MARCH: factors associated with weight loss in patients with newly diagnosed type 2 diabetes treated with acarbose or metformin

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Abstract

Introduction: In this secondary analysis of the Metformin and AcaRbose in Chinese as the initial Hypoglycaemic treatment (MARCH) trial, we evaluated what demographic and clinical factors were associated with reduction in weight. We also assessed the effects of acarbose and metformin treatment on weight reduction.

Material and methods: We analyzed the demographic and clinical laboratory values from the 784 patients with type 2 diabetes of the MARCH study who were treated for 48 weeks with acarbose or metformin. We determined the association of the different parameters with a weight reduction of ≥ 2 kg in patients using univariate and multivariate analysis.

Results: In patients treated with acarbose, males were less likely than females to lose ≥ 2 kg of weight ($p = 0.025$). Higher baseline HbA_{1c} levels and lower decreases from baseline in fasting plasma glucose (FPG) levels after 48 weeks of treatment were negatively associated with losing ≥ 2 kg of weight (both, $p < 0.05$). Higher baseline glucagon AUC was also positively associated with reducing weight by ≥ 2 kg ($p = 0.010$). In patients treated with metformin, change from baseline in whole body insulin sensitivity increased the odds of having a weight reduction of ≥ 2 kg ($p = 0.014$).

Conclusions: This study found that for both acarbose and metformin, control of FPG significantly impacted weight loss. Baseline AUC for glucagon in patients treated with acarbose and an increase of whole body insulin sensitivity after 48 weeks of treatment with metformin were important factors for weight reduction.

Key words: weight loss, type 2 diabetes, metformin, acarbose, MARCH trial.

Introduction

Being overweight or obese can increase the risk of cardiovascular disease in patients with type 2 diabetes. Achieving good weight control is a critical component of managing diabetes [1, 2]. This is of particular concern given that many patients with type 2 diabetes are obese and that some types of antidiabetic agents (insulin, thiazolidinediones, and sulfonylurea) have the unwanted side effect of promoting weight gain [1]. In addition, a significant percentage of Chinese patients with newly diagnosed type 2 diabetes are overweight [1].

Several drugs, but not all, used to treat and manage type 2 diabetes promote weight gain. Metformin and acarbose, an α-glucosidase inhibitor, are

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used to treat type 2 diabetes and are not associated with weight gain and also decrease the risk of cardiovascular disease [3, 4]. Acarbose slows carbohydrate digestion and inhibits postprandial increases in plasma glucose levels [4]. Evidence suggests that stimulation of the fasting and postprandial levels of the glucagon-like peptide (GLP-1) by acarbose and metformin may impact the benefit of these drugs on weight and other clinical parameters [5, 6].

The **M**etformin and **A**ca**R**bose in **C**hinese as the initial **H**ypoglycaemic treatment (MARCH) study was a 48-week, randomized, controlled, non-inferiority, multi-center study that included 788 patients newly diagnosed with type 2 diabetes [7]. MARCH evaluated the effectiveness of acarbose and metformin in treating Chinese patients. Both treatments can reduce bodyweight, and acarbose treatment resulted in more weight reduction than metformin treatment at weeks 24 and 48 [7]. In this secondary analysis, we used univariate and multivariate analysis to evaluate what demographic and clinical characteristics impact weight reduction in patients from the MARCH study who were treated with acarbose or metformin.

Material and methods

Study participants and study design

The MARCH trial (Chinese Clinical Trial Registry number: ChiCTR-TRC-08000231) was performed in accordance with the Declaration of Helsinki, and was approved by the appropriate ethic committees of the different Chinese clinical sites [7]. All patients gave their written informed consent [7].

The MARCH study design and methods were previously described in detail by Yang *et al*. [7] and Wang *et al*. [8]. Patients were randomized, after a 4-week run-in period, to receive up to 1500 mg of sustained-release metformin hydrochloride (500 mg per tablet, Beijing Double Crane Pharma, Beijing, China) once daily or up to 300 mg/day of acarbose (100 mg three times daily) (Bayer Healthcare, Beijing, China) with 24-week monotherapy and, as needed, a 24-week add-on therapy with insulin secretagogues. During the 4-week pre-randomization run-in period, dietary education was provided by trained dietitians and total daily calories were calculated based on standardized body weight and labor intensity. Patients were asked to perform 30 min of moderate exercise each day such as brisk walking, jogging, cycling, or swimming. As per the Chinese 2007 management guidelines for type 2 diabetes, add-on therapy with insulin secretagogues was initiated at week 24 in patients whose glycated haemoglobin (HbA$_{1c}$) levels were > 7%, whose fasting plasma glucose (FPG) was > 7 mmol/l, or whose postprandial glucose was > 10 mmol/l for three consecutive days.

Measurements

Baseline demographic and patient clinical characteristics were obtained including body weight, waist and hip circumference, body mass index (BMI), GLP-1 levels, glucose sensitivity, fasting serum insulin (FINS), total cholesterol, levels of low-density lipoproteins (LDL) and high-density lipoproteins (HDL), and levels of triglycerides. Biochemical and anthropometric measurements were also performed at weeks 24 and 48. Area under the concentration curve (AUC) was used to evaluate serum levels of insulin, glucagon, and GLP-1.

Statistical analysis

In order to investigate the factors associated with weight change, the median change in weight from baseline to the 48-week follow-up endpoint was used; 2 kg was the median value of the reduction of body weight of all the subjects in the MARCH trial. Hence, a considerable weight change was defined as ≥ 2 kg over the 48-week follow-up period. Both baseline demographics and clinic variables and change from baseline at weeks 24 and 48 for certain clinical variables were assessed. Variables with normal distribution were presented as means and standard deviations (SD), and the independent *t* test was used to compare variables between patient groups that had weight that changed by < 2 kg or ≥ 2 kg. Variables without normal distribution were presented as medians and inter-quartile ranges (IQRs), and the Wilcoxon rank sum test was used to compare the differences between two weight groups. Univariate and multivariate logistic regression models were performed to evaluate factors associated with ≥ 2 kg reduction in weight. Factors found in the univariate analysis to be associated with decreased weight were included in the multivariate analysis. For multivariate analysis, baseline factors and the changes from baseline at week 24 and week 48 were separated into different models.

Statistical analysis

Tests were considered significant if the two-sided *p*-value was < 0.05. Statistical analyses were performed using the SAS 9.2 statistics software (SAS Inc., Cary, NC, USA).

Results

Baseline demographics and clinical characteristics

Patients who were treated with acarbose and who lost < 2 kg or ≥ 2 kg of weight differed in baseline demographic and clinical characteristic (Table I). A greater percentage of patients who lost ≥ 2 kg compared with those who lost < 2 kg

Table I. Baseline characteristics according to weight decrease < 2 kg vs. ≥ 2 kg in subjects treated with acarbose

Parameter	Weight decreased < 2 kg (N = 145)	Weight decreased ≥ 2 kg (N = 192)	P-value
Demographic characteristics:			
Gender:			0.041*
Male	96 (47.52%)	106 (52.48%)	
Female	49 (36.3%)	86 (63.7%)	
Age [years]	50 (43–55)	51 (44–57.5)	0.161
BMI [kg/m^2]	25.24 (23.44–26.58)	26.23 (24.63–28.08)	0.001*
Waist circumference [cm]	89.33 ±8.53	89.63 ±8.07	0.749
1-day energy intake from carbohydrates [cal]	220.25 (185.61–268.7)	215.05 (166.65–267.18)	0.23
1-day energy intake from non-carbohydrates [cal]	107.57 (81.57–137.57)	103.85 (73.02–127.56)	0.091
Clinical characteristics:			
Systolic blood pressure [mm Hg]	122 (115–130)	125 (120–131.5)	0.132
Diastolic blood pressure [mm Hg]	78.63 ±8.14	80.45 ±8.08	0.043*
Total cholesterol [mmol/l]	5.12 (4.38–5.76)	5.18 (4.57–5.99)	0.355
LDL cholesterol [mmol/l]	3 (2.51–3.55)	3.1 (2.5–3.57)	0.722
HDL cholesterol [mmol/l]	1.2 (1–1.42)	1.18 (1.05–1.39)	0.813
Triglycerides [mmol/l]	1.77 (1.26–2.52)	1.84 (1.2–2.7)	0.877
Glycemic characteristics:			
HbA$_{1c}$ (%):			
Baseline	7.5 (6.8–8.3)	7.1 (6.5–7.9)	0.001*
Difference between 24 weeks and baseline	−1 (−1.8– −0.2)	−1 (−1.6– −0.4)	0.715
Difference between 48 weeks and baseline	−0.8 (−1.5– −0.2)	−1 (−1.7– −0.3)	0.081
FPG [mmol/l]:			
Baseline	8.7 (7.85–9.9)	8.6 (7.65–9.75)	0.357
Difference between 24 weeks and baseline	−1.65 (−2.6– −0.75)	−1.8 (−3.05– −0.93)	0.032*
Difference between 48 weeks and baseline	−1.5 (−2.25– −0.55)	−2.18 (−3.1– −1.13)	< 0.001*
2h-PPG [mmol/l]:			
Baseline	12.74 ±2.78	12.36 ±2.8	0.22
Difference between 24 weeks and baseline	−2.51 ±3.03	−3.43 ±2.8	0.004*
Difference between 48 weeks and baseline	−2.31 ±3.2	−3.59 ±3.05	< 0.001*
Insulin, glucagon, and GLP-1 characteristics:			
HOMA-B:			
Baseline	47.1 (29.16–74.3)	48.19 (28.86–76.2)	0.996
Difference between 24 weeks and baseline	4.33 (−24.08–23.52)	3.65 (−19.55–29.58)	0.493
Difference between 48 weeks and baseline	−3.05 (−24.35–19.85)	0.05 (−18.91–26.28)	0.358
HOMA-IR:			
Baseline	3.79 (2.49–6.06)	3.84 (2.44–6.13)	0.864
Difference between 24 weeks and baseline	−1.07 (−3.02–0.75)	−1.5 (−3.72– −0.15)	0.069
Difference between 48 weeks and baseline	−1.19 (−3.5–0.28)	−1.69 (−4– −0.39)	0.028*

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Table I. Cont.

Parameter	Weight decreased < 2 kg (N = 145)	Weight decreased ≥ 2 kg (N = 192)	P-value
Early insulin secretion index:			
Baseline	2.33 (0.8–4.23)	2.62 (1.21–4.8)	0.096
Difference between 24 weeks and baseline	1.04 (–2.12–3.94)	0.89 (–2.52–3.77)	0.495
Difference between 48 weeks and baseline	0.39 (–2.78–3.49)	0.54 (–2.52–4.21)	0.889
Whole body insulin sensitivity index:			
Baseline	4.1 (2.86–5.56)	3.78 (2.57–5.89)	0.438
Difference between 24 weeks and baseline	1.77 (–0.14–4.53)	3.33 (0.81–6.48)	0.001*
Difference between 48 weeks and baseline	1.96 (–0.09–4.01)	3.94 (1.33–7.11)	< 0.001*
AUC for serum insulin [μIU/ml × min]:			
Baseline	4109.55 (3014.4–5676.15)	4653.3 (3347.55–6527.7)	0.092
Difference between 24 weeks and baseline	–790.35 (–1875–385.2)	–1253.25 (–2661–202.35)	0.093
Difference between 48 weeks and baseline	–371.1 (–1634.4–756.3)	–1448.78 (–3199.28– –121.05)	< 0.001*
AUC for glucagon [pg/ml × min]			
Baseline	11873.85 (9289.5–15032.25)	12447.75 (10174.05–17038.5)	0.06
Difference between 24 weeks and baseline	–461.7 (–4019.4–3575.55)	–1209.45 (–5413.2–3302.85)	0.211
Difference between 48 weeks and baseline	–1493.48 (–5351.63–2853.23)	–2677.35 (–6003.75–1195.5)	0.072
AUC for plasma GLP-1 [pmol × min]:			
Baseline	3032.33 (1845.53–4829.4)	2490.23 (1643.78–4181.78)	0.05
Difference between 24 weeks and baseline	897.15 (–836.7–2640.9)	1188.45 (–300.3–2760.6)	0.14
Difference between 48 weeks and baseline	787.95 (–723.15–2745.3)	1443 (–180–2620.05)	0.247

*FPG – fasting plasma glucose, 2h-PPG – 2 h postprandial glucose. *P < 0.05, significant differences between weight decreased < 2 kg vs. ≥ 2 kg.*

of weight over the course of the study were female (63.7% vs. 36.3%, respectively; $p = 0.041$), had higher baseline BMI (26.23 kg/m² vs. 25.24 kg/m²; $p = 0.001$), and had lower baseline HbA$_{1c}$ ($p < 0.001$). Patients with ≥ 2 kg of weight reduction also had greater decreases from baseline in FPG and 2-hour postprandial glucose (2 h-PPG) (FPG at week 48; –2.18 mmol/l vs. –1.5 mmol/l; $p < 0.001$; 2 h-PPG at week 48: –3.59 vs. –2.31; $p < 0.001$) and greater increases from baseline in the whole body insulin sensitivity index at weeks 24 and 48 (week 24: 3.33 vs. 1.77, $p = 0.001$; week 48: 3.94 vs., 1.96, $p < 0.001$). Patients with ≥ 2 kg weight loss also had greater decreases from baseline in HOMA-IR (–1.69 vs. –1.19, $p = 0.028$) and larger reductions from baseline in insulin AUC (–1448.78 μIU/ml × min vs. –371.1 μIU/ml × min; $p < 0.001$) at week 48.

In patients treated with metformin, ≥ 2 kg weight loss compared with < 2 kg reduction in weight was associated with higher baseline BMI (26.08 kg/m² vs. 25.21 kg/m², respectively; $p = 0.002$), lower baseline HbA$_{1c}$ (7.3 vs. 7.7; $p = 0.003$), lower baseline 2h-PPG (12.34 vs. 13.01; $p = 0.04$), and higher baseline HOMA-B (57.61 vs. 45.2; $p = 0.007$) (Table II). Metformin patients with ≥ 2 kg weight reduction also had greater decreases from baseline in HOMA-B (–3.02 vs. 6.35, $p = 0.048$) and HOMA-IR (–2.21 vs. –1.48, $p = 0.004$), and a larger reduction from baseline in FPG (at week 48: –2.35 vs. –1.73; $p = 0.033$) at weeks 48. Patients treated with metformin who lost ≥ 2 kg of weight also had greater increases from baseline in the whole body insulin sensitivity index at 24 and 48 weeks (week 24: 2.24 vs. 1.89, $p = 0.047$; week 48: 2.98 vs. 1.8, $p < 0.001$).

Acarbose treated patients

Univariate analysis identified the following demographic and clinical characteristics as being associated with a ≥ 2 kg loss in weight: gender,

Table II. Baseline characteristics according to weight decrease < 2 kg vs. ≥ 2 kg in subjects treated with metformin

Parameter	Weight decreased < 2 kg (N = 144)	Weight decreased ≥ 2 kg (N = 183)	P-value
Demographic characteristics:			
Gender:			0.176
Male	94 (47%)	106 (53%)	
Female	50 (39.37%)	77 (60.63%)	
Age [years]	49 (41–56.5)	52 (44–57)	0.099
BMI [kg/m^2]	25.21 (23.61–26.79)	26.08 (24.21–28.39)	0.002*
Waist circumference [cm]	89.3 ±8.33	89.96 ±8.2	0.473
1-day energy intake from carbohydrates [cal]	210.07 (167.89–257.83)	219.09 (162.14–264.7)	0.772
1-day energy intake from non-carbohydrates [cal]	105.57 (75.79–137.59)	99.15 (74.65–130.44)	0.384
Clinical characteristics:			
Systolic blood pressure [mm Hg]	120 (118–130)	125 (120–135)	0.098
Diastolic blood pressure [mm Hg]	78.88 ±7.54	81.33 ±7.1	0.003*
Total cholesterol [mmol/l]	5.12 (4.31–5.93)	5.13 (4.43–5.88)	0.96
LDL cholesterol [mmol/l]	2.97 (2.41–3.65)	2.95 (2.42–3.58)	0.872
HDL cholesterol [mmol/l]	1.18 (1–1.36)	1.18 (1.03–1.38)	0.893
Triglycerides [mmol/l]	1.98 (1.39–2.83)	1.99 (1.38–2.76)	0.844
Glycemic characteristics:			
HbA$_{1c}$ (%):			
Baseline	7.7 (6.85–8.7)	7.3 (6.7–7.9)	0.003*
Difference between 24 weeks and baseline	−1.1 (−2– −0.5)	−1.1 (−1.7– −0.5)	0.521
Difference between 48 weeks and baseline	−0.8 (−1.9– −0.2)	−1 (−1.7– −0.5)	0.424
FPG [mmol/l]:			
Baseline	8.75 (7.88–9.98)	8.65 (7.95–9.65)	0.627
Difference between 24 weeks and baseline	−1.9 (−2.7– −1.2)	−2.1 (−3.05– −1.3)	0.213
Difference between 48 weeks and baseline	−1.73 (−2.88– −0.98)	−2.35 (−3.25– −1.15)	0.033*
2h-PPG:			
Baseline	13.01 (10.74–15.1)	12.26 (10–14.63)	0.04*
Difference between 24 weeks and baseline	−2.55 (−4.47–0.1)	−2.75 (−4.6– −1)	0.324
Difference between 48 weeks and baseline	−1.91 (−4.39–0.2)	−2.58 (−4.82– −0.57)	0.124
Insulin, glucagon, and GLP-1 characteristics:			
HOMA-B:			
Baseline	45.2 (27.42–68.19)	57.61 (35.67–79.82)	0.007*
Difference between 24 weeks and baseline	10.77 (−5.88–29.24)	2.15 (−19.35–31.78)	0.120
Difference between 48 weeks and baseline	6.35 (−10.47–28.97)	−3.02 (−28.64–27.45)	0.048*
HOMA-IR:			
Baseline	4.41 (2.64–6.4)	4.42 (2.71–6.79)	0.512
Difference between 24 weeks and baseline	−1.46 (−3.31– −0.05)	−1.99 (−3.66– −0.49)	0.123
Difference between 48 weeks and baseline	−1.48 (−3.25–0.18)	−2.21 (−4.71– −0.91)	0.004*

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Table II. Cont.

Parameter	Weight decreased < 2 kg (N = 144)	Weight decreased ≥ 2 kg (N = 183)	P-value
Early insulin secretion index:			
Baseline	2.56 (1–3.96)	2.52 (1.1–4.64)	0.732
Difference between 24 weeks and baseline	0.69 (–2.37–3.25)	1.87 (–1.19–4.66)	0.059
Difference between 48 weeks and baseline	0.41 (–2.36–2.37)	1.22 (–1.08–3.26)	0.017*
Whole body insulin sensitivity index:			
Baseline	3.79 (2.63–5.53)	3.34 (2.47–5.41)	0.406
Difference between 24 weeks and baseline	1.89 (0.16–4.89)	2.24 (0.95–5.7)	0.047*
Difference between 48 weeks and baseline	1.8 (–0.12–3.79)	2.98 (1.24–6.25)	< 0.001*
AUC for serum insulin [µIU/ml × min]			
Baseline	4154.48 (2994.75–6009)	4708.95 (3286.65–6520.65)	0.171
Difference between 24 weeks and baseline	–106.2 (–1377.45–1030.65)	–451.95 (–2229.45–696.45)	0.080
Difference between 48 weeks and baseline	–499.2 (–1588.2–1320.45)	–584.85 (–2296.35–696)	0.110
AUC for glucagon [pg/ml × min]:			
Baseline	12689.03 (9594.15–17729.25)	12507.6 (9700.95–15334.5)	0.201
Difference between 24 weeks and baseline	35.03 (–4197.15–5356.65)	–350.1 (–4138.05–3260.7)	0.524
Difference between 48 weeks and baseline	–1823.7 (–5935.5–2001.9)	–2461.65 (–5740.8–1197.6)	0.390
AUC for plasma GLP-1 [pmol × min]:			
Baseline	2878.2 (1748.1–4873.2)	2773.05 (1702.2–4896.45)	0.896
Difference between 24 weeks and baseline	1131 (–143.4–2738.85)	1115.4 (–877.05–2763.45)	0.553
Difference between 48 weeks and baseline	1448.55 (–550.58–2825.48)	1252.05 (–411.45–3047.1)	0.928

*FPG – fasting plasma glucose, 2h-PPG – 2 h postprandial glucose. *P < 0.05, significant differences between weight decreased < 2 kg vs. ≥ 2 kg.*

baseline HbA_{1c} levels, and glucagon and GLP-1 AUCs (p-values < 0.05) (Table III). Change from baseline in FPG and PPG levels and the whole body insulin sensitivity index at weeks 24 and 48, and in HOMA-IR and in insulin AUC at week 48 were also associated with a ≥ 2 kg weight reduction (p-values ≤ 0.038).

The factors significantly associated with loss of ≥ 2 kg of weight detected by univariate analyses were included in multivariate analyses. For baseline factors, multivariate analysis revealed that gender, HbA_{1c} levels and glucagon AUC were associated with ≥ 2 kg of weight loss (Table IV). A reduction in weight of ≥ 2 kg was less likely for males than females (OR = 0.58, p = 0.025) and in patients with higher baseline levels of HbA_{1c} (OR = 0.77, p = 0.012). Reduction in ≥ 2 kg of weight was positively associated with higher

baseline glucagon AUC (OR = 1.00006, p = 0.010). No significant associations were found for reduction in weight of ≥ 2 kg and any assessed factors at week 24 (all p > 0.05). Smaller increases from baseline at week 48 in FPG (OR = 0.65, p = 0.0002) and insulin AUC (OR = 0.9998, p = 0.008) were negatively associated with ≥ 2 kg reduction in weight.

Metformin treatment

Univariate analysis found that in patients treated with metformin the demographic and clinical characteristics that influenced a reduction of weight of ≥ 2 kg were baseline HbA_{1c} levels and PPG levels, changes at 48 weeks in FPG, whole body insulin sensitivity index, and insulin AUC (all p-values < 0.05) (Table V). Since no changes from baseline at week 24 were significantly

Table III. Univariate analyses to detect baseline factors associated with weight change of ≥ 2 kg in subjects treated with acarbose

Parameter	Univariate analysis	
	OR (95% CI)	*P*-value
Gender (ref = female)	0.63 (0.4–0.98)	0.042*
Age [years]	1.02 (0.99–1.04)	0.151
Waist circumference [cm]	1.004 (0.98–1.03)	0.748
1-day energy intake from carbohydrates [cal]	0.998 (0.996–1.001)	0.258
1-day energy intake from non-carbohydrates [cal]	0.997 (0.992–1.001)	0.146
Total cholesterol [mmol/l]	1.1 (0.9–1.35)	0.334
LDL cholesterol [mmol/l]	1.02 (0.8–1.3)	0.895
HDL cholesterol [mmol/l]	0.97 (0.45–2.08)	0.931
Triglycerides [mmol/l]	1.04 (0.94–1.14)	0.475
HbA_{1c} (%):		
Baseline	0.76 (0.63–0.92)	0.004*
Difference between 24 weeks and baseline	0.99 (0.83–1.18)	0.934
Difference between 48 weeks and baseline	0.9 (0.75–1.07)	0.229
FPG [mmol/l]:		
Baseline	0.92 (0.76–1.1)	0.349
Difference between 24 weeks and baseline	0.84 (0.72–0.99)	0.034*
Difference between 48 weeks and baseline	0.7 (0.59–0.82)	< 0.001*
2h-PPG [mmol/l]:		
Baseline	0.95 (0.88–1.03)	0.22
Difference between 24 weeks and baseline	0.9 (0.83–0.97)	0.005*
Difference between 48 weeks and baseline	0.88 (0.82–0.94)	< 0.001*
HOMA-B:		
Baseline	1.001 (0.9976–1.004)	0.579
Difference between 24 weeks and baseline	0.9998 (0.998–1.001)	0.809
Difference between 48 weeks and baseline	1.001 (0.999–1.003)	0.514
HOMA-IR:		
Baseline	1.01 (0.95–1.07)	0.71
Difference between 24 weeks and baseline	0.95 (0.89–1.01)	0.099
Difference between 48 weeks and baseline	0.94 (0.88–0.996)	0.038*
Early insulin secretion index:		
Baseline	1.02 (0.99–1.06)	0.134
Difference between 24 weeks and baseline	0.997 (0.98–1.01)	0.666
Difference between 48 weeks and baseline	1.002 (0.99–1.01)	0.654
Whole body insulin sensitivity index:		
Baseline	0.999 (0.92–1.08)	0.989
Difference between 24 weeks and baseline	1.08 (1.02–1.14)	0.009*
Difference between 48 weeks and baseline	1.15 (1.08–1.22)	< 0.001*

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Table III. Cont.

Parameter	Univariate analysis	
	OR (95% CI)	*P*-value
AUC for serum insulin at baseline [µIU/ml × min]:		
Baseline	1.0001 (0.99997–1.0002)	0.163
Difference between 24 weeks and baseline	0.9999 (0.9998–1.00002)	0.12
Difference between 48 weeks and baseline	0.9998 (0.9997–0.9999)	< 0.001*
AUC for glucagon [pg/ml × min]:		
Baseline	1.00005 (1.00001–1.00009)	0.019*
Difference between 24 weeks and baseline	0.99997 (0.9999–1.00001)	0.115
Difference between 48 weeks and baseline	0.99996 (0.9999–0.999999)	0.047*
AUC for plasma GLP-1 [pmol × min]:		
Baseline	0.9999 (0.9998–0.999995)	0.041*
Difference between 24 weeks and baseline	1.0001 (0.99999–1.0002)	0.103
Difference between 48 weeks and baseline	1.00005 (0.99995–1.0001)	0.326

*FPG – fasting plasma glucose, 2h-PPG – 2 h postprandial glucose. *P < 0.05, significantly associated with considerable weight change.*

Table IV. Multivariate analyses to detect factors associated with weight change of ≥ 2 kg in subjects treated with acarbose

Variable	Multivariate analysis	
	OR (95% CI)	*P*-value
For baseline variables:		
Gender (ref = female)	0.58 (0.37–0.93)	0.025*
HbA$_{1c}$ (%)	0.77 (0.63–0.95)	0.012*
AUC for glucagon [pg/ml × min]	1.00006 (1.00001–1.0001)	0.010*
AUC for plasma GLP-1 [pmol × min]	0.9999 (0.9998–1.00004)	0.230
For differences at 24 weeks:		
ΔFPG between 24 weeks and baseline	0.89 (0.75–1.05)	0.170
ΔPPG between 24 weeks and baseline	0.92 (0.84–1.01)	0.072
ΔWhole body insulin sensitivity index between 24 weeks and baseline	1.06 (0.999–1.12)	0.056
For differences at 48 weeks:		
ΔFPG between 48 weeks and baseline	0.67 (0.54–0.83)	0.0002*
ΔPPG between 48 weeks and baseline	0.95 (0.86–1.05)	0.323
ΔHOMA-IR between 48 weeks and baseline	1.01 (0.93–1.11)	0.754
ΔWhole body insulin sensitivity index between 48 weeks and baseline	1.06 (0.98–1.14)	0.151
ΔAUC for serum insulin between 48 weeks and baseline	0.9998 (0.9997–0.99995)	0.008*
ΔAUC for glucagon between 48 weeks and baseline	0.99998 (0.9999–1.00002)	0.250

*Baseline factors and the changes from baseline at week 24 and week 48 were separated into different models. FPG – fasting plasma glucose, 2h-PPG – 2 h postprandial glucose. *P < 0.05, significantly associated with considerable weight change.*

associated with a reduction of weight of ≥ 2 kg in univariate analyses, no multivariate analysis was performed for changes at week 24. At week 48, multivariate analysis revealed that baseline HbA$_{1c}$ levels were negatively associated with ≥ 2 kg weight reduction (OR = 0.80, *p* = 0.036). In addition, the analysis revealed that increase from baseline in the whole body insulin sensitivity index at week 48 increased the likelihood of weight reduction (OR = 1.10, *p* = 0.014) (Table VI).

Table V. Univariate analyses to detect the baseline factors associated with weight change of ≥ 2 kg in subjects treated with metformin

Variable	Univariate analysis	
	OR (95% CI)	P-value
Gender (ref = female)	0.73 (0.47–1.15)	0.176
Age [years]	1.02 (0.995–1.04)	0.127
Waist circumference [cm]	1.01 (0.98–1.04)	0.472
1-day energy intake from carbohydrates [cal]	1.0004 (0.9974–1.0034)	0.794
1-day energy intake from non-carbohydrates [cal]	0.997 (0.99–1.002)	0.269
Total cholesterol [mmol/l]	1.01 (0.84–1.23)	0.908
LDL cholesterol [mmol/l]	0.96 (0.76–1.21)	0.717
HDL cholesterol [mmol/l]	1.14 (0.57–2.27)	0.716
Triglycerides [mmol/l]	0.99 (0.89–1.11)	0.887
HbA_{1c} (%):		
Baseline	0.77 (0.64–0.92)	0.005*
Difference between 24 weeks and baseline	1.08 (0.9–1.31)	0.396
Difference between 48 weeks and baseline	0.96 (0.81–1.14)	0.666
FPG [mmol/l]:		
Baseline	0.94 (0.77–1.14)	0.522
Difference between 24 weeks and baseline	0.91 (0.77–1.08)	0.284
Difference between 48 weeks and baseline	0.83 (0.72–0.97)	0.016*
2h-PPG [mmol/l]:		
Baseline	0.93 (0.86–0.996)	0.039*
Difference between 24 weeks and baseline	0.94 (0.88–1.01)	0.113
Difference between 48 weeks and baseline	0.94 (0.88–1.004)	0.063
HOMA-B:		
Baseline	1.006 (0.9997–1.012)	0.061
Difference between 24 weeks and baseline	0.999 (0.99–1.003)	0.531
Difference between 48 weeks and baseline	0.999 (0.997–1.002)	0.678
HOMA-IR:		
Baseline	0.999 (0.94–1.06)	0.965
Difference between 24 weeks and baseline	0.99 (0.93–1.05)	0.740
Difference between 48 weeks and baseline	0.97 (0.92–1.02)	0.193
Early insulin secretion index:		
Baseline	0.99 (0.97–1.01)	0.322
Difference between 24 weeks and baseline	1.01 (0.99–1.02)	0.502
Difference between 48 weeks and baseline	1.01 (0.99–1.04)	0.166
Whole body insulin sensitivity index:		
Baseline	0.97 (0.9–1.06)	0.49
Difference between 24 weeks and baseline	1.05 (0.995–1.12)	0.075
Difference between 48 weeks and baseline	1.12 (1.05–1.18)	< 0.001*

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Table V. Cont.

Variable	Univariate analysis	
	OR (95% CI)	*P*-value
AUC for serum insulin [µIU/ml × min]:		
Baseline	1.0001 (0.99998–1.0002)	0.138
Difference between 24 weeks and baseline	0.9999 (0.9998–1.000001)	0.052
Difference between 48 weeks and baseline	0.9999 (0.9998–0.9999998)	0.0497*
AUC for glucagon [pg/ml × min]:		
Baseline	0.99996 (0.99992–1.000002)	0.062
Difference between 24 weeks and baseline	0.99998 (0.9999–1.00002)	0.406
Difference between 48 weeks and baseline	0.99998 (0.9999–1.00002)	0.382
AUC for plasma GLP-1 [pmol × min]:		
Baseline	1.00002 (0.99991–1.0001)	0.779
Difference between 24 weeks and baseline	0.99997 (0.9999–1.0001)	0.528
Difference between 48 weeks and baseline	0.99999 (0.9999–1.0001)	0.755

*FPG – fasting plasma glucose, 2h-PPG – 2 h postprandial glucose; *p < 0.05, significantly associated with considerable weight change.*

Table VI. Multivariate analyses to detect the factors associated with weight change of ≥ 2 kg in subjects treated with metformin

Variable	Multivariate analysis	
	OR (95% CI)	*P*-value
For baseline variables:		
HbA$_{1c}$ (%)	0.80 (0.65–0.99)	0.036*
2h-PPG [mmol/l]	0.96 (0.89–1.04)	0.348
For differences at 48 weeks:		
ΔFPG between 48 weeks and baseline	0.90 (0.77–1.06)	0.214
ΔWhole body insulin sensitivity index between 48 weeks and baseline	1.10 (1.02–1.18)	0.014*
ΔAUC for serum insulin between 48 weeks and baseline	0.99999 (0.9999–1.0001)	0.909

*Baseline factors and the changes from baseline at week 24 and week 48 were separated into different models. FPG – fasting plasma glucose, 2h-PPG – 2 h postprandial glucose. *P < 0.05, significantly associated with considerable weight change.*

Discussion

In this sub-analysis of the MARCH trial, we evaluated what demographic and clinical factors were associated with reduction in weight at the end of the 48-week follow-up period. We assessed the effect of baseline values of different parameters on weight loss in patients treated with acarbose or metformin. Multivariate analysis indicated that in patients treated with acarbose, males were less likely than females to lose weight. In addition, higher baseline HbA$_{1c}$ levels and smaller decreases from baseline in FPG levels after 48 weeks of treatment were negatively associated with weight reduction, and higher baseline glucagon AUC was positively associated with weight loss. In patients treated with metformin, lower decreases in FPG levels from baseline after 48 weeks of treatment

were negatively associated with weight reduction. In addition, greater changes from baseline in whole body insulin sensitivity after 48 weeks of treatment increased the likelihood of weight reduction in metformin patients.

Acarbose and metformin are associated with weight loss in type 2 diabetes, although the exact mechanisms are not entirely clear [9]. Acarbose appears to mediate its weight loss effect through promoting GLP-1 levels [4]. Metformin is thought to reduce weight via regulatory pathways in the brain, and also via adipose and gut-derived signals [5, 9]. Similar to acarbose, metformin may also reduce hunger and alter carbohydrate absorption by raising GLP-1 levels [10, 11]. We saw little effect of GLP-1 levels on weight loss in our analysis for both acarbose and metformin. These findings may be

limited by the sample size. It is possible that larger sample sizes may have had greater sensitivity for detecting the effect of changes in GLP-1 levels on weight. Additional studies designed to evaluate the relationship of GLP-1 and weight reduction in type 2 diabetes patients treated with metformin or acarbose are necessary.

We found that baseline glucagon AUC is significantly associated with weight loss in patients treated with acarbose but not in those treated with metformin. Previous studies have found that GLP-1, whose levels are affected by acarbose therapy, can affect glucagon levels [4, 11–18]. However, our findings did not reveal an association of GLP-1 with weight reduction, possibly suggesting that the effect of acarbose on glucagon levels can act independently of GLP-1 to influence weight. We also found that change in the whole body insulin sensitivity index from baseline after 48 weeks of metformin but not acarbose therapy was associated with weight loss. The difference between the two drugs with regard to the importance of insulin and glucagon control and weight loss may reflect the complexity of glycemic control and the insulin-glucagon interaction. Additional studies are necessary to further understand how the two therapies act to influence weight.

Our findings suggest that subjects with better glycemic control with metformin or acarbose treatment were more likely to lose weight. These findings are consistent with prior studies that found an association of glycemic control with weight loss [16–19]. The study of Bluher *et al.* specifically evaluated the hypothesis that the degree of weight change with the dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin was dependent on the level of baseline glycemic control [18]. Using linear regression analysis, they identified an FPG level (14.6 mmol/l) in which there was no change in weight. FPG levels below this neutral point resulted in weight loss and above this point resulted in weight gain. They also found a similar relationship between baseline HbA_{1c} levels and weight change. The authors concluded that treatment results in weight loss when glucose or HbA_{1c} levels are below a renal threshold. Due to the complexity of the regulatory pathways involved in controlling caloric intake, fat metabolism, insulin resistance, etc. [20, 21], the exact role of different factors related to glycemic control in influencing weight is unclear. It is possible that our findings are more reflective of the importance of glucose homoeostasis for other bodily processes, including weight, and not a specific role for any given factor.

The findings and interpretation of this study are limited by the fact that this was a secondary analysis of the MARCH study. In addition, we only evaluated a subset of baseline parameters and clinical factors associated with type 2 diabetes using multivariate analysis. It is possible that other parameters/factors may also influence weight loss. As this was a secondary analysis of the MARCH study, we were unable to assess other variables, such as exercise, diet, etc., which may have impacted weight loss. A study in rats found that weight loss associated with metformin or sitagliptin, and the type of diet (high fat, high protein, or mixed diet), influenced the effect of drugs on triglyceride and postprandial blood glucose levels [22]. Also, it is unclear whether lifestyle changes impacted the findings as they were not factored into body weight determination. Although we cannot actually determine to what extent any patient changes in lifestyle measures during or after the 4-week education/preparation period influenced weight loss, we know that no significant changes were noted in patients' weight during the 4-week run-in period before the study began, when measured by treatment group [19]. The MARCH study was performed using solely Chinese patients. Therefore, it is not clear how the findings relate to other ethnic groups and geographical regions. In addition, the BMI in the patient population in the MARCH study ranged from 19 kg/m^2 to 30 kg/m^2; hence, our population did not include obese patients, and it is unclear whether our findings would be similar in an obese population of patients.

In conclusion, this study found that for both acarbose and metformin, the levels of FPG significantly impacted weight loss. In addition, baseline AUC for glucagon in patients treated with acarbose and change from baseline in whole body insulin sensitivity after 48 weeks of therapy in metformin-treated patients were important factors for weight reduction.

Conflict of interest

The authors declare no conflict of interest.

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