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ABOUT COVER

Editorial board member of *World Journal of Diabetes*, Dr. Klobucar Majanovic attended medical school in Rijeka, Croatia. She then trained in Internal Medicine at the Clinical Hospital Center Rijeka, Croatia, where she also completed a Fellowship in Endocrinology and Diabetology. Dr. Klobucar Majanovic is currently Associate Professor of Internal Medicine and Head of the Outpatient Clinic and Educational Center for Diabetes and Obesity at Clinical Hospital Center Rijeka, Croatia. She also serves as Vice President of the Croatian Society for Diabetes and Metabolic Diseases and Vice President of the Croatian Society for Obesity. Her main clinical and research interests are diabetes prevention and treatment, and management of obesity and nutrition. She received the Etzwiler International Scholar Award, Class of 2018. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, *etc.*.

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ORIGINAL ARTICLE

Clinical Trials Study

Factors associated with improvement in waist-to-height ratio among newly diagnosed type 2 diabetes patients treated with acarbose or metformin: A randomized clinical trial study

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Author contributions: Yang WY was the principal investigator of the trial; Song LL drafted the manuscript; Wang X was the co-investigator; Yang ZJ developed design of the trial; Kong XM provided important advice and guidance regarding the statistical analysis; and Chen XP and Zhang B contributed to the trial.

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Abstract

BACKGROUND

The waist-to-height ratio (WHtR) is a promising anthropometric measure used to evaluate cardiovascular risk in diabetes and metabolic syndrome patients. The metformin and acarbose in Chinese as the initial hypoglycaemic treatment trial demonstrated that acarbose and metformin reduced the WHtR after 24 wk of treatment.

AIM

To investigate the factors associated with a decrease in the WHtR in newly diagnosed Chinese type 2 diabetes patients receiving acarbose or metformin monotherapy.

METHODS

At 24 wk, 343 patients in the acarbose treatment and 333 patients in the metformin treatment were included in this analysis. On the basis of the reduction in the WHtR, these participants were divided into the following two groups: Low ΔWHtR group and high ΔWHtR group. Metabolic and related parameters associated with a high ΔWHtR were investigated using univariate and multivariate logistic regression analyses.

RESULTS

A significant decrease in the WHtR was observed in both treatment groups (acarbose: -0.015, 95% confidence interval [CI]: -0.018 to -0.012, $P < 0.001$; metformin: -0.013, 95%CI: -0.016 to -0.010, $P < 0.001$). In both the acarbose and metformin groups, the WHtR of the women was more likely to be reduced than that of the men. In the acarbose group, a lower baseline area under the curve of glucagon-like peptide 1 (AUCGLP-1) was associated with a high ΔWHtR (odds ratio [OR] = 0.796, $P < 0.001$), while a higher baseline AUCGLP-1 was associated

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with a high ΔWHtR in the patients treated with metformin (OR = 1.133, P = 0.025). Regarding the changes from baseline, an increase in AUCGLP-1 was associated with a high ΔWHtR in the acarbose (OR = 1.121, P = 0.016) but not metformin group. A higher reduction in high-density lipoprotein cholesterol/non-high-density lipoprotein cholesterol was also associated with a high ΔWHtR in the acarbose arm (OR = 20.735, P = 0.001). In the metformin arm, a higher reduction in fasting plasma glucose (OR = 0.843, P = 0.039) and total cholesterol was associated with a high ΔWHtR (OR = 0.743, P = 0.013).

CONCLUSION

A lower glucagon-like peptide 1 level and higher increase in glucagon-like peptide 1 are associated with a high reduction in the WHtR in newly diagnosed Chinese diabetes patients receiving treatment with acarbose.

Key Words: Waist-to-height ratio; Abdominal obesity; Type 2 diabetes; Association; Acarbose; Metformin

Core Tip: Obesity, especially abdominal obesity is an important risk factor for cardiovascular diseases in type 2 diabetes. The metformin and acarbose in Chinese as the initial hypoglycaemic treatment trial demonstrated that acarbose and metformin not only reduced glycosylated hemoglobin but also reduced weight and waist circumference after 24 wk of treatment with acarbose or metformin. Waist-to-height ratio waist-to-height ratio is a new anthropometric measure as an indicator of abdominal obesity and a better alternative to waist circumference. In this analysis, we demonstrated different association of glucagon-like peptide 1 and some other parameters with reduction of waist-to-height ratio in acarbose or metformin treated patients.

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INTRODUCTION

The prevalence of diabetes has been increasing worldwide in past decades. As reported in the latest International Diabetes Federation Diabetes Atlas (9th edition), the global diabetes prevalence is estimated to be 9.3% (463 million) and is estimated to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045[1]. In the Chinese population, the estimated prevalence of diabetes increased from 9.7% in the 2007 survey[2] to 10.9% in the 2013 survey[3]. The prevalence of newly diagnosed diabetes is also high as follows: In the 2013 survey, 6.9% of the population was diagnosed with diabetes for the first time[3]. Another survey of Chinese adults in northwest China reported that approximately 7.5% of the interviewees had newly diagnosed type 2 diabetes mellitus (T2DM)[4]. The grim situation in which millions of people suffer from diabetes is placing a heavy burden on national health systems.

To alleviate the harmfulness of diabetes, integrated management is quite important and includes obesity, dyslipidemia, hypertension, *etc*. Most T2DM patients are characterized by suffering from overweightness or obesity, especially abdominal obesity, which is associated with a high risk of cardiovascular diseases and mortality. Therefore, the weight loss effect of antidiabetic drugs is an advantage when selecting treatment for obese T2DM patients. Various indexes, including the waist circumference (WC), hip circumference (HC), and waist-to-height ratio (WHtR), have been explored to evaluate abdominal obesity. The WHtR is a new anthropometric measure that has been proposed as an indicator of abdominal obesity and a better

alternative to WC[5-8]. It has been reported that the WHtR is closely and independently associated with T2DM[9]. A high WHtR was also associated with cardiovascular disease risk in a Mexican population as a better marker of cardiovascular risk than other anthropometric indexes[10]. The WHtR has also been confirmed to be more strongly associated with stroke risk than the body mass index (BMI) likely because the BMI cannot discriminate between general and abdominal obesity[6].

Acarbose and metformin are considered first-line oral antidiabetic drugs. It is well known that metformin has a significant weight loss effect in most studies; regarding acarbose, the effect on weight loss is positive or neutral as reported in different studies, which is likely attributed to population differences. The effect of acarbose on weight loss seems to be more pronounced in Eastern than in Western populations with hyperglycemia[11]. This inconsistency might be explained by differences in dietary habits as the standard Asian diet is characterized by a higher percentage of carbohydrates. However, the mechanism is still not absolutely clear. The metformin and acarbose in Chinese as the initial hypoglycaemic treatment (MARCH) trial was a head-to-head comparison study of metformin and acarbose as initial therapy for T2DM after the failure of therapeutic lifestyle modification for the first time in a Chinese population[12,13]. As the MARCH study demonstrated, both acarbose and metformin have similar efficacy as initial therapy in reducing glycated hemoglobin A1c (HbA1c). Interestingly, acarbose reduced body weight more than metformin[12]. Further analysis should be conducted to investigate the effect of acarbose in improving abdominal obesity. In addition, the mechanisms of acarbose-induced weight loss are still unclear. Whether α-glucosidase inhibitors change incretins and whether changes in glucagon-like peptide 1 (GLP-1) are involved in the improvement in abdominal obesity after treatment with acarbose or metformin should be analyzed. Therefore, in this post hoc analysis, we demonstrated the effect of acarbose or metformin on the WHtR, and investigated the factors associated with changes in the WHtR (ΔWHtR) and the possible role of GLP-1 in the weight loss effect of acarbose.

MATERIALS AND METHODS

Study design and participants

The MARCH study is a multicenter, open-label, non-inferior, parallel randomized controlled trial. The Chinese Clinical Trial Registry number is ChiCTR-TRC-08000231. This study was designed to determine whether acarbose is non-inferior to metformin in lowering blood glucose levels in Chinese patients with newly diagnosed T2DM patients. The protocol was approved by the Ethics Committee of each clinical center.

The participants were recruited from diabetes outpatient clinics at 11 centers. All patients were diagnosed with T2DM according to the 1999 World Health Organization criteria within the past 12 mo. The patients had not received oral antidiabetic drugs or received treatment no longer than 1 mo that had been discontinued 3 mo before enrolment. The inclusion criteria and exclusion criteria were explained in detail in our published article[12].

The non-inferiority margin of 0.3% (absolute) was chosen, and an estimated standard deviation of 1.3% for HbA1c was used in the sample size calculation. To achieve 80% power to show the non-inferiority of acarbose compared with metformin, the total number of subjects required to complete the study is at least 590. Assuming a 20% drop-out rate, the total number that should be enrolled in the study is 738 (369 patients per treatment group). In total, 788 eligible patients with fasting plasma glucose (FPG) between 7.0 and 11.1 mmol/L were randomly assigned (1:1) to each of the two groups treated with acarbose or metformin (block size 8). After the 4-wk run-in phase, the patients were assigned to receive sustained-release metformin hydrochloride up to 1500 mg once daily (500 mg per tablet, Beijing Double Crane Pharma, Beijing, China) or up to 100 mg of acarbose three times daily (50 mg per tablet, Bayer Healthcare, Beijing, China). The randomization codes were generated by statisticians from the statistics office of China-Japan Friendship Hospital using SAS (version 9.0) and concealed in envelopes. The investigators at each center enrolled the participants, unsealed the randomization codes, and assigned the patients to the interventions. At week 24, add-on therapy with insulin secretagogues was initiated in the patients who had FPG higher than 7 mmol/L or postprandial glucose greater than 10 mmol/L for 3 consecutive days by self-monitored blood glucose. The primary outcome was reduction in HbA1c at 24 wk and 48 wk. The key secondary outcomes included the proportion of patients with HbA1c of 6.5% or less and changes in FPG, 2-h PPG, bodyweight, insulin, glucagon, GLP-1, insulin sensitivity, or β-cell function.

The adverse events were also assessed. A detailed description is provided in our published article[12].

In total, 351 patients in the acarbose group and 347 patients in the metformin group completed the 24-wk treatment. The losses and exclusions after randomization were previously described in the published article[12].

Measurements

Both the baseline characteristics and changes from the baseline clinical variables after 24 wk of treatment were compared between the low ΔWHtR and high ΔWHtR groups. The glucose metabolism variables included HbA1c, FPG, 2-h PPG, homoeostatic model assessment of insulin resistance (HOMA-IR), and whole-body insulin sensitivity index (WBISI). Hormone secretion parameters included fasting insulin (FINS), HOMA-β, early insulin secretion index (I30/G30), and the area under the curve (AUC) of insulin and AUCGLP-1. The anthropometric measurements included body weight, WC, HC, BMI, and WHtR. The lipid metabolic parameters included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-C, and HDL-C-to-non-HDL-C ratio (HDL-C/non-HDL-C). The cardiovascular parameters included systolic blood pressure and diastolic blood pressure. The following formulas were used to calculate some of the indexes mentioned above: HOMA-IR = FINS (μIU/mL) × FBG (mmol/L)/22.5; HOMA-B = 20 × FINS (μIU/mL)/[FBG (mmol/L) - 3.5; I30/G30 = ΔI30 ($insulin_{30\ min}$ - $insulin_{0\ min}$) /ΔG30 ($glucose_{30\ min}$ - $glucose_{0\ min}$); and WBISI = 10000/square root of [(mean plasma insulin × mean plasma glucose during OGTT) × (fasting plasma insulin × fasting plasma glucose). The AUC was calculated with the following equations: AUCinsulin = ($insulin_{0\ min}$ + $insulin_{30min}$) × 30/2 + ($insulin_{30\ min}$ + $insulin_{120\ min}$) × 90/2 + ($insulin_{120\ min}$ + $insulin_{180\ min}$) × 60/2 and AUCGLP-1 = ($GLP\text{-}1_{0\ min}$ + $GLP\text{-}1_{30min}$) × 30/2 + ($GLP\text{-}1_{30\ min}$ + $GLP\text{-}1_{120\ min}$) × 90/2 + ($GLP\text{-}1_{120\ min}$ + $GLP\text{-}1_{180\ min}$) × 60/2.

Statistics analysis

Based on changes in WHtR at week 24 (ΔWHtR), the participants were divided into the following two groups using the median as the cutoff (-0.012): High ΔWHtR group and low ΔWHtR group. The variables with a normal distribution are presented as the mean and standard deviation, and the variables with a skewed distribution are presented as the median and interquartile range. The comparison of the variables with a normal distribution was performed by an independent-samples *t*-test, while the comparison of the variables with a skewed distribution was performed by the Kruskal-Wallis test. For the analysis of the changes in the parameters associated with the WHtR improvement level, the statistical analysis consisted of a univariate logistic regression analysis, followed by a stepwise multivariate logistic analysis. The univariate analyses were performed using single regression models to assess the association between each explanatory variable and the outcome. Then, the factors that were significantly associated with a high ΔWHtR were subjected to a multivariate analysis using an enter process at an α-level of 0.05. In the analysis of the baseline factors associated with a high ΔWHtR at week 24, only the variables measured at baseline were included as explanatory variables. In the analysis of the associated changes in the treatment parameters, the baseline parameters were also included. The acarbose and metformin arms were evaluated independently.

RESULTS

Baseline characteristics of participants involved in this post hoc analysis

Of the 676 subjects with complete data who were included in this subgroup analysis, 343 were randomized into the acarbose arm, and 333 were randomized into the metformin arm. Baseline differences in the WC, HC, TG, FINS, HOMA-IR, and I30/G30 were found between the two ΔWHtR groups. Compared with the low ΔWHtR group, the high ΔWHtR group had greater percentages of females (44.4% *vs* 33.3%, $P = 0.046$) and older participants (51.80 ± 8.83 *vs* 49.43 ± 9.36 years, $P = 0.016$), larger WC (90.61 ± 8.36 *vs* 88.16 ± 8.27 cm, $P = 0.007$), larger hip circumference (100.38 ± 7.68 *vs* 97.52 ± 7.05 cm, $P < 0.001$), higher FINS (11.17 *vs* 10.30 μIU/mL, $P = 0.012$), and higher HOMA-IR (4.00 *vs* 3.58, $P = 0.003$). Moreover, the baseline TG (1.69 *vs* 1.88 mmol/L, $P = 0.020$), I30/G30 (2.44 *vs* 2.78, $P = 0.012$), and AUCGLP-1 (2.41 *vs* 3.24 nmol × min, $P = 0.001$) were lower in this group (Table 1).

In the metformin arm, the female percentage was higher (46.5% *vs* 34.1%, $P = 0.025$) in the high ΔWHtR group. The WBISI (69.45 *vs* 66.16, $P = 0.031$) and HDL-C/NHDL-C

Table 1 Baseline characteristics of patients in different change of waist-to-height ratio groups treated with acarbose

	High ΔWHtR	Low ΔWHtR	*P* value
n	178	165	
Demographic characteristics			
Age, yr	51.80 ± 8.83	49.43 ± 9.36	0.016
Males/Females, *n*	99/79	110/55	0.046
Anthropometric measurements			
Waist circumference, cm	90.61 ± 8.36	88.16 ± 8.27	0.007
Hip circumference, cm	100.38 ± 7.68	97.52 ± 7.05	< 0.001
Body weight, kg	69.98 ± 10.84	70.41 ± 10.08	0.701
Body mass index, kg/m^2	25.83 ± 2.70	25.46 ± 2.49	0.193
Glucose metabolism variables			
HbA1c, %	7.44 ± 1.10	7.54 ± 1.40	0.437
FPG, mmol/L	8.27 ± 1.34	8.18 ± 1.45	0.561
PPG, mmol/L	12.54 ± 2.59	12.70 ± 3.16	0.608
Blood pressure and lipid profile			
Systolic blood pressure, mmHg	124.08 ± 12.44	122.85 ± 13.45	0.379
Diastolic blood pressure, mmHg	79.06 ± 8.95	79.48 ± 9.06	0.665
TC, mmol/L	5.20 ± 1.06	5.30 ± 1.13	0.363
HDL-C, mmol/L	1.24 ± 0.28	1.23 ± 0.30	0.683
LDL-C, mmol/L	3.10 ± 0.86	3.11 ± 0.93	0.943
NHDL-C, mmol/L	3.96 ± 1.01	4.08 ± 1.10	0.292
HDL-C/NHDL-C	0.32 (0.25 to 0.40)	0.30 (0.24 to 0.38)	0.324
TG, mmol/L	1.69 (1.15-2.35)	1.88 (1.36-2.78)	0.020
Hormones and insulin sensitivity			
FINS, μIU/mL	11.17 (7.48 to 16.01)	10.30(6.38 to 15.85)	0.012
I30/G30	2.44 (1.12 to 4.40)	2.78 (0.87 to 4.62)	0.012
HOMA-β	48.31 (29.04 to 75.66)	46.49 (27.61 to 72.66)	0.195
AUCinsulin, μIU/L × min	4.71 (3.28 to 6.54)	4.33 (3.06 to 5.65)	0.300
AUCGLP-1, nmol × min	2.41 (1.96 to 4.06)	3.24 (1.96 to 5.19)	0.001
HOMA-IR	4.00 (2.55 to 6.36)	3.58 (2.25 to 6.02)	0.003
WBISI	68.43 (49.29 to 100.96)	78.34 (51.86 to 119.52)	0.610

WHtR: Change of waist-to-height ratio; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; HDL-C/non-HDL-C: HDL-C-to-non-HDL-C ratio; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; FINS: Fasting plasma insulin; HOMA: Homeostasis model assessment-; IR: Insulin resistance; WBISI: Whole body insulin sensitivity index; AUC: Area under the curve; GLP-1: Glucagon-like peptide 1.

were slightly higher in the high ΔWHtR group than in the low ΔWHtR group (0.32 *vs* 0.30, $P < 0.001$) (Table 2).

Changes from baseline after 24 wk of acarbose or metformin treatment

Following the 24-wk treatment, the patients in the acarbose arm with a high ΔWHtR had lost an average of 3.63 kg (5.28%) of body weight, 1.60 BMI units, 5.6 cm of WC, and 4.5 cm of HC. In contrast, the patients with a low ΔWHtR lost 1.29 kg (1.84%) and 0.1 cm of HC and gained 0.56 BMI units and 0.9 cm of WC.

Regarding glycemic control, the patients with a high ΔWHtR had greater reductions in FPG (-1.47 *vs* -1.10 mmol/L, $P = 0.024$), FINS (-4.73 μIU/mL *vs* -2.88 μIU/mL, $P =$

Table 2 Baseline characteristics of patients in different change of waist-to-height ratio groups treated with metformin

	High ΔWHtR	Low ΔWHtR	*P* value
n	157	176	
Demographic characteristics			
Age	51.34 ± 9.10	49.48 ± 9.24	0.043
Males/Females, *n*	84/73	116/60	0.025
Anthropometric measurements			
Waist circumference, cm	90.64 ± 8.23	88.95 ± 8.19	0.063
Hip circumference	99.07 ± 7.43	98.38 ± 7.39	0.396
Body weight, kg	69.52 ± 10.61	71.40 ± 10.75	0.111
Body mass index, kg/m^2	25.90 ± 2.60	25.59 ± 2.61	0.276
Glucose metabolism variables			
HbA1c, %	7.56 ± 1.23	7.60 ± 1.19	0.758
FPG, mmol/L	8.44 ± 1.41	8.45 ± 1.43	0.924
PPG, mmol/L	12.51 ± 3.00	12.50 ± 2.97	0.975
Blood pressure and lipid profile			
Systolic blood pressure, mmHg	124.53 ± 12.25	123.02 ± 13.85	0.293
Diastolic blood pressure, mmHg	79.99 ± 6.37	78.16 ± 9.12	0.035
TC, mmol/L	5.30 ± 1.21	5.17 ± 1.04	0.267
HDL-C, mmol/L	1.24 ± 0.30	1.24 ± 0.33	0.846
LDL-C, mmol/L	3.11 ± 0.96	2.97 ± 0.89	0.160
NHDL-C, mmol/L	4.06 ± 1.21	3.92 ± 1.02	0.254
HDL-C/NHDL-C	0.32 (0.25 to 0.40)	0.30 (0.24 to 0.38)	< 0.001
TG, mmol/L	2.00 (1.43-2.79)	1.90 (1.27-3.86)	0.293
Hormones and insulin sensitivity			
FINS, μIU/mL	11.35 (7.76 to 20.75)	12.48 (7.24 to 24.11)	0.361
HOMA-β	48.27 (31.02 to 72.20)	56.43 (28.51 to 76.43)	0.417
I30/G30	2.39 (1.13 to 4.46)	2.72 (0.97 to 4.49)	0.609
AUCinsulin, μIU/L × min	4.57 (3.20 to 6.18)	4.58 (3.06 to 6.86)	0.424
AUCGLP-1, nmol × min	3.10 (1.75 to 5.03)	2.61 (1.64 to 4.27)	0.076
HOMA-IR	4.34 (2.68 to 6.00)	4.30 (2.74 to 6.93)	0.165
WBISI	69.45 (50.39 to 103.22)	66.16 (43.84 to 98.52)	0.031

WHtR: Change of waist-to-height ratio; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; HDL-C/non-HDL-C: HDL-C-to-non-HDL-C ratio; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; FINS: Fasting plasma insulin; HOMA: Homeostasis model assessment-; IR: Insulin resistance; WBISI: Whole body insulin sensitivity index; AUC: Area under the curve; GLP-1: Glucagon-like peptide 1.

0.012), HOMA-IR (-2.30 *vs* -1.53, P = 0.003), and NHDL-C (-0.55 mmol/L *vs* -0.27 mmol/L, P = 0.021) from baseline. In contrast, greater increases in HDL-C (0.07 mmol/L *vs* -0.01 mmol/L, P = 0.012), HDL-C/NHDL-C (0.08 *vs* 0.03, P < 0.001), and AUCGLP-1 (1.41 *vs* 0.65 nmol × min, P = 0.002) were presented in the patients in the high ΔWHtR group (Table 3).

In the metformin arm, the patients with a high ΔWHtR had lost an average of 2.85 kg (4.10%) of body weight, 1.30 BMI units, 5.5 cm of WC, and 3.0 dm of HC. In contrast, the patients with a low ΔWHtR lost 0.95 kg (1.84%), 0.40 BMI units, 1.0 cm of WC, and 0.2 cm of HC.

Regarding glucose control, a greater reduction in FPG (-2.03 mmol/L *vs* -1.60

Table 3 Changes in key endpoints from baseline to week 24 of patients in different change of waist-to-height ratio groups treated with acarbose

	High ΔWHtR	Lower ΔWHtR	*P* value
Anthropometric measurements			
Body weight, kg	-3.63 (-4.08 to -3.18)	-1.29 (-1.81 to -0.79)	< 0.001
Body mass index, kg/m^2	-1.60 (-1.79 to -1.41)	-0.56 (-0.72 to -0.39)	< 0.001
Waist circumference, cm	-5.57 (-6.05 to -5.09)	0.87 (-0.42 to 1.32)	< 0.001
Hip circumference	-4.49 (-5.22 to -3.77)	-0.13 (-0.72 to 0.45)	< 0.001
Glucose metabolism variables			
HbA1c, %	-1.19 (-1.36 to -1.01)	-1.11 (-1.32 to -0.90)	0.511
FPG, mmol/L	-1.47 (-1.67 to -1.27)	-1.10 (-1.35 to 0.84)	0.024
PPG, mmol/L	-3.21 (-3.62 to -2.81)	-2.82 (-3.32 to -2.32)	0.546
Blood pressure and lipid profile			
Systolic blood pressure, mmHg	-2.11 (-3.97 to -0.25)	-0.42 (-2.29 to 1.44)	0.207
Diastolic blood pressure, mmHg	-1.79 (-3.26 to -0.32)	-2.35 (-3.63 to -1.07)	0.574
TC, mmol/L	-0.48 (-0.62 to 0.34)	-0.27 (-0.43 to 0.12)	0.103
HDL-C, mmol/L	0.07 (-0.03 to 0.11)	-0.01 (-0.05 to 0.03)	0.012
LDL-C, mmol/L	-0.22 (-0.34 to -0.09)	-0.07 (-0.20 to 0.07)	0.158
NHDL-C, mmol/L	-0.55 (-0.69 to -0.41)	-0.27 (-0.42 to -0.11)	0.021
HDL-C/NHDL-C	0.08 (0.06 to 0.10)	0.03 (0.01 to 0.05)	< 0.001
TG, mmol/L	-0.62 (-0.87 to -0.37)	-0.90 (-0.42 to -0.07)	0.562
Hormones and insulin sensitivity			
HOMA-β	-0.58 (-10.07 to 8.92)	10.09 (-13.30 to 33.49)	0.195
I30/G30	-0.02 (-2.93 to 2.90)	1.43 (-0.09 to 2.95)	0.012
FINS, μIU/mL	-4.73 (-6.27 to -3.19)	-2.88 (-4.80 to -0.95)	0.012
AUCinsulin, μIU/L × min	-1.47 (-1.86 to -1.07)	-0.794 (-1.16 to -0.43)	0.092
AUCGLP-1, nmol × min	1.41 (1.04 to 1.78)	0.65 (1.87 to 1.11)	0.002
HOMAIR	-2.30 (-2.87 to -1.74)	-1.53 (-2.19 to -0.87)	0.003
WBISI	69.38 (56.59 to 82.17)	47.78 (34.63 to 60.93)	0.610

WHtR: Change of waist-to-height ratio; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; HDL-C/non-HDL-C: HDL-C-to-non-HDL-C ratio; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; FINS: Fasting plasma insulin; HOMA: Homeostasis model assessment; IR: Insulin resistance; WBISI: Whole body insulin sensitivity index; AUC: Area under the curve; GLP-1: Glucagon-like peptide 1.

mmol/L, P = 0.005), diastolic blood pressure (-2.69 mmHg *vs* -0.28 mmHg, P = 0.018), TC (-0.53 mmol/L *vs* -0.19 mmol/L, P = 0.004), LDL-C (-0.33 mmol/L *vs* -0.12 mmol/L, P = 0.047), NHDL-C (-0.53 mmol/L *vs* -0.18 mmol/L, P = 0.001), and TG (-0.38 mmol/L *vs* -0.18 mmol/L, P = 0.003) and a greater increase in HDL-C/non-HDL-C (0.05 *vs* 0.00, P = 0.003) were observed in the patients with the high ΔWHtR. Regarding early insulin secretion, the I30/G30 increased more in the high ΔWHtR group (60.38 *vs* 41.50, P = 0.031). No difference was found in the change in AUCGLP-1 (Table 4).

Baseline factors associated with high ΔWHtR

In the patients who received the acarbose treatment, the univariate analyses identified that age, sex, baseline FINS, and AUCGLP-1 were associated with a high ΔWHtR (Table 5). The multivariate analysis showed that only sex (female, OR = 1.654, P = 0.045) and lower AUCGLP-1 (OR = 0.796, P < 0.001) were associated with a high ΔWHtR in the patients receiving acarbose treatment after adjusting for the baseline WHtR (Table 5).

Table 4 Changes in key endpoints from baseline to week 24 of patients in different change of waist-to-height ratio groups treated with metformin

	High ΔWHtR	Low ΔWHtR	*P* value
Anthropometric measurements			
Body weight, kg	-2.85 (-3.28 to -2.44)	-0.95 (-1.37 to -0.52)	< 0.001
Body mass index, kg/m^2	-1.30 (-1.48 to -1.12)	-0.40 (-0.59 to 0.22)	< 0.001
Waist circumference, cm	-5.51(-6.11 to -4.90)	-1.01 (-0.60 to 1.42)	< 0.001
Hip circumference	-2.96 (-3.75 to -2.17)	-0.15 (-0.82 to 0.52)	< 0.001
Glucose metabolism variables			
HbA1c, %	-1.34 (-1.52 to 1.167	-1.14 (-1.31 to 0.96)	0.106
FPG, mmol/L	-2.03 (-2.24 to -1.81)	-1.60 (-1.81 to -1.39)	0.005
PPG, mmol/L	-2.91 (-3.37 to -2.44)	-2.30 (-2.79 to -1.81)	0.659
Blood pressure and lipid profile			
Systolic blood pressure, mmHg	-2.42 (-4.36 to -0.49)	-0.60 (-2.47 to 1.48)	0.172
Diastolic blood pressure, mmHg	-2.69 (-4.10 to -1.29)	-0.28 (-1.69 to 1.15)	0.018
TC, mmol/L	-0.53 (-0.68 to -0.39)	-0.19 (-0.35 to -0.03)	0.004
HDL-C, mmol/L	0.06 (0.03 to 0.10)	-0.01 (-0.05 to -0.03)	0.458
LDL-C, mmol/L	-0.33 (-0.46 to -0.20)	-0.12 (-0.25 to -0.00)	0.047
NHDL-C, mmol/L	-0.53 (-0.68 to -0.39)	-0.18 (-0.33 to -0.02)	0.001
HDL-C/NHDL-C	0.05 (0.05 to 0.07)	0.00 (-0.03 to 0.03)	0.003
TG, mmol/L	-0.38 (-0.00 to 0.76)	-0.18 (-0.42 to 0.06)	0.003
Hormones and insulin sensitivity			
FINS, μIU/mL	-3.76 (-4.95 to -2.58)	-3.47 (-5.03 to -1.93)	0.361
HOMA-β	12.13 (5.20 to 19.06)	12.50 (2.72 to 22.28)	0.417
I30/G30	60.38 (47.81 to 72.94)	41.50 (30.72 to 52.29)	0.031
AUCinsulin, μIU/L × min	-0.35 (-0.72 to 0.014)	-0.56 (-0.91 to -0.21)	0.743
AUCGLP-1, nmol × min	0.75 (0.25 to 1.26)	1.17 (0.77 to 1.56)	0.340
HOMAIR	-2.20 (-2.67 to -1.73)	-2.06 (-2.63 to -1.49)	0.165
WBISI	0.44 (-2.55 to 3.43)	0.14 (-2.34 to 2.62)	0.609

WHtR: Change of waist-to-height ratio; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; TG: Triglycerides; HDL-C/non-HDL-C: HDL-C-to-non-HDL-C ratio; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; FINS: Fasting plasma insulin; HOMA: Homeostasis model assessment-; IR: Insulin resistance; WBISI: Whole body insulin sensitivity index; AUC: Area under the curve; GLP-1: Glucagon-like peptide 1.

In the patients who received metformin treatment, the univariate analyses identified that age, sex, and baseline AUCGLP-1 were associated with a high ΔWHtR. The multivariate analysis also revealed that the female patients achieved a greater reduction in the WHtR (OR = 1.718, *P* = 0.020). In contrast to acarbose, a higher baseline AUCGLP-1 (OR = 1.133, *P* = 0.025) was associated with a high ΔWHtR (Table 5).

We further performed a subgroup analysis and divided all patients into the following two groups according to the median of the baseline AUCGLP-1: Low AUCGLP-1 group and high AUCGLP-1 group. The effect in reducing the WHtR was compared between the acarbose and metformin treatments within each AUCGLP-1 group. In the low AUCGLP-1 group, the ΔWHtR of patients receiving acarbose treatment was higher than that of patients receiving metformin treatment (-0.013 *vs* -0.006, *P* = 0.017, Supplementary Table 1, while no difference was found in the high AUCGLP-1 group. A logistic regression analysis (after adjusting for sex, age, and baseline WHtR) further confirmed that there was a greater likelihood (OR = 2.085, *P* =

Table 5 Baseline factors associated with a high change of waist-to-height ratio

	Univariate		Multivariate	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Acarbose				
Age	1.032 (1.008 to 1.056)	0.009	1.023 (0.998 to 1.049)	0.070
Sex	1.554 (1.006 to 2.401)	0.047	1.654 (1.011 to 2.546)	0.045
AUCGLP-1, nmol × min	0.134 (0.043 to 0.420)	0.001	0.796 (0.705 to 0.898)	< 0.001
Metformin				
Age	1.025 (1.001 to 1.049)	0.043	1.013 (0.988 to 1.039)	0.313
Sex	1.684 (1.086 to 2.612)	0.020	1.718 (1.091 to 2.704)	0.020
AUCGLP-1, nmol × min	2.808 (0.979 to 8.059)	0.055	1.133 (1.016 to 1.263)	0.025

AUCGLP-1: Area under the curve of glucagon-like peptide 1.

0.001) that the acarbose treatment resulted in a higher reduction in the WHtR than the metformin treatment in the low AUCGLP-1 group (Supplementary Table 1).

Changes in treatment parameters associated with high ΔWHtR

The univariate analyses showed that in the acarbose arm, ΔFINS, ΔAUCinsulin, ΔAUCGLP-1, ΔFPG, ΔHDL-C, and ΔHDL-C/Non-HDL-C were found to be associated with a high ΔWHtR. The multivariate analysis revealed that only a greater increase in ΔAUCGLP-1 (OR = 1.121, P = 0.016) and a greater increase in HDL-C/non-HDL-C (OR = 20.735, P = 0.001) were associated with a high ΔWHtR (Table 6).

In the metformin arm, the associations between a high ΔWHtR and ΔFPG, ΔTG, ΔTC, ΔLDL-C, ΔNHDL-C, ΔHDL-C/non-HDL-C, and Δ diastolic blood pressure were detected using univariate analyses. The multivariate analysis identified that greater reductions in FPG (OR = 0.843, P = 0.039) and TC (OR = 0.743, P = 0.013) were associated with a high ΔWHtR (Table 6).

DISCUSSION

In the MARCH trial, the WHtR was significantly reduced after the treatment with either acarbose or metformin in newly diagnosed T2DM patients. As an indicator of abdominal obesity with better performance than other anthropometric measurements, changes in the WHtR can be employed more simply and feasibly in diabetes, obesity, and metabolic syndrome. In this post hoc analysis of the MARCH trial, the multivariate logistic regression analysis revealed several factors associated with a high ΔWHtR for acarbose treatment, including sex, GLP-1 level, FPG, and the lipid profile.

In both groups treated with acarbose or metformin, the percentage of females was higher in the high ΔWHtR group. The multivariate analysis confirmed the association between sex and a high ΔWHtR, indicating that female patients are more likely to achieve better improvement in abdominal obesity. The sex-related specific effects on weight loss of antidiabetic therapy have been reported regardless of glycemic control. The relative body weight reductions among the women were significantly larger than those among the men at all estimated baseline body weight points in a German diabetes study[14]. Another study reported that women had a significantly higher reduction in body weight after treatment with metformin or sulfonylurea, whereas men displayed significantly higher HbA1c reductions[15]. Combined therapy with exenatide and metformin in overweight or obese patients also showed the superiority of women over men in reducing weight and waist circumference[16]. Similar sex differences in weight loss were presented after different antidiabetic treatments; however, these changes may not be drug related but rather indicate that women are more successful than man in their weight reduction attempts[14].

It is well known that metformin reduces weight and improves abdominal obesity in T2DM patients by suppressing appetite. Acarbose also has a significant effect on weight loss, especially in Eastern populations, but the mechanism is still unclear. At week 24, in the MARCH trial, a comparative reduction in the WHtR and an increase in

Table 6 Association between changes in glucagon-like peptide 1 and a high change of waist-to-height ratio

	Univariate		Multivariate	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Acarbose				
AUCinsulin, μIU/L × min	0.897 (0.814 to 0.987)	0.027	0.922 (0.830 to 1.024)	0.127
AUCGLP-1, nmol × min	1.136 (1.044 to 1.237)	0.003	1.121 (1.022 to 1.230)	0.016
HDL-C/NHDL-C	17.934 (3.165 to 101.613)	0.001	20.735 (3.416 to 125.871)	0.001
Metformin				
FPG, mmol/L	0.803 (0.687 to 0.938)	0.006	0.843 (0.717 to 0.992)	0.039
TC	0.707 (0.560 to 0.893)	0.004	0.743 (0.587 to 0.940)	0.013

AUC: Area under the curve; GLP-1: Glucagon-like peptide 1; HDL-C/non-HDL-C: HDL-C-to-non-HDL-C ratio; FPG: Fasting plasma glucose; TC: Total cholesterol.

the AUCGLP-1 were observed after the treatment with acarbose or metformin. GLP-1 is an important gastrointestinal incretin that improves glycemic and weight control. GLP-1 regulates glucose and lipid metabolism by inhibiting appetite (enhancing satiety and delaying gastric emptying) and affecting the secretion of other metabolic hormones, including insulin, glucagon, and peptide YY[17,18]. Alpha-glucosidase inhibitors and metformin have been reported to increase the circulating GLP-1 levels likely by both stimulating GLP-1 secretion and inhibiting dipeptidyl peptidase IV activity in healthy people and T2DM patients[19-23]. It has been speculated that the positive effect on GLP-1 partially mediates the effect of α-glucosidase on weight loss. In this study, an association between ΔAUCGLP-1 and a high ΔWHtR was identified in the patients treated with acarbose. This finding indicates that the increased circulating GLP-1 levels induced by acarbose possibly promote improvement in abdominal obesity.

In this study, the baseline AUCGLP-1 levels were also associated with a high WHtR reduction in the patients receiving the acarbose or metformin treatment. However, interestingly, a different association was found in the two treatment groups. In the patients treated with acarbose, the baseline AUCGLP-1 was negatively associated with a high ΔWHtR; in contrast, the baseline AUCGLP-1 was positively associated with a high ΔWHtR in the patients treated with metformin. These results may suggest that in newly diagnosed T2DM patients, the AUCGLP-1 before treatment can be a predictor of weight management for drug selection in newly diagnosed T2DM. Further stratified analysis confirmed that in the low baseline AUCGLP-1 group, the acarbose treatment could lead to a greater decrease in the WHtR than metformin, while no difference was observed in the high baseline AUCGLP-1 group. Since no similar results have been reported in published research, more clinical trials are warranted to confirm these associations. In addition, more evidence is needed to determine whether acarbose should be preferred in newly diagnosed T2DM patients with relatively low GLP-1 levels.

The WHtR has been reported as a good predictor of dyslipidemia with a superior association over WC and BMI in populations of various nationalities and ethnic groups. Studies have found a similar association between a high WHtR and total cholesterol, high triglycerides, low HDL-c, and high LDL-c. Whether a reduction in the WHtR is associated with the amelioration of dyslipidemia has not been clarified. It has been reported that lifestyle modifications can have a positive impact on both the HDL quantity and quality in addition to reducing visceral adipose tissue[24]. In this study, it was confirmed that a reduction in the WHtR was associated with improvement in the lipid profile after both the acarbose and metformin treatment. In the acarbose-treated patients, a reduction in the WHtR was associated with an increase in the HDL-C-to-non-HDL-C ratio, while a reduction in TC was associated with changes in the WHtR in the metformin-treated patients. These results likely indicate that acarbose and metformin improve the lipid profile by targeting different lipids.

The association between glycemic control and a reduction in the WHtR was also identified in the patients treated with metformin, which is similar to a previous study restricted to fasting plasma glucose. WC and WHtR were both positively associated with diabetes risk in the univariate and multivariable models[25]. These subjects with

the greatest weight gain or greatest increase in WC had a 1.53-fold or 1.37-fold increased risk of diabetes; those with the greatest weight loss had a 46% decreased risk of diabetes[26]. Only fasting glucose was associated with changes in the WHtR, which may be explained by the mechanism that a reduction in visceral adiposity more often improves insulin sensitivity but not insulin secretion. There was no correlation between glucose metabolism and changes in the WHtR in the acarbose arm likely because the major hypoglycemic effect of acarbose was on 2-h PPG rather than FPG.

The limitation of this subgroup analysis is its post hoc nature, including the absence of an evaluation of the effect of lifestyle change on the WHtR. In addition, a placebo-controlled trial could be more effective in illustrating the factors associated with a reduction in the WHtR after antidiabetic treatment.

CONCLUSION

In conclusion, we have identified that the alleviation of abdominal obesity is likely associated with sex and the GLP-1 level in both treatments with acarbose and metformin in the MARCH study. An increase in circulating GLP-1 is possibly involved in the effect of reducing abdominal obesity of acarbose but not metformin in newly diagnosed T2DM. Moreover, patients with a low GLP-1 level might benefit more from acarbose in reducing the WHtR than metformin.

ARTICLE HIGHLIGHTS

Research background

Many type 2 diabetes mellitus (T2DM) patients are characterized by abdominal obesity, which is associated with a high risk of cardiovascular diseases and mortality. The waist-to-height ratio (WHtR) reflects abdominal obesity and is a promising measure for the evaluation of cardiovascular risk. The metformin and acarbose in Chinese as the initial Hypoglycaemic treatment trial demonstrated that acarbose and metformin reduced the WHtR after 24 wk of treatment. The factors associated with the reduction in the WHtR after monotherapy of acarbose or metformin are unclear.

Research motivation

We attempted to investigate whether the factors associated with the WHtR reduction after the acarbose or metformin treatment differ in newly diagnosed T2DM. We also attempted to clarify the role of glucagon-like peptide 1 (GLP-1) in reducing the WHtR under treatment with two classical oral antidiabetic drugs.

Research objectives

We aimed to identify the factors associated with WHtR reduction after 24 wk within the acarbose and metformin groups.

Research methods

Logistic regression analyses were performed using SPSS statistical software (version 25.0). Further stratified analysis was performed to investigate the associations between GLP-1 and WHtR reduction under acarbose or metformin treatment.

Research results

In this study, we found a sex difference in WHtR reduction in both the acarbose and metformin treatments. An increase in the area under the curve of GLP-1was associated with a high ΔWHtR in the acarbose group. We also identified that a higher reduction in high-density lipoprotein cholesterol/non-high-density lipoprotein cholesterol was associated with a high ΔWHtR in the acarbose arm, while a higher reduction in fasting plasma glucose and total cholesterol was associated with a high ΔWHtR in the metformin group.

Research conclusions

Our study showed that the baseline GLP-1 level and increase in GLP-1 level are associated with WHtR reduction under acarbose treatment in newly diagnosed T2DM. Additionally, in the low baseline area under the curve of GLP-1 group, the acarbose treatment could lead to a greater decrease in the WHtR than metformin.

Research perspectives

This study could provide new evidence for oral antidiabetic drug selection in newly diagnosed Chinese T2DM.

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