**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 57734

**Manuscript Type:** 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**

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

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

**Lu-Lu Song, Xin Wang, Zhao-Jun Yang, Xiao-Mu Kong, Xiao-Ping Chen, Bo Zhang, Wen-Ying Yang,** Department of Endocrinology, China-Japan Friendship Hospital, Beijing 100029, China

**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.

**Corresponding author: Wen-Ying Yang, MD, Professor,** Department of Endocrinology, China-Japan Friendship Hospital, No. 2 Yinghua East Street, Chaoyang District, Beijing 100029, China. yangwenying@zryhyy.com.cn

**Received:** June 30, 2020

**Revised:** August 13, 2020

**Accepted:** September 14, 2020

**Published online:**

**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 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

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; In press

**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.

**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](#_ENREF_12),[13](#_ENREF_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](#_ENREF_12" \o "Yang, 2014 #19)]. 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 (insulin30 min - insulin0 min)/ΔG30 (glucose30 min - glucose0 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 = (insulin0 min + insulin30min) × 30/2 + (insulin30 min + insulin120 min) × 90/2 + (insulin120 min + insulin180 min) × 60/2 and AUCGLP-1 = (GLP-10 min + GLP-130min) × 30/2 + (GLP-130 min + GLP-1120 min) × 90/2 + (GLP-1120 min + GLP-1180 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.

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

***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* = 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* 0.01, *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.

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 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* -0.42 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.

***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).

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* = 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 2).

***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 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[[19-2](#_ENREF_19)3]. 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.

**ACKNOWLEDGEMENTS**

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

**REFERENCES**

1 **Cho NH**, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge 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: 10.1177/0145721715598382]

5 **Rådholm K**, Chalmers J, Ohkuma T, Peters S, Poulter N, Hamet 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.13311]

6 **Winter Y**, Pieper L, Klotsche J, Riedel O, Wittchen 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: 31308018 DOI: 10.2337/dc19-0612]

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, Luszcz 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: 16123501 DOI: 10.2337/diacare.28.9.2249]

10 **Rangel-Baltazar E**, Cuevas-Nasu L, Shamah-Levy T, Rodríguez-Ramírez S, Méndez-Gómez-Humarán 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). *Nutrients* 2019; **11**: [PMID: 31234359 DOI: 10.3390/nu11061402]

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, Lu 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: 24622668 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, Hood 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 [PMID: 26876794 DOI: 10.1016/S2213-8587(15)00482-9]

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, Rehfeld JF, Holst JJ, Vilsbøll 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.2017-01091]

24 **Boyer M**, Lévesque V, Poirier P, Marette A, 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.jacl.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]

**Footnotes**

**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.

**Conflict-of-interest statement:** All the authors have nothing to disclose.

**Data sharing statement:** No additional data are available.

**CONSORT 2010 statement:** The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** June 28, 2020

**First decision:** July 30, 2020

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Raghow R **S-Editor:** Zhang L **L-Editor:** Wang TQ **P-Editor:**

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **High △WHtR** | **Low △WHtR** | ***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 |
| 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.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **High △WHtR** | **Low △WHtR** | | ***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, 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.

**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 △WHtR** | **Lower △WHtR** | ***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) | -0.794 (-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.

**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 △WHtR** | **Low △WHtR** | ***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/m2 | -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.

**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.

**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.