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Original Article

Effects of exenatide on fat redistribution in centrally obese patients with type 2 diabetes mellitus

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Abstract: Objective: This study investigated the effects of exenatide on total body fat redistribution in centrally obese patients with T2DM. Design: In a prospective, single-arm study, 38 centrally obese patients with T2DM were treated with exenatide for a total of 18 weeks. The patients' glucose and insulin levels, and their lipid parameters were measured before and after exenatide treatment. Homeostatic model assessments of β-cell function and insulin resistance (HOMA-B and HOMA-IR) were also calculated, and the android fat mass, android/gynoid (A/G) ratio, and visceral adipose tissue (VAT) area were measured by dual-energy X-ray absorptiometry (DXA). Results: Thirty-three patients completed the study. Exenatide treatment induced significant decreases in body mass index (BMI) and glycated hemoglobin (HbA1c). In addition, there were significant improvements in β-cell function and insulin resistance, and the android fat mass, A/G ratio, and VAT area were all significantly decreased. Changes in the A/G ratio were significantly correlated with the changes in HbA1c and HOMA-B, while changes in the VAT area were significantly correlated with changes in HOMA-IR. Conclusion: Exenatide treatment can induce a redistribution of adipose tissues, which may possibly contribute to improved glucose homeostasis and insulin responsiveness in centrally obese patients with T2DM.

Keywords: Glucagon-Like Peptide 1, body fat distribution, diabetes mellitus, type 2

Introduction

As the occurrence and development of type 2 diabetes mellitus (T2DM) is strongly related to obesity, especially visceral fat adiposity [1], weight reduction is an important strategy in the treatment of T2DM. A new class of antidiabetic drugs applied in the management of patients with T2DM is the glucagon-like peptide-1 receptor agonists (GLP-1RAs), which reduce blood glucose concentrations during periods of hyperglycemia by stimulating insulin secretion and reducing glucose-dependent glucagon secretion [2, 3]. In addition to islet cells, the GLP-1 receptor (GLP-1R) has been found in a variety sites, including brain and adipose tissues [4], which are considered the main points of weight regulating. And as a result, a number of studies [5-7] have shown that GLP-1RAs can induce weight loss and concluded that weight loss makes contribution to metabolic improvements.

However, few studies focused on the effect of GLP-1RAs on regional adipose distribution. As is known, the regional distribution of adipose tissue is more important than the total amount of body fat in predicting morbid complications associated with obesity [1]. Thus, we investigated the effects of the GLP-1RA exenatide on the redistribution of total body fat, insulin resistance, and lipid parameters in T2DM patients with central obesity.

Material and methods

Patients

Patients were prospectively recruited to this single-arm study from our department. The inclusion criteria were a diagnosis of central obesity (waist circumference >90 cm in males and >85 cm in females), known T2DM with inadequate glycemic control (HbA1c≥7.0%), and at least 8 weeks' treatment on a stable dose of oral antidiabetic drugs (maximal doses of metformin with or without sulfonylureadrugs). Exclusion criteria included acute or severe chronic complications of diabetes, impaired re-

nal function (serum creatinine >133 μmol/L), liver dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] levels more than 2.5 times the upper limit of normal), treatment with medications known to affect weight, and a history of severe gastrointestinal disease such as pancreatitis.

The study was approved by the Shanghai Tenth People's Hospital Ethics Committee. All patients were asked to sign an informed consent form prior to their participation in the study. The study was registered with ClinicalTrials.gov (No.: NCT02118376).

Study interventions

After a screening period of 1 week, a total of 38 patients were recruited to the study. Exenatide administration was commenced at a dosage of 5 μg subcutaneously (injected at an abdominal site) twice daily for the first 4 weeks after which the dosage was increased to 10 μg twice daily for the remaining 14 weeks of the study. If hypoglycemia occurred (blood glucose concentration <3.9 mmol/L), other oral antidiabetic drugs that were being taken were either given in reduced dosages or discontinued. If nausea or vomiting occurred, the dosage of exenatide was adjusted, but if treatment was still not tolerated after dosage adjustment, the patient was withdrawn from the study. During the whole study, patients were advised against bringing any intentional lifestyle change, including eating habits and physical exercise.

Determination of body composition

The patients' physical parameters were determined by a trained physician. Height (cm) was measured to the nearest 0.5 cm using a stadiometer. Waist circumference (WC) (cm) was taken at the midpoint between the lower edge of the rib cage and the anterior superior iliac spine. Weight (kg) and body mass index (BMI) were measured using simple anthropometric measuring instrument (Omron HBF-358, Japan).

All study participants underwent dual-energy X-ray absorptiometry (DXA) before and after exenatide treatment to determine their fat distribution and the estimated visceral adipose tissue (eVAT) area. For the android region, the lower boundary was the top of the pelvis line of demarcation, while the upper boundary was above the lower boundary at a position equivalent to 20% of the distance between the pelvis and the femoral neck. Lateral boundaries were the lines for the arms when in the normal position for a whole-body scan. The gynoid region was defined with the upper boundary positioned below the pelvis cut line by 1.5 times the height of the android region. The lower boundary was positioned such that it was equal to 2 times the height of the android region. The lateral boundaries were the outer leg lines of demarcation [8].

Blood biochemistry parameters

Blood samples were collected from all patients following an overnight fast before and after 18 weeks of exenatide treatment. Serum concentrations of glucose, ALT, AST, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) were measured by enzymatic methods using an autoanalyzer. Insulin was measured by chemiluminescence immunoassay, while HbA1c was determined by high-performance liquid chromatography. Formulae used to calculate HOMA-B (homeostatic model assessment of β-cell function) and HOMA-IR (homeostatic model assessment of insulin resistance) were: HOMA-B = 20 • fasting serum insulin/(fasting serum glucose - 3.5). HOMA-IR = fasting serum glucose (mmol/L) • fasting serum insulin (μU/mL)/22.5 [9].

Statistical analysis

All statistical analyses were performed using SPSS® 19.0 software (SPSS Inc, Chicago, IL, USA). Normally distributed and continuous variables were presented as means ± standard deviation (SD). Non-normally distributed variables (HOMA-B, and HOMA-IR) were logarithmically transformed (lnHOMA-B and lnHOMA-IR, respectively) before analysis. For comparisons of data obtained before and after exenatide treatment, the paired Student's *t*-test was used. Pearson's correlation analysis was used when applicable to examine bivariate relationships. *P*-values less than 0.05 were considered to indicate statistical significance.

Results

Characteristics of patients

Of the 38 patients who underwent baseline screening, 33 completed the study. The 5 pa-

Table 1. Characteristics of the 33 patients who completed the study at baseline and after exenatide treatment

Characteristic	Before treatment	After treatment	t	*P*-value
Weight, kg	95.7±16.5	93.8±17.2	3.307	0.003
BMI, kg/m^2	32.9±5.2	32.2±5.5	3.644	0.001
Waist circumference, cm	106.3±9.5	102.9±7.9	3.043	0.005
Waist-to-hip ratio	0.98±0.06	0.95±0.05	2.979	0.005
Systolic BP, mmHg	137.9±16.3	134.1±13.2	1.699	0.099
Diastolic BP, mmHg	84.4±10.0	81.6±9.4	1.639	0.111
Fat, %	35.4±6.9	35.2±7.0	0.671	0.507
Total body fat, kg	34.1±9.9	33.3±10.3	2.262	0.031
Trunk fat, kg	18.70±4.82	18.24±4.96	2.190	0.036
Limb fat, kg	13.84±5.43	13.41±5.72	1.189	0.243
Android fat, kg	3.41±0.99	3.17±0.97	2.974	0.006
Gynoid fat, kg	4.55±1.48	4.44±1.53	1.352	0.186
A/G ratio	0.77±0.13	0.73±0.13	2.243	0.032
eVAT area, cm^2	212.3±51.2	191.6±49.6	4.212	<0.001
FBG, mmol/L	9.54±4.23	7.68±2.97	3.141	0.004
HbA1c, %	8.7±1.4	7.3±1.5	8.446	<0.001
lnHOMA-B	4.6±1.1	4.8±1.0	-2.077	0.046
lnHOMA-IR	2.14±0.63	1.78±0.75	3.552	0.001
TC, mmol/L	5.34±1.01	5.49±1.16	-0.867	0.393
TG, mmol/L	2.94±2.17	2.65±2.10	0.815	0.421
HDL-C, mmol/L	1.16±0.26	1.12±0.25	1.208	0.236
LDL-C, mmol/L	3.27±0.66	3.18±0.99	0.495	0.625
FFA, mmol/L	0.58±0.21	0.51±0.22	2.323	0.027

Values are means ± SD. A/G ratio, android/gynoid ratio; BP, blood pressure; eVAT, estimated visceral adipose tissue; FBG, fasting blood glucose; FFA, free fatty acids; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; lnHOMA-B, logarithmically-transformed homeostatic model assessment of β-cell function; lnHOMA-IR, logarithmically-transformed homeostatic model assessment of insulin resistance; TC, total cholesterol; TG, triglyceride.

tients who dropped out all initiated treatment after baseline assessments but 2 declined follow-up, 2 developed unrelated medical issues requiring withdrawal from study, and 1 discontinued exenatide treatment due to adverse gastrointestinal effects.

The baseline characteristics of the 33 patients (19 males and 14 females) who completed the study are shown in **Table 1**. Their mean age and body mass index were 43.5 years and 32.9 kg/m^2, respectively.

Changes in physical parameters and fat distribution

The patients' weight was significantly reduced by a mean of 1.9 kg after exenatide treatment (*P* = 0.003), and the BMI was significantly decreased from 32.9±5.2 kg/m^2 to 32.2±5.5 kg/m^2 (*P* = 0.001). In addition, the mean WC was significantly decreased from 106.3±9.5 cm to 102.9±7.9 cm (*P* = 0.005) after exenatide treatment, and the waist-to-hip ratio was significantly decreased from 0.98±0.06 to 0.95±0.05 (*P* = 0.005) (**Table 1**). Although systolic and diastolic blood pressures were reduced by means of 3.8 mmHg and 2.6 mmHg, respectively, these changes did not reach statistical significance.

While fat percentage of the body was not significantly decreased after exenatide treatment (35.4±6.9% vs 35.2±7.0%), the total body fat mass was significantly reduced by a mean of 0.8 kg (*P* = 0.031), which was almost half of the total weight loss. The trunk fat mass was significantly decreased by mean of 0.46 kg (*P* = 0.036), and the limb fat mass did not decreased significantly (mean reduction 0.33 kg; *P* = 0.243).

The android fat mass was significantly reduced by a mean of 0.24 kg (*P* = 0.006), which was about a third of the total body fat mass reduction. Although the decrease in the gynoid fat mass did not reach statistical significance, the android/gynoid (A/G) ratio was significantly decreased from 0.77±0.13 at baseline to 0.73±0.13 after exenatide treatment (*P* = 0.034). In addition, the eVAT area was also significantly reduced (from 212.3±51.2 cm^2 to 191.6±49.6 cm^2 after treatment; *P*<0.001).

Changes in biochemistry parameters

Exenatide treatment was associated with significant mean reductions of 1.4% in HbA1c (*P*<0.001) and 1.86 mmol/L in fasting blood glucose (*P* = 0.004). Mean lnHOMA-B was significantly increased from 4.6±1.1 at baseline to 4.8±1.0 after treatment (*P* = 0.046), while mean lnHOMA-IR was significantly re-

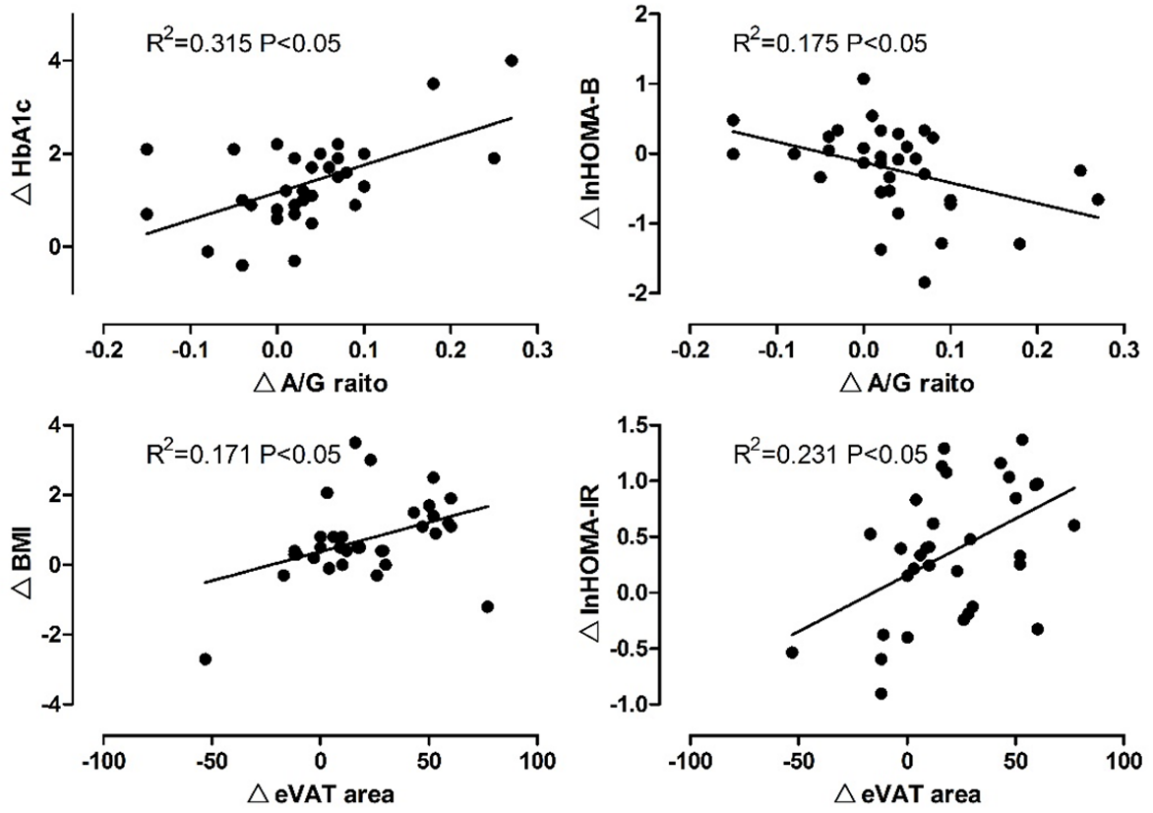

Figure 1. Correlation of changes in the A/G ratio and eVAT area with changes in various metabolic parameters. A/G ratio, android/gynoid ratio; BMI, body mass index; eVAT, estimated visceral adipose tissue HbA1c, glycated hemoglobin; lnHOMA-B, logarithmically-transformed homeostatic model assessment of β-cell function; lnHOMA-IR, logarithmically-transformed homeostatic model assessment of insulin resistance.

duced from 2.14±0.63 to 1.78±0.75 (P = 0.002). Although changes in TC, HDL-C, LDL-C and TG, were not statistically significant, the level of free fatty acids (FFAs) was significantly decreased from 0.58±0.21 mmol/L at baseline to 0.51±0.22 mmol/L after exenatide treatment (P = 0.027) (**Table 1**).

Association between fat redistribution and metabolic improvements

The reduction in the A/G ratio was significantly correlated with the decrease in HbA1c and the increase in lnHOMA-B, while the change in eVAT area was significantly correlated with the change in lnHOMA-IR (**Figure 1**).

Discussion

This study is the first to use A/G ratio to evaluate the effect of exenatide on whole body fat redistribution. Its main findings are that exenatide can significantly reduce the A/G ratio in patients with type 2 diabetes (which represents fat redistribution from central to peripheralareas), and that its effects on fat redistribution are correlated with improvements in glucose homeostasis.

GLP-1RAs are a recently introduced class of antidiabetic drugs that have been shown to induce weight loss in addition to reducing blood glucose levels. Both exenatide and liraglutide have been reported to produce weight decreases when used in the treatment of patients with T2DM and obese patients without T2DM [2, 10-13]. In the present study of centrally obese patients with T2DM, exenatide treatment for 18 weeks decreased weight by a mean of 1.9 kg. This result is consistent with a recent meta-analysis of studies of GLP-1RAs on weight loss in patients with T2DM which found that exenatide 10 μg twice daily (the same dosage that was used in our study) produced a greater mean weight loss of 1.92 kg

in comparison with placebo [14]. The fat mass was reduced by 0.8 kg after exenatide treatment, composed of 42% of body weight reduction. A former study [15] on Liraglutide found that the reduction of fat mass composed almost 2/3 of weight loss. However, studies [10, 16] on exenatide demonstrated that fat mass reduction was about 50% of weight loss, which is more close to our study.

It is well known that weight loss, especially when there is a decrease of visceral adipose tissue, is associated with improvements in glucose homeostasis and insulin resistance in patients with T2DM. However, few studies have focused on changes in visceral adipose tissue and fat redistribution with exenatide treatment, especially in T2DM patients with central obesity. In the patients we studied, the WC and waist-to-hip ratio were both significantly decreased, which is consistent with the findings of previous studies [12, 17, 18]. However, both parameters are not reliable for evaluating fat distribution.

To the best of our knowledge, most previous studies of exenatide treatment have only focused on weight loss and changes in total fat mass [2, 19, 20], although a few have evaluated local fat distribution by using magnetic resonance images of hepatic adipose tissue or ultrasound images of fat thickness [17, 21]. Several earlier studies used DXA as fat mass measurement only focused on the total fat mass and android fat mass or trunk fat mass, without regarding the A/G ratio and fat distribution [22, 23]. This is the first study to use DXA to assess whole body fat distribution when evaluating the effects of exenatide on fat distribution and metabolic parameters.

DXA is a convenient method for measuring total fat mass and regional fat mass. Specific DXA regions of interest such as visceral adipose tissue and android fat are useful for predicting metabolic risks [24, 25]. Therefore, android fat mass and the A/G ratio measured by DXA may be reliable and precise parameters to estimate visceral adipose tissue and fat distribution [26]. A recent study conducted in a large Chinese population [27] demonstrated that android fat mass and the A/G ratio measured by DXA can reliably represent central fat accumulation, and are associated with metabolic risks beyond those associated with total fat. Similarly, a study by Lee et al. [26] found that visceral adipose tissue measured by DXA may be a good predictor of metabolic risks. In the present study, we found that exenatide treatment had a greater effect on android (central) adipose tissue than on gynoid (peripheral) adipose tissue. Although the android fat mass was significantly decreased, there was no significant decrease in the gynoid fat mass. We also found that the A/G ratio was significantly decreased (indicating redistribution of fat from central to peripheralareas), as was the visceral adipose tissue area. These results suggest that exenatide treatment can decrease fat mass, and especially visceral adipose tissue.

As well as the changes in fat distribution, exenatide treatment also improved glucose homeostasis and insulin responsiveness in this study. The fasting blood glucose level and HbA1c were both significantly decreased after exenatide treatment, and lnHOMA-B was increased and lnHOMA-IR decreased. These results indicate that exenatide treatment not only improves glucose homeostasis, but is also able to improve β-cell function and decrease insulin resistance. A recent study that investigated the effects of exenatide in drug-naïve patients with T2DM [18] found that it can enhance the insulin secretion rate and increase β-cell sensitivity to glucose, and this has also been demonstrated in several other studies with exenatide [28-30].

In addition to glucose metabolism, we also investigated changes in other metabolic parameters with exenatide treatment, including blood pressure and the lipid profile. However, we found no significant changes in TC, HDL-C, LDL-C, and TG after exenatide treatment, although the free fatty acid (FFA) level was significantly reduced. This could be due to the decrease of adipose tissue. As reported by previous studies [31, 32], chronic exposure to FFAs can produce diminished insulin secretion and, subsequently, insulin resistance. A recent meta-analysis [33] that examined 35 randomized, controlled trials of GLP-1RAs found that these drugs can improve TC, LDL-C, and TG levels, though whether they produce an increase or a decrease in HDL-C levels was unclear. The absence of significant changes in lipid parameters in the present study may have been due to its relatively small sample size and the wide range of baseline lipid values.

We also investigated the relationship between changes in fat distribution and improvements in metabolic parameters in this study, and found that there were some significant correlations. This may suggest that the ability of exenatide to improve glucose metabolism may be partly due to redistribution of adipose tissue from central to peripheral areas. This suggestion is supported by a recent study in Chinese patients demonstrating that a decrease in intrahepatic fat was associated with an improvement of HbA1c [21].

A major limitation of our study is that the population sample was relatively small and, as a result, we could not conclusively determine whether exenatide treatment has an effect on lipid parameters, which are important metabolic factors in centrally obese patients with T2DM. Moreover, the study was a single-arm one without a placebo control group. Thus, further studies are needed to determine whether local fat redistribution induced by exenatide is associated with metabolic risks and if so, what the mechanisms behind this are.

Conclusion

In conclusion, the findings of this study suggest that treatment of centrally obese T2DM patients with exenatide can reduce the total fat mass and induce fat redistribution from central to peripheral areas. This effect of exenatide may contribute to its effect in improving glucose homeostasis.

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Disclosure of conflict of interest

None.

Authors' contribution

Jiaqi Chen, Hang Sun, Le Bu, and Shen Qu designed the study. Jiaqi Chen, Hang Sun, Xingchun Wang, Lijun Fang, and Yan Li collected and analyzed the data. Jiaqi Chen, Hang Sun, and Xingchun Wang drafted the manuscript. All authors critically reviewed the manuscript, and all have read and approved the final version submitted.

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