Current Therapeutic Research 75 (2013) 88–92

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/cuthre

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

Hua Wang, MD[1], Yafang Ni, MS[1], Shuo Yang, BS[2], Huizhi Li, BS[1], Xu Li, MD[1], Bo Feng, MD[1,*]

[1] Department of Endocrinology, East Hospital, Tongji University School of Medicine, Shanghai, China
[2] Department of Radiology, East Hospital, Tongji University School of Medicine, Shanghai, China

ARTICLE INFO

Article history:
Accepted 9 October 2013

Key Words:
body composition
fat distribution
monodrug therapy
newly diagnosed type 2 diabetes

ABSTRACT

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 circumstance, 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.

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 al[7] 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 Rodrıguez-Moctezuma et al[8] 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

* Address correspondence to: Bo Feng, MD, Department of Endocrinology, East Hospital, Tongji University School of Medicine, 150 Jimo Rd, Pudong District, Shanghai 200120, China.
E-mail address: fengbo2010@sohu.com (B. Feng).

0011-393X/$ - see front matter © 2013. The Authors. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.curtheres.2013.10.002

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 adipocytokines) 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 [HbA_{1c}] 7%–10%)[9] 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 $> 1.5 \times$ 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.[10] Patients with extraordinary body weight (ie, body mass index < 18.5 or > 35 kg/m^2) 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 $\sim$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 initiated dose of each group was according to 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 $HbA_{1c} < 7.0\%$. 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. HbA_{1c} 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).[11] All scans were performed with the following parameters: 120 kV, 250 mA, thickness of 3 mm, increment of 1.5 mm, pitch of 1.173. 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 χ^2 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) HbA_{1c} 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.

Table
Baseline and follow-up evaluation in patients with newly diagnosed type 2 diabetes mellitus after monodrug therapy*

Characteristic	Gliclazide		Metformin		Acarbose	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Male/female, n	21/9	21/9	18/11	18/11	18/9	18/9
Age, y	55.89 (10.5)		54.0 (10.3)		54.7 (8.9)	
Height, cm	167.4 (7.8)		165.2 (8.5)		167.0 (8.8)	
Body weight, kg	70.4 (11.7)	71.2 (11.0)	71.6 (12.7)	68.4 (12.2)	70.4 (11.7)	70.0 (12.1)
Waist, cm	86.4 (9.6)	86.7 (9.4)	88.1 (9.8)	87.5 (9.5)	88.4 (10.9)	88.4 (11.4)
SBP, mm Hg	125.1 (9.4)	127.1 (7.0)	126.4 (9.0)	128.2 (8.6)	126.7 (13.7)	127.2 (10.3)
DBP, mm Hg	76.3 (7.4)	75.1 (6.6)	74.9 (7.0)	76.1 (5.9)	75.0 (6.7)	73.3 (6.6)
FPG, mmol/L	8.82 (1.74)	6.59 (1.09)†	8.24 (1.23)	6.16 (0.98)‡	8.86 (1.61)	6.36 (0.64)§
2hGlu, mmol/L	16.16 (3.28)		15.81 (2.83)		17.05 (3.06)	
2hPG, mmol/L		10.70 (2.13)†		10.22 (1.36)‡		10.09 (1.60)§
HbA_{1c}, %	8.40 (0.93)	6.46 (0.51)†	8.07 (0.77)	6.37 (0.48)‡	8.06 (0.82)	6.44 (0.34)§
TC, mmol/L	5.23 (1.02)	4.65 (0.90)	5.02 (0.85)	4.40 (0.70)‡	4.95 (0.85)	4.41 (0.86)¶
TG, mmol/L	2.12 (1.25)	1.86 (1.19)	1.93 (0.53)	1.58 (0.55)‖	2.02 (0.97)	1.65 (0.51)
HDL-C, mmol/L	1.05 (0.33)	1.04 (0.32)	1.09 (0.32)	1.18 (0.35)	1.08 (0.24)	1.11 (0.37)
LDL-C, mmol/L	2.60 (0.68)	2.46 (0.75)	2.72 (0.67)	2.39 (0.65)	2.54 (0.60)	2.31 (0.71)
Leptin, ng/mL	5.65 (4.92)	6.38 (4.53)	7.31 (4.43)	6.01 (5.08)	6.16 (3.98)	5.69 (4.10
Adiponectin, μg/mL	2.55 (2.44)	3.34 (3.66)	3.03 (1.69)	5.38 (3.21)‡	2.64 (1.67)	3.31 (2.10)
Drug dose/d	48.0 (14.9) mg	61.0 (14.7) mg†	1.00 (0.33) g	1.23 (0.43) g‖	138.0 (23.4) mg	181.5 (73.6) mg§
Body fat, %	29.02 (6.94)	27.54 (6.83)	30.95 (7.49)	26.50 (7.65)‖	28.01 (8.07)	26.68 (7.85)
Fat mass, kg	19.22 (5.68)	18.44 (5.67)	20.79 (6.45)	17.28 (6.12)‖	18.49 (6.13)	17.40 (5.77)
Lean mass, kg	46.56 (8.31)	48.22 (8.27)	45.62 (9.49)	46.04 (9.64)	46.54 (8.98)	46.93 (9.39)
BMC mass, kg	2.69 (0.55)	2.67 (0.55)	2.56 (0.61)	2.49 (0.56)	2.60 (0.59)	2.56 (0.55)
SAT, cm^2	159.1 (72.9)	158.7 (73.7)	197.3 (78.5)	195.2 (79.6)	169.3 (60.8)	165.4 (53.2)
VAT, cm^2	108.3 (58.1)	108.2 (56.7)	131.3 (57.4)	129.0 (56.8)	106.3 (42.8)	104.0 (38.2)
VAT/SAT	0.71 (0.22)	0.72 (0.23)	0.68 (0.19)	0.68 (0.19)	0.64 (0.13)	0.64 (0.15)

Waist = waist circumstance; SBP = systolic blood pressure; DBP = diastolic blood pressure; FPG = fasting plasma glucose; 2hGlu = 2-hour plasma glucose in oral glucose tolerance test; 2hPG = 2-hour postprandial plasma glucose; HbA_{1c} = glycosylated hemoglobin; TC = total cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SAT = subcutaneous adipose tissue area; VAT = visceral adipose tissue area.

*Values are presented as mean (SD). Patients were arrayed according to the time of study: 0 months (baseline) and 6 months (follow-up).
†Comparison between 6 months and 0 months in gliclazide group, $P < 0.01$.
‡Comparison between 6 months and 0 months in metformin group, $P < 0.01$.
§Comparison between 6 months and 0 months in acarbose group, $P < 0.01$.
‖Comparison between 6 months and 0 months in metformin group, $P < 0.05$.
¶Comparison between 6 months and 0 months in acarbose group, $P < 0.05$.

Waist circumstance 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, 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

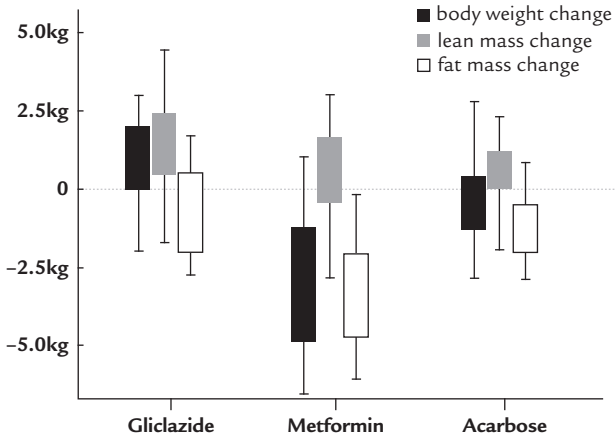

Figure. Boxplot indicating body weight change (black), lean mass change (gray), and fat mass change (white). Comparison between gliclazide and metformin group in body weight change ($P = 0.000$), lean mass change ($P = 0.004$), and fat mass change ($P = 0.000$); comparison between gliclazide and acarbose group in body weight change ($P = 0.020$), lean mass change ($P = 0.003$), and fat mass change ($P = 0.453$); and comparison between metformin and acarbose group in body weight change ($P = 0.000$), lean mass change ($P = 0.872$), and fat mass change ($P = 0.000$) .

M0 vs 3.34 [3.66] μg/mL at M6) in the gliclazide group. Mean (SD) serum fasting leptin had no significant change (7.31 [4.43] ng/mL at M0 vs 6.01 (5.08) ng/mL at M6) and mean (SD) adiponectin significantly increased 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 accumulation 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 disease.[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 Rodrıguez-Moctezuma et al,[8] 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 indicated body fat mass was a better indicator of high coronary heart disease risk than waist circumstance 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 composition 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 significant 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 recommended 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. Moreover, 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.

Acknowledgments

This work was supported by a Young Medical Talents Training Program Grant of Pudong Health Bureau of Shanghai (No. PWRq2012-08) and the Key Disciplines Group Construction Project of Pudong Health Bureau of Shanghai (No. PWZxkq2010-04). All authors contributed equally to the creation of the manuscript. The authors thank the staff of Shanghai East Hospital for their facilitation of the patient sample collection.

Conflicts of Interest

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

References

[1] Barnett A, Allsworth J, Jameson K, et al. A review of the effects of antihyperglycaemic agents on body weight: the potential of incretin targeted therapies. *Curr Med Res Opin.* 2007;23:1493–1507.
[2] Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycaemic therapies. *Diabetes Obes Metab.* 2007;9:96–102.
[3] Hermansen K, Mortensen LS. Bodyweight changes associated with antihyperglycaemic agents in type 2 diabetes mellitus. *Drug Saf.* 2007;30:1127–1142.

[4] Dervaux N, Wubuli M, Megnien JL, et al. Comparative associations of adiposity measures with cardiometabolic risk burden in asymptomatic subjects. *Atherosclerosis.* 2008;201:413–417.
[5] Schütt M, Kern W, Zimmermann A, et al. Association of antidiabetic therapies to glycemic control and to body weight in type 2 diabetes: a German multicenter analysis on 9294 patients. *Exp Clin Endocrinol Diabet.* 2010;118:490–495.
[6] Janghorbani M, Amini M, Salehi-Marzijarani M. Weight change, blood pressure, lipids and glycemic control among patients with type 2 diabetes. *Ann Nutr Metab.* 2011;58:141–149.
[7] Lee CG, Boyko EJ, Barrett-Connor E, et al. Insulin sensitizers may attenuate lean mass loss in older men with diabetes. *Diabetes Care.* 2011;34:2381–2386.
[8] Rodríguez-Moctezuma JR, Robles-López G, López-Carmona JM, et al. Effect of metformin on the body composition in subjects with risk factors for type 2 diabetes. *Diabetes Obes Metab.* 2005;7:189–192.
[9] Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. *Am Fam Physician.* 2009;79:29–36.
[10] Helou R. Should we continue to use the Cockcroft-Gault formula? *Nephron Clin Pract.* 2010;116:c172–c185.
[11] Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: standardized technique for measurement at CT. *Radiology.* 1999;211:283–286.
[12] Ridderstråle M, Gudbjörnsdottir S, Eliasson B, et al. Obesity and cardiovascular risk factors in type 2 diabetes: results from the Swedish National Diabetes Register. *J Intern Med.* 2006;259:314–322.
[13] Cusi K. The role of adipose tissue and lipotoxicity in the pathogenesis of type 2 diabetes. *Curr Diab Rep.* 2010;10:306–315.
[14] Palmer AJ, Roze S, Valentine WJ, et al. Deleterious effects of increased body weight associated with intensive insulin therapy for type 1 diabetes: increased blood pressure and worsened lipid profile partially negate improvements in life expectancy. *Curr Med Res Opin.* 2004;20(Suppl 1):S67–S73.
[15] Sun G, French CR, Martin GR, et al. Comparison of multifrequency bioelectrical impedance analysis with dual-energy X-ray absorptiometry for assessment of percentage body fat in a large, healthy population. *Am J Clin Nutr.* 2005;81:74–88.
[16] Plank LD. Dual-energy X-ray absorptiometry and body composition. *Curr Opin Clin Nutr Metab Care.* 2005;8:305–309.
[17] Beeson WL, Batech M, Schultz E, et al. Comparison of body composition by bioelectrical impedance analysis and dual-energy X-ray absorptiometry in Hispanic diabetics. *Int J Body Compos Res.* 2010;8:45–50.
[18] Shuster A, Patlas M, Pinthus JH, et al. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. *Br J Radiol.* 2012;85:1–10.
[19] Lahmann PH, Lissner L, Gullberg B, et al. A prospective study of adiposity and all-cause mortality: the Malmö Diet and Cancer Study. *Obes Res.* 2002;10:361–369.
[20] Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Normal weight obesity: a risk factor for cardiometabolic dysregulation and cardiovascular mortality. *Eur Heart J.* 2010;31:737–746.
[21] Heitmann BL, Erikson H, Ellsinger BM, et al. Mortality associated with body fat, fat-free mass and body mass index among 60-year-old Swedish men-a 22-year follow-up. The study of men born in 1913. *Int J Obes Relat Metab Disord.* 2000;24:33–37.