The Effects of Gliclazide, Metformin, and Acarbose on Body Composition in Patients with Newly Diagnosed Type 2 Diabetes Mellitus

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A B S T R A C T

Background: Although numerous clinical trials have evaluated the body weight change achieved using diabetes medications alone or in combinations, the composition of body weight change in these clinical trials has rarely been assessed.

Objective: We aimed to evaluate the effects of gliclazide, metformin, and acarbose monotherapy on body composition, fat distribution, and other cardiometabolic risk factors in patients with newly diagnosed type 2 diabetes.

Methods: A total of 86 patients with newly diagnosed type 2 diabetes mellitus were randomly assigned to receive gliclazide, metformin, or acarbose for 6 months. Dual-energy x-ray absorptiometry; abdominal computed tomography scans; and measurements of adiponectin, leptin, and lipid levels were performed before and after 6-month monodrug therapy.

Results: Blood glucose and glycosylated hemoglobin levels significantly improved after 6 months of monodrug therapy. During the 6 months of use of the 3 antidiabetes medications, the majority of participants experienced fat mass loss and lean mass gain. Metformin monotherapy in patients with newly diagnosed type 2 diabetes led to a significant decrease in percent body fat (P = 0.029) and body fat mass (P = 0.038). Levels of serum total cholesterol (P = 0.004), triglycerides (P = 0.014), and adiponectin (P = 0.001) took a favorable turn after metformin treatment. The 3 antidiabetes medications caused no significant change in abdominal fat distribution, waist circumference, and blood pressure during the 6 months.

Conclusions: Our results suggest metformin therapy in patients with newly diagnosed type 2 diabetes can improve cardiometabolic risk markers. Moreover, body composition change induced by gliclazide and acarbose was not likely to be simple fat deposition.

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Introduction

It is well known that obesity and diabetes mellitus have a close relationship. The established pharmacotherapies for diabetes can improve glycemic control and thus reduce the risk of diabetes-related complications. However, weight gain is a frequent side effect of antihyperglycemia therapy in patients with type 2 diabetes mellitus.1–3 It has been shown that weight gain increases the risk of cardiovascular disease, but the amount of body fat, rather than the amount of excess body weight, may be a better indicator for the health risks of type 2 diabetes mellitus and cardiovascular disease.4 Although numerous clinical trials have evaluated the body weight change induced by diabetes medications alone or in combinations,5,6 the composition of body weight change in these clinical trials has rarely been assessed.7,8 A study by Lee et al7 indicated that metformin may attenuate lean mass loss in older men with diabetes, but oral glucose tolerance testing was not performed in their study. Patients’ classification was assessed by prescription medication inventory without regard for the confused effect of antihyperglycemic drug combinations. The study by Rodriguez-Moctezuma et al8 indicated that metformin may attenuate lean mass loss in older men with diabetes, but oral glucose tolerance testing was not performed in their study. Patients’ classification was assessed by prescription medication inventory without regard for the confused effect of antihyperglycemic drug combinations. The study by Rodríguez-Moctezuma et al9 indicated that the administration of metformin for 2 months improved the parameters of body composition (ie, a decrease in body weight and fat with an increase in lean mass) in patients without diabetes but with risk factors for type 2 diabetes. Body composition in their study was...
measured by bioelectrical impedance and abdominal fat distribution was not involved.

Our study evaluated the effects of monodrug therapy on cardiometabolic risk profile (ie, body weight, body composition, fat distribution, blood pressure, lipid profile, and adipokines) in patients with newly diagnosed type 2 diabetes. Sulfonylureas, metformin, and α-glucosidase inhibitors are commonly used in the treatment of patients with type 2 diabetes. We chose Diamicron MR (Servier, Hawthorne, Victoria, Australia), Glucophage (Bristol-Myers Squibb, New York, NY), and Precose (Bayer Healthcare Pharmaceuticals, Wayne, NJ) as representatives of gliclazide, metformin, and acarbose, respectively, according to the report “Pharmaceutical Sales in the East China in 2009” by IMS Health.

Patients and Methods

Patients

A total of 90 patients (drug-naive) with hyperglycemia [glycosylated hemoglobin [HbA1c] 7%–10%) were recruited from our outpatient clinic between October 2010 and December 2011. They were patients newly diagnosed with type 2 diabetes according to the results of oral glucose tolerance test (World Health Organization 1999 criteria). Patients with severe congestive heart failure (ie, New York Heart Association functional class III–IV), liver dysfunction (ie, aspartate aminotransferase and/or alanine aminotransferase > 1.5 × upper limit of normal), and renal dysfunction (ie, creatinine clearance < 90 mL/min; creatinine clearance was estimated from serum creatinine concentration using the Cockcroft-Gault formula) were excluded. Patients with extraordinary body weight (ie, body mass index < 18.5 or > 35 kg/m²) and obvious dyslipidemia (ie, serum total cholesterol ≥ 6.22 mmol/L, triglycerides ≥ 2.26 mmol/L, and low-density lipoprotein cholesterol ≥ 4.14 mmol/L) were also excluded. Patients receiving antidiabetes treatment before the study, or taking pharmacologic agents known to affect carbohydrate homeostasis or influence lipid levels were also excluded. No patient enrolled in this study was diagnosed with type 1 diabetes mellitus.

After 4 weeks of diet treatment (energy intake ~ 30 kcal/kg ideal body weight per day), the enrolled patients were divided into 3 groups by simple randomization (random number generation in Excel; Microsoft Corp, Redmond, WA). They were randomized to take gliclazide, metformin, or acarbose. The baseline dose of each group was considered to be the level of blood glucose. The maximum dose of gliclazide, metformin, and acarbose was 120 mg/d, 1,700 mg/d, and 300 mg/d, respectively. The therapeutic target was defined as HbA1c < 7.0%. The study protocol was approved by the Ethics Review Board of Tongji University. Written informed consent was obtained from all participants and all of the procedures were done in accordance with the Declaration of Helsinki and relevant policies in China.

Methods

All patients underwent both physical and laboratory examination at baseline (M0) and 6 months (M6) later. Waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the midaxillary line. After an overnight fast for 10 to 12 hours, blood samples were taken to test plasma glucose levels and lipids profile. HbA1c was analyzed by high-performance liquid chromatography. The concentrations of leptin and adiponectin were determined by ELISA kits (Millipore Co, Ltd, Billerica, MA).

Dual-energy x-ray absorptiometry (DEXA) measurement

Body composition was measured by DEXA scan (Lunar DPX-IQ; GE Healthcare, Little Chalfont, Buckinghamshire, UK). Patients in light clothes were measured and head-to-toe scans were performed when they were lying down in a comfortable state on the examination bed. The examination took approximately 15 to 20 minutes. Body composition, including body fat and lean mass, was measured separately for arm, leg, trunk, and total. The results were presented in kilograms for total body lean mass, fat mass, and bone mineral content.

Computed tomography (CT) measurement

The abdominal subcutaneous and visceral fat areas were quantified by using a 64-channel multidetector CT scanner (Brilliance 64; Philips, Eindhoven, the Netherlands). With patients in a supine position, a cross-sectional scan at 3-mm thickness was obtained, centered at the L4 vertebral body to evaluate the distribution of abdominal adipose tissue. The reorganized fat density results ranged between −190 and −30 HU. The cross-sectional subcutaneous fat boundary was defined using a manual cursor. Visceral adipose tissue area (VAT) was calculated as total abdominal adipose tissue area minus subcutaneous adipose tissue area (SAT). All scans were performed with the following parameters: 120 kV, 250 mA, thickness of 3 mm, increment of 1.5 mm, pitch of 1.17. All imaging films were read by 1 radiologist (Dr. S. Yang). The original image was analyzed with the Mimics 10.0 software (Materialise Co, Leuven, Belgium).

Statistical analysis

Comparisons of differences between normally distributed data were carried out with a 2-tailed Student t test and 1-way ANOVA, and non-normally distributed data with a Mann-Whitney U test between groups. Categorical data were expressed as rates and compared by a χ² test. A P value < 0.05 was considered statistically significant. For statistical analyses, SPSS version 13.0 (IBM-SPSS Inc, Armonk, NY) was used.

Results

Eighty-six patients (age range 35–75 years, mean (SD) 54.9 (9.8) years; 57 men and 29 women) completed the study. Two patients withdrew because of side effects caused by metformin and acarbose. Two patients were reluctant to follow-up. These 4 patients were excluded from the data analysis. There was no significant difference in baseline demographics, glycemic or lipid parameters, body parameters, or other laboratory data among the 3 groups (Table).

Glycemic control and lipid profile

For the most part, the patients enrolled achieved glycemic control during the 6 months. Mean (SD) HbA1c improved from M0 (8.40% [0.93%]) to M6 (6.46% [0.51%]) in the gliclazide group; from M0 (8.07% [0.77%]) to M6 (6.37% [0.48%]) in the metformin group; and from M0 (8.06% [0.82%]) to M6 (6.44% [0.34%]) in the acarbose group. Total cholesterol and triglyceride levels decreased significantly (P = 0.004 and P = 0.014, respectively) during the 6 months in the metformin group. High-density lipoprotein cholesterol and low-density lipoprotein cholesterol showed no significant change after treatment.
As a result, the visceral to subcutaneous fat ratio remained unchanged. During the 6 months of therapy, gliclazide and acarbose were not associated with significant body weight change, and metformin caused no significant reduction in mean (SD) body weight (71.6 [12.7] kg at M0 vs 68.4 [12.2] kg at M6). As for body composition, metformin led to a decrease in mean (SD) percent body fat (30.95% [7.49%] at M0 vs 26.50% [7.65%] at M6; \( P = 0.029 \)) and fat mass (20.79 [6.45] kg at M0 vs 17.28 [6.12] kg at M6; \( P = 0.038 \)), but mean (SD) lean mass changed nonsignificantly from 45.62 (9.49) kg to 46.04 (9.64) kg. The body fat percent, fat mass, and lean mass in the gliclazide and acarbose groups sustained no significant change during the 6 months. During 6-months of follow-up, patients in the gliclazide group lost 1.5% total body fat, the metformin group lost 4.5% total body fat, and the acarbose group lost 1.3% total body fat. Compared with the other patients, patients treated with metformin showed significant changes in body weight and body fat mass (Figure). The bone mineral content of patients in each group sustained no significant change during the 6 months.

**Waist circumference and abdominal adipose tissue**

The waist circumference of each group showed no significant change during the 6 months. No significant change in SAT and VAT was observed during the 6 months of monodrug treatment. As a result, the visceral to subcutaneous fat ratio remained unchanged.

Body weight, body fat mass, and lean mass (DEXA measurement)

During 6 months of therapy, gliclazide and acarbose were not associated with significant body weight change, and metformin caused no significant reduction in mean (SD) body weight (71.6 [12.7] kg at M0 vs 68.4 [12.2] kg at M6). As for body composition, metformin led to a decrease in mean (SD) percent body fat (30.95% [7.49%] at M0 vs 26.50% [7.65%] at M6; \( P = 0.029 \)) and fat mass (20.79 [6.45] kg at M0 vs 17.28 [6.12] kg at M6; \( P = 0.038 \)), but mean (SD) lean mass changed nonsignificantly from 45.62 (9.49) kg to 46.04 (9.64) kg. The body fat percent, fat mass, and lean mass in the gliclazide and acarbose groups sustained no significant change during the 6 months. During 6-months of follow-up, patients in the gliclazide group lost 1.5% total body fat, the metformin group lost 4.5% total body fat, and the acarbose group lost 1.3% total body fat. Compared with the other patients, patients treated with metformin showed significant changes in body weight and body fat mass (Figure). The bone mineral content of patients in each group sustained no significant change during the 6 months.

**Leptin and adiponectin concentrations**

Mean (SD) serum fasting leptin had no significant change (5.65 [4.92] ng/mL at M0 vs 6.38 [4.53] ng/mL at M6) and mean (SD) adiponectin also had no significant change (2.55 [2.44] μg/mL at M0 vs 2.55 [2.44] μg/mL at M6).
patients with newly diagnosed type 2 diabetes can signi-
ificantly increase from 3.03 (1.69) μg/mL to 5.38 (3.21) μg/mL
\( (P = 0.001) \) in the metformin group. Mean (SD) serum fasting
leptin had no significant change from M0 (6.16 [3.98] ng/mL)
to M6 (5.69 [4.10] ng/mL) and mean (SD) adiponectin also had
no significant change from M0 (2.64 [1.67] μg/mL) to M6 (3.31
[2.10] μg/mL) in the acarbose group.

Discussion

Increased body weight is associated with insulin resistance,
type 2 diabetes mellitus, and increases the risk of cardiovascular
disease.\(^{12–14}\) It is widely accepted that medication-induced weight
gain is an unfavorable result for patients with type 2 diabetes. Obesity is a nutritional disorder characterized by abnormal accu-
mulation of body fat. The amount of body fat, rather than the
amount of excess body weight, may be a better indicator for the
health risks of type 2 diabetes mellitus and cardiovascular dis-
ease.\(^{4}\) The loss or gain of fat and lean mass that accompany body
weight change may not be equally effective in altering the
metabolic profile of patients with type 2 diabetes mellitus.

Our study was designed to examine body composition changes
following monodrug therapy in patients with newly diagnosed
type 2 diabetes mellitus. We used DEXA, which is considered
the reference measure, because it is more accurate than bioelectrical
impedance for body fat measurement.\(^{15–17}\) We also used CT, which
is considered the gold-standard method to evaluate the abdominal
fat distribution.\(^{18}\) We chose metformin, gliclazide, and acarbose
because they are often-used antihyperglycemia drugs. During
6 months of monodrug treatment, metformin led to significant
percent body fat and fat mass decreases, whereas percent body
fat and fat mass in the gliclazide and acarbose groups
remained unchanged. The SAT and VAT of each group sustained
no significant change during the 6 months. In the study by
Rodríguez-Moctezuma et al,\(^{5}\) 2-month metformin use improved
the parameters of body composition (ie, a decrease in body weight
and fat with an increase in lean mass),\(^{8}\) although their study
design had some differences from ours. For example, the patients
in our study were newly diagnosed with type 2 diabetes mellitus,
whereas patients without diabetes but with risk factors for type 2
diabetes mellitus were enrolled in their study. Body composition
in our study was measured by DEXA, whereas body composition in
their study was measured by bioelectrical impedance and fat
distribution was not involved. Further, the length of follow-up
was 6 months in our study and 2 months in their study. Despite
these differences, our studies came to similar results. Serum total
cholesterol \( (P = 0.004) \), triglycerides \( (P = 0.014) \), and adiponectin
\( (P = 0.001) \) levels took a favorable turn after metformin treatment
for 6 months. This indicates that metformin monotherapy in
patients with newly diagnosed type 2 diabetes can significantly
improve cardiometabolic risk markers. Alain Simon’s study indi-
cated body fat mass was a better indicator of high coronary heart
disease risk than waist circumference and body mass index.\(^{4}\)
Furthermore, body fat percentage has a strong connection with
all-cause and cardiovascular mortality.\(^{19–21}\) During 6 months of
therapy, most patients in our study experienced fat mass loss and
lean mass gain, especially in the metformin group. Although there
was no statistically significant difference in the gliclazide and
acarbose groups, the medication-induced change in body compo-
sition may not be unfavorable for the metabolic profile in patients
with newly diagnosed type 2 diabetes. Several questions remain unanswered: Would gliclazide and acarbose monotherapy lead to
similar results if the treatment time was increased? and, Would
monotherapy with either or both of those drugs reduce the risk of
cardiovascular disease events in patients with type 2 diabetes mellitus? These need further study.

Limitations

A limitation of our study is the small sample size, which did not
allow us to analyze the results by gender. Men and women are
significantly different in the body fat percentage and serum levels of
leptin and adiponectin. A larger sample size may result in more
accurate results.

In our study, percent body fat and fat mass decreased after
6-month monotherapy with metformin. Lean mass had no signi-
ificant change. Body composition in the gliclazide and acarbose
groups sustained no significant change. Different follow-up
lengths may come to different results. It is necessary to prolong
the follow-up length and increase observation times.

DEXA has been shown to provide an accurate assessment of
body composition and has been used as reference methods for
comparison of other techniques, but it also has its limitations in
the assessment of body composition.\(^{16}\)

During September 2010, the European Medicines Agency rec-
commended that the drug rosiglitazone should be suspended in
Europe. The US Food and Drug Administration determined that the
drug could remain in the US market but made some significant
restrictions. Rosiglitazone was recommended to be removed from
our hospital formulary in December 2010. Rosiglitazone works as
an insulin sensitizer in the thiazolidinedione class and was widely
used as glucose-lowering agent. Our hospital had no pioglitazone
drug in our formulary, so it was not brought into our study.

Conclusions

Our study suggests metformin monotherapy in patients with
newly diagnosed type 2 diabetes can improve the parameters of
body composition and other cardiometabolic risk markers. More-
over, gliclazide- and acarbose-induced body composition change is
not likely to be simple fat deposition, and may have no unfavorable
effect on cardiometabolic risk profile.

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Conflicts of Interest

The authors have indicated that they have no conflicts of
interest regarding the content of this article.

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