/L)	81.6 (20.1)
Fasting C-peptide (pmol/L)	1201 (469)
GAD antibodies	4 (2.2%)

Notes: Data are n (%) or mean (standard deviation). Genotype *CREBRF* rs373863828 minor allele carrier: AA/AG, vs non-carrier: GG.
Abbreviations: BMI, body mass index; BP, blood pressure; TG, triglycerides; GAD, glutamic acid decarboxylase. *Other medications include acarbose or dapagliflozin.

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Statistical Analysis

Our previous work in this trial had shown a mean difference in HbA1c of −4.9 mmol/mol (SD of 13.29) observed over the 16-week consecutive treatment period after pioglitazone vs vildagliptin in the WORTH cohort.[23] Examining this differential response within the Māori and/or Pacific subset (n = 189) and assuming the same variance for both *CREBRF* variant carriers (assumed 25% prevalence) vs homozygous reference (assumed 75%), we would have 90% power to detect a minimum difference in HbA1c between the two test medications of 7.3 mmol/mol (2.8%) and 80% power to detect a minimum difference of 6.3 mmol/mol (2.7%) between variant and reference groups.

Primary and secondary outcomes were evaluated using valid visit data collected within the scheduled assessment periods, and no imputation methods were applied in the analysis. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Baseline demographic and clinical characteristics for all randomised Māori and/or Pacific participants are summarised in Table 1. Continuous variables are presented as means with standard deviations (SD), while categorical variables are shown as frequencies and percentages. To determine whether HbA1c outcomes differed between A-allele carriers and non-carriers for the two medications, we utilised a linear mixed model with both fixed and random effects. The fixed effects included baseline outcome values, treatment period, medication type, rs373863828 genotype (ie, AA/AG vs GG), and its interaction with the medication type. Patients were incorporated as clusters in the random effects. Model-adjusted mean differences between the two medications were calculated for each patient group, along with the interaction effect between medications and genotype groups, expressed with a 95% confidence interval (CI). For secondary outcomes like the changes in DTSQ scores measured at the end of the trial, generalised linear regression was used. All statistical tests were two-sided with a 5% significance level. The study followed the CONSORT 2010 statement extension for randomised crossover trials.[26] All methods were conducted in accordance with ethical approval from the NZ Health and Disability.

Results

Baseline Data

The *CREBRF* rs373863828 A-allele was present in 21.7% (36/166) of those reporting Māori and/or Pacific ethnicity. Please refer to Supplementary Table 1 for further details on the distribution of the genotypes (ie, AA, AG, GG) and also the allele frequencies (ie, A, G) under different genetic models. Individuals with the AA/AG genotype had a higher baseline mean weight than those with the GG genotype (121.4 kg vs 106.6 kg; $p<0.01$; Table 2). Additionally, A-allele carriers had a higher BMI of (121.4 kg vs 106.6 kg; $p<0.01$; Table 2).

Outcomes

No significant interaction between HbA1c response and the presence of the A-allele was observed in the overall group (interaction effect 0.43 mmol/mol, 95% CI −4.83, 5.69; $p=0.87$; Table 3). However, an interaction in weight change response was observed with genotype: participants with the AA/AG genotype had less weight gain between pioglitazone

Table 2 Descriptive Data at Baseline and After Each Treatment

Characteristic	Baseline		Pioglitazone		Vildagliptin	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
HbA1c (mmol/mol [%])						
Māori/Pacific	166	75.78 (12.0) [9.1]	122	60.95 (12.4) [7.7]	122	67.2 (14.7) [8.3]
AA/AG	36	75.9 (12.1) [9.1]	28	61.7 (15.3) [7.8]	28	68.2 (16.1) [8.4]
GG	130	75.1 (11.9) [9.0]	94	60.7 (11.5) [7.7]	94	66.8 (14.3) [8.3]
Weight (kg)						
Māori/Pacific	166	109.8 (25.7)	95	113.9 (28.9)	106	112.1 (27.9)
AA/AG	36	121.4 (30.5)	21	127.6 (31.0)	24	122.9 (33.1)
GG	130	106.6 (23.3)	74	110.0 (27.2)	82	108.9 (25.6)

(*Continued*)

Table 2 (Continued).

Characteristic	Baseline		Pioglitazone		Vildagliptin	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Systolic blood pressure (mmHg)						
Māori/Pacific	166	131.0 (15.5)	96	128.2 (16.6)	104	129.23 (14.4)
AA/AG	36	129.1 (15.6)	21	122.1 (15.3)	25	129.9 (12.6)
GG	130	131.5 (15.5)	75	129.9 (16.7)	79	129.0 (15.0)
***DTSQ total score**						
Māori/Pacific	166	29.5 (6.1)	114	30.7 (5.2)	121	30.1 (6.8)
AA/AG	36	28.7 (6.1)	24	29.7 (7.5)	30	31.8 (4.6)
GG	130	29.7 (6.1)	90	30.5 (5.8)	91	29.6 (7.4)

Notes: Genotype *CREBRF* rs373863828 minor allele carrier: AA/AG, vs non-carrier: GG. *Questions contained in the DTSQ are shown in Table 4.
Abbreviations: SD, standard deviation; HbA1c, haemoglobin A1c; TG, triglycerides; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

Table 3 The Estimated Medication Effects on Patient Outcomes and Its Interaction with CREBRF rs373863828-A Carrier Status

Characteristic	Pioglitazone vs Vildagliptin		Difference Between Genotype Groups	
	Mean Estimate (95% CI)	p-value	Mean Estimate (95% CI)	p-value
HbA1c (mmol/mol [%])				
Genotype AA/AG	−5.51 (−10.13, −0.90)	**0.02**	0.43 (−4.83, 5.69)	0.870
Genotype GG	−5.95 (−8.46, −3.44)	**<0.0001**		
Weight (kg)				
Genotype AA/AG	−0.18 (−1.60, 1.24)	0.80	−1.66 (−3.27, −0.05)	**0.043**
Genotype GG	1.49 (0.72, 2.25)	**0.0002**		
Systolic blood pressure (mmHg)				
Genotype AA/AG	−5.42 (−12.13, 1.30)	0.112	−7.28 (−14.93, 0.37)	0.062
Genotype GG	1.86 (−1.82, 5.55)	0.316		
***DTSQ total score**				
Genotype AA/AG	−2.49 (−5.63, 0.65)	0.119	−3.58 (−7.16, 0.00)	0.050
Genotype GG	1.10 (−0.62, 2.80)	0.209		

Notes: P-values for statistically significant differences are shown in bold. All valid patient data collected at baseline and after each medication treatment were used in the analysis; missing data were not imputed. Genotype *CREBRF* rs373863828 minor allele carrier: AA/AG, vs non-carrier: GG. *Questions contained in the DTSQ are shown in Table 4.
Abbreviations: CI, confidence interval; HbA1c, haemoglobin A1c; DTSQ, Diabetes Treatment Satisfaction Questionnaire.

vs vildagliptin in the overall group (interaction effect −1.66 kg, 95% CI −3.27, −0.05; p=0.04; Table 3). There was no interaction between the difference in systolic BP or total DTSQ scores (Table 3). Total and individual DTSQ scores at baseline and after each treatment by genotypes are shown in Table 4.

Discussion

This study showed that there was no difference in the relative glucose-lowering response between pioglitazone and vildagliptin by *CREBRF* rs373863828 minor A-allele carrier status. However, there was an interaction by the genetic variant for a weight gain response. Individuals with the rs373863828 AA/AG genotype, compared to those with the GG genotype, experienced significantly lower weight gain (approximately 2 kg) after pioglitazone relative to vildagliptin.

Notably, carriers of the *CREBRF* minor A-allele were approximately 14 kg heavier than other Māori and Pacific participants without this variant. This is much higher than would be expected based on the known association of this genetic variant with a higher BMI, with a mean increase of 1.4 kg/m^2.[14] However, the known association of this genetic variant with a lower risk of T2D suggests that individuals who do develop T2D in the presence of the *CREBRF* minor A-allele do so at

Table 4 DTSQ Scores at Baseline and After Each Treatment by CREBRF Genotype

	DTSQ Scores					
	Baseline		Pioglitazone		Vildagliptin	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
***Overall DTSQ score**						
Genotype AA/AG	36	28.7 (6.1)	24	29.7 (7.5)	30	31.8 (4.6)
Genotype GG	130	29.6 (6.1)	90	30.7 (5.2)	91	29.6 (7.4)
1. How satisfied are you with your current treatment						
Genotype AA/AG	36	4.9 (1.4)	24	5.3 (1.3)	30	5.4 (1.0)
Genotype GG	130	4.9 (1.3)	90	5.1 (1.3)	91	4.8 (1.6)
2. How often have you felt your blood sugars have been unacceptably high recently?						
Genotype AA/AG	36	3.4 (2.1)	24	1.5 (1.7)	30	1.8 (2.0)
Genotype GG	130	3.6 (2.0)	90	1.4 (1.8)	91	1.6 (1.8)
3. How often have you felt your blood sugars have been unacceptably low recently?						
Genotype AA/AG	36	0.9 (1.6)	24	0.5 (1.0)	30	0.7 (1.4)
Genotype GG	130	1.5 (1.7)	90	0.8 (1.3)	91	0.6 (1.4)
4. How convenient have you been finding your treatment recently?						
Genotype AA/AG	36	4.8 (1.6)	24	5.1 (1.6)	30	5.4 (0.9)
Genotype GG	130	5.0 (1.3)	90	5.0 (1.1)	91	4.9 (1.7)
5. How flexible have you been finding your treatment recently?						
Genotype AA/AG	36	4.7 (1.4)	24	5.1 (1.5)	30	5.2 (1.6)
Genotype GG	130	4.7 (1.5)	90	5.1 (1.2)	91	5.1 (1.4)
6. How satisfied are you with your understanding of your diabetes?						
Genotype AA/AG	36	5.1 (1.2)	24	5.1 (1.7)	30	5.4 (1.0)
Genotype GG	130	4.9 (1.3)	90	5.2 (1.2)	91	5.2 (1.1)
7. Would you recommend this form of treatment to someone else with your kind of diabetes?						
Genotype AA/AG	36	4.6 (1.9)	24	4.0 (2.6)	30	4.8 (2.0)
Genotype GG	130	5.2 (1.5)	90	5.1 (1.6)	91	4.6 (2.0)
8. How satisfied would you be to continue with your present form of treatment?						
Genotype AA/AG	36	4.5 (1.8)	24	5.3 (1.6)	30	5.6 (1.1)
Genotype GG	130	4.9 (1.6)	90	5.1 (1.5)	91	4.8 (1.7)

Notes: Genotype *CREBRF* rs373863828 minor allele carrier: AA/AG, vs non-carrier: GG. *Derived from the sum of responses to question 1 and questions 4–8 each rated on a scale from 0 to 6, with a high score (maximum 36) representing high treatment satisfaction.
Abbreviation: DTSQ, Diabetes Treatment Satisfaction Questionnaire.

a much higher body weight than those without this variant. Even with a significantly higher BMI, *CREBRF* carriers exhibited a similar differential glucose-lowering response to pioglitazone vs vildagliptin compared to non-carriers.

The finding that rs373863828 A-allele carriers had a lower weight gain response to pioglitazone vs vildagliptin, relative to non-carriers, was unexpected. This was not due to differences in adherence, as similar pill count returns were observed across genotype groups for both medications. This is despite previous research having shown a greater weight gain response in heavier patients treated with pioglitazone.[5] While the 2 kg lower weight gain response to pioglitazone among individuals with the *CREBRF* variant is clinically noteworthy, the potential benefits must be carefully weighed against the logistical and cost implications of genotyping to identify such individuals.

This study investigates the impact of vildagliptin and pioglitazone specifically in individuals carrying the CREBRF rs373863828-A allele, which is most prevalent in Māori and Pacific populations. This targeted approach limits the

generalisability of our findings to other ancestral populations where the allele is less common. However, it is crucial given the disproportionate burden of T2D in Māori and Pacific communities, and the need for precision medicine strategies.

The mechanisms underpinning thiazolidinedione-induced weight gain include increased body fat through *PPARG* activation and increased body fluid volume due to *PPARG* mediated increase in sodium reabsorption in the distal renal tubules.[27,28] In this context, *CREBRF* knockout mice have been shown to exhibit reduced glucocorticoid activity,[29,30] which is relevant because glucocorticoids have a significant influence on positive fluid balance through increased aldosterone-related sodium reabsorption in the renal tubules.[31] Hence, a plausible mechanism by which pioglitazone treatment might result in less weight gain among *CREBRF* variant carriers is through reduced fluid retention. However, follow-up in vitro or in vivo studies is necessary to further elucidate this potential mechanism and confirm the role of *CREBRF* in modulating fluid balance and treatment response to thiazolidinediones.

Limitations of this study include a small sample size, which limited the ability to detect differences below 6 mmol/mol in HbA1c by genotype. Additionally, the use of an open-label trial was chosen for lower cost and complexity, which may have resulted in altered adherence, although pill counts were checked. There is also the potential for both observer and participant bias introduced in an open-label design. Thirdly, the use of a crossover trial design has the potential for a carryover effect, although sensitivity analysis showed no significance for a carryover effect. This crossover trial design with 16-week period for each diabetes medication treatment has been shown to be a robust method for assessing differential responses to therapy within individuals by baseline characteristics, as reported in the TriMaster study.[7]

Conclusions

The principal finding indicates there is no differential effect of relative glucose-lowering response of pioglitazone vs vildagliptin by *CREBRF* rs373863828 A-allele carrier status. However, there is a notable reduction in weight gain following pioglitazone compared to vildagliptin in carriers of the A-allele. This work underscores the need for further mechanistic studies to understand how the *CREBRF* variant may affect the weight gain response to pioglitazone. Additionally, this study highlights the necessity for larger studies to investigate the pharmacogenetic impact of the *CREBRF* rs373863828-A variant in diabetes medication responses in Māori and Pacific populations.

Data Sharing Statement

The data presented in this study are available upon a reasonable request from the corresponding author due to consent restrictions.

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Disclosure

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