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

Lu-Lu Song, Xin Wang, Zhao-Jun Yang, Xiao-Mu Kong, Xiao-Ping Chen, Bo Zhang, Wen-Ying Yang

ORCID number: Lu-Lu Song 0000-0003-0705-8873; Xin Wang 0000-0003-3176-1243; Zhao-Jun Yang 0000-0001-8707-3859; Xiao-Mu Kong 0000-0002-5920-4759; Xiao-Ping Chen 0000-0002-5894-2661; Bo Zhang 0000-0003-3060-7859; Wen-Ying Yang 0000-0002-7997-9404.

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.

Institutional review board statement: The study was reviewed and approved by the China-Japan Friendship Hospital Institutional Review Board.

Clinical trial registration statement: This study is registered at Chinese Clinical Trial Registry Center. The registration number is ChiCTR-TRC-08000231.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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...
Obesity, especially abdominal obesity, is an important risk factor for Type 2 diabetes. 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 = 0.016). 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

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

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.

Citation: Song LL, Wang X, Yang ZJ, Kong XM, Chen XP, Zhang B, Yang WY. 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. World J Diabetes 2020; 11(11): 514-526
URL: https://www.wjgnet.com/1948-9358/full/v11/i11/514.htm
DOI: https://dx.doi.org/10.4239/wjd.v11.i11.514

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. In the Chinese population, the estimated prevalence of diabetes increased from 9.7% in the 2007 survey to 10.9% in the 2013 survey. 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. Another survey of Chinese adults in northwest China reported that approximately 7.5% of the interviewees had newly diagnosed type 2 diabetes mellitus (T2DM). 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...
Acarbose, GLP-1, and abdominal obesity

Song LL et al. Acarbose, GLP-1, and abdominal obesity

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 article13.

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 ΔWHR and high ΔWHR 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_{30min} - insulin_{min}) /ΔG30 (glucose_{30min} - glucose_{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_{min} + insulin_{30min}) × 30/2 + (insulin_{30min} + insulin_{60min}) × 90/2 + (insulin_{60min} + insulin_{90min}) × 60/2 and AUCGLP-1 = (GLP-1_{0min} + GLP-1_{30min}) × 30/2 + (GLP-1_{30min} + GLP-1_{120min}) × 90/2 + (GLP-1_{120min} + GLP-1_{180min}) × 60/2.

**Statistics analysis**

Based on changes in WHtR at week 24 (ΔWHR), the participants were divided into the following two groups using the median as the cutoff (-0.012): High ΔWHR group and low ΔWHR 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 ΔWHR 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 ΔWHR 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, FINS, HOMA-IR, and I30/G30 were found between the two ΔWHR groups. Compared with the low ΔWHR group, the high ΔWHR 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 ± 7.68 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 ΔWHR 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/m²   | 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    |
| TC, 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    |
| AUInsulin, μIU/L × min   | 4.71 (3.28 to 6.54) | 4.33 (3.06 to 5.65) | 0.300    |
| AUCGLP-1, mmol × min     | 2.41 (1.96 to 4.06) | 3.24 (1.96 to 5.19) | 0.001    |
| HOMA-IR                  | 4.00 (2.05 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/m²      | 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, mmol × 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.

Regarding glucose control, a greater reduction in FPG (-2.03 mmol/L vs -1.60 mmol/L, P = 0.012), HOMA-IR (-2.30 vs -1.53, P = 0.003), and NHDLC (-0.55 vs -0.27 mmol/L, P = 0.021) from baseline. In contrast, greater increases in HDL-C (0.07 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 mmol × min, P = 0.002) were presented in the patients in the high ΔWHtR group (Table 3).
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/m²    | -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) | -0.79 (-1.16 to -0.43) | 0.092   |
| AUCGLP-1, mmol × 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/C: HDL-C-to-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 the acarbose treatment, the univariate analyses identified that age, sex, baseline FINS, and AUCGLP-1 were associated with a high ΔWHtR. 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.
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 (1.191 to 2.356) | 0.054   |
| 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) | 0.060   |
| Sex            | 1.684 (1.086 to 2.612) | 0.020             | 1.718 (1.091 to 2.704) | 0.025   |
| AUCGLP-1, nmol × min | 2.808 (0.979 to 8.059) | 0.055             | 1.133 (1.016 to 2.163) | 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 men 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        | 17.954 (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 (0.586 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.

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-1 was 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.

ACKNOWLEDGEMENTS

We thank to all investigators for their effort in this clinical trial.

REFERENCES

1 Cho NH, Shaw JE, Karurunga S, Huang Y, da Rocha Fernandes JD, Ohrooge AW, Malanda B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018; 138: 271-281 [PMID: 29496507 DOI: 10.1016/j.diabres.2018.02.023]

2 Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J. China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med 2010; 362: 1090-1101 [PMID: 20335585 DOI: 10.1056/NEJMoa0908292]

3 Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, Li Y, Zhao Z, Qin X, Jin D, Zhou M, Tang X, Hu Y, Wang L. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. JAMA 2017; 317: 2515-2523 [PMID: 28655017 DOI: 10.1001/jama.2017.7596]

4 Zhu S, Hu J, McCoy TP, Li G, Zhu J, Lei M, Yuan J, Peng J, Kong L. Socioeconomic Status and the Prevalence of Type 2 Diabetes Among Adults in Northwest China. Diabetes Educ 2015; 41: 599-608 [PMID: 26246592 DOI: 10.1177/0145721715559382]

5 Rådholm K, Chalmers J, Ohkuma T, Peters S, Poultier N, Harnett P, Harrap S, Woodward M. Use of the waist-to-height ratio to predict cardiovascular risk in patients with diabetes: Results from the ADVANCE-ON study. Diabetes Obes Metab 2018; 20: 1903-1910 [PMID: 29603537 DOI: 10.1111/dom.13131]

6 Winter Y, Pieper L, Klotsche J, Riedel O, Wittechen HU. Obesity and Abdominal Fat Markers in Patients with a History of Stroke and Transient Ischemic Attacks. J Stroke Cerebrovasc Dis 2016; 25: 1141-1147 [PMID: 26915603 DOI: 10.1016/j.jstrokecerebrovasdis.2015.12.026]

7 Lo K, Liu Q, Allison M, Feng YQ, Chan K, Phillips L, Manson J, Liu S. Prospective Associations of Waist-to-Height Ratio With Cardiovascular Events in Postmenopausal Women: Results From The Women's Health Initiative. Diabetes Care 2019; 42: e148-e149 [PMID: 31208018 DOI: 10.2337/dci-19-0612]

8 Harding JL, Shaw JE, Anstey KJ, Adams R, Balkau B, Brennan-Olsen SL, Briffa T, Davis TM, Davis WA, Dobson A, Flicker L, Giles G, Grant J, Huxley R, Knuiman M, Luszczy M, MacInnis RJ, Mitchell P, Pasco JA, Reid C, Simmons D, Simons L, Tonkin A, Woodward M, Peeters A, Magliano DJ. Comparison of anthropometric measures as predictors of cancer incidence: A pooled collaborative analysis of 11 Australian cohorts. Int J Cancer 2015; 137: 1699-1708 [PMID: 25810218 DOI: 10.1002/ijc.29529]

9 Tseng CH. Waist-to-height ratio is independently and better associated with urinary albumin excretion rate than waist circumference or waist-to-hip ratio in Chinese adult type 2 diabetic women but not men. Diabetes Care 2005; 28: 2249-2251 [PMID: 16123504 DOI: 10.2337/diacare.28.9.2249]

10 Rangel-Baltazar E, Cuevas-Nasu L, Shamah-Levy T, Rodríguez-Ramírez S, Méndez-Gómez-Humarín I, Rivera JA. Association between High Waist-to-Height Ratio and Cardiovascular Risk among Adults Sampled by the 2016 Half-Way National Health and Nutrition Survey in Mexico (ENSANUT MC 2016). Nutrition 2019; 11 [PMID: 31234359 DOI: 10.3930/nut.11061402]

11 Li Y, Tong Y, Zhang Y, Huang L, Wu T, Tong N. Acarbose monotherapy and weight loss in Eastern and Western populations with hyperglycaemia: an ethnicity-specific meta-analysis. Int J Clin Pract 2014; 68: 1318-1332 [PMID: 24853116 DOI: 10.1111/ijcp.12467]

12 Yang W, Liu J, Shan Z, Tian H, Zhou Z, Ji Q, Weng J, Jia W, Liu J, Liu J, Xu Y, Yang Z, Chen W. Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomized trial. Lancet Diabetes Endocrinol 2014; 2: 46-55 [PMID: 24622688 DOI: 10.1016/S2213-8587(13)70021-4]

13 Zhang JP, Wang N, Xing XY, Yang ZJ, Wang X, Yang WY. Efficacy of acarbose and metformin in newly diagnosed type 2 diabetes patients stratified by HbA1c levels. J Diabetes 2016; 8: 559-567 [PMID: 26331290 DOI: 10.1111/1753-0407.12337]

14 Schnell O, Weng J, Sheu WH, Watada H, Kalra S, Soegondo S, Yamamoto N, Rathod R, Zhang C, Grzeszczak W. Acarbose reduces body weight irrespective of glycemic control in patients with diabetes: results of a worldwide, non-interventional, observational study data pool. J Diabetes Complications 2016; 30: 628-637 [PMID: 26935335 DOI: 10.1016/j.jdiacomp.2016.01.023]

15 Schütt M, Zimmermann A, Hoad R, Hummel M, Seufert J, Siegel E, Tytko A, Holl RW; DPV initiative; German BMBF Competence Network Diabetes Mellitus. Gender-specific Effects of Treatment with Lifestyle, Metformin or Sulfonylurea on Glycemic Control and Body Weight: A German Multicenter Analysis on 9 108 Patients. Exp Clin Endocrinol Diabetes 2015; 123: 622-626 [PMID: 26285070 DOI: 10.1055/s-0035-1559608]

16 Quan H, Zhang H, Wei W, Fang T. Gender-related different effects of a combined therapy of Exenatide and Metformin on overweight or obesity patients with type 2 diabetes mellitus. J Diabetes Complications 2016; 30: 686-692 [PMID: 26873871 DOI: 10.1016/j.jdiacomp.2016.01.013]

17 Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol 2016; 4: 525-536
18 Chia CW, Egan JM. Incretins in obesity and diabetes. *Ann N Y Acad Sci* 2020; **1461**: 104-126 [PMID: 31392745 DOI: 10.1111/nyas.14211]

19 Moritoh Y, Takeuchi K, Hazama M. Chronic administration of voglibose, an alpha-glucosidase inhibitor, increases active glucagon-like peptide-1 levels by increasing its secretion and decreasing dipeptidyl peptidase-4 activity in ob/ob mice. *J Pharmacol Exp Ther* 2009; **329**: 669-676 [PMID: 19208898 DOI: 10.1124/jpet.108.148056]

20 Ueno H, Tsuchimochi W, Wang HW, Yamashita E, Tsubouchi C, Nagamine K, Sakoda H, Nakazato M. Effects of Miglitol, Acarbose, and Sitagliptin on Plasma Insulin and Gut Peptides in Type 2 Diabetes Mellitus: A Crossover Study. *Diabetes Ther* 2015; **6**: 187-196 [PMID: 26055217 DOI: 10.1007/s13300-015-0113-3]

21 Lee A, Patrick P, Wishart J, Horowitz M, Morley JE. The effects of miglitol on glucagon-like peptide-1 secretion and appetite sensations in obese type 2 diabetics. *Diabetes Obes Metab* 2002; **4**: 329-335 [PMID: 12190996 DOI: 10.1046/j.1463-1326.2002.00219.x]

22 Borg MJ, Jones KL, Sun Z, Horowitz M, Rayner CK, Wu T. Metformin attenuates the postprandial fall in blood pressure in type 2 diabetes. *Diabetes Obes Metab* 2019; **21**: 1251-1254 [PMID: 30615231 DOI: 10.1111/dom.13632]

23 Brønden A, Albér A, Rohde U, Rehfell JD, Holst JJ, Vilsboll T, Knop FK. Single-Dose Metformin Enhances Bile Acid-Induced Glucagon-Like Peptide-1 Secretion in Patients With Type 2 Diabetes. *J Clin Endocrinol Metab* 2017; **102**: 4153-4162 [PMID: 28938439 DOI: 10.1210/jc.2017-01291]

24 Boyer M, Lévesque V, Poirier P, Mathieu P, Després JP, Larose É, Arsenault BJ. Impact of a 1-year lifestyle modification program on plasma lipoprotein and PCSK9 concentrations in patients with coronary artery disease. *J Clin Lipidol* 2016; **10**: 1353-1361 [PMID: 27919352 DOI: 10.1016/j.jcldl.2016.08.014]

25 Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, Giovannucci EL. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. *Eur J Epidemiol* 2018; **33**: 1113-1123 [PMID: 30117031 DOI: 10.1007/s10654-018-0433-5]

26 Fan Y, Wang R, Ding L, Meng Z, Zhang Q, Shen Y, Hu G, Liu M. Waist Circumference and its Changes Are More Strongly Associated with the Risk of Type 2 Diabetes than Body Mass Index and Changes in Body Weight in Chinese Adults. *J Nutr* 2020; **150**: 1259-1265 [PMID: 32006008 DOI: 10.1093/jn/nxaa014]
