Exogenetic insulin increased bone mineral densityin middle-aged male patients with type 2 diabetes mellitus

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Abstract: We aimed to evaluate the influence of exogenetic insulin on bone mineral density (BMD) in Type 2 Diabetes Mellitus (T_2DM). Group A included 120 cases of middle-aged male patients with type 2 diabetes mellitus were administrated exogenetic insulin (40 cases in Group A_1: for less than 1 year; 40 cases in Group A_2:for 1 to 3 years; 40cases in Group A_3: for 3 to 5 years), and another 120 cases (Group B) of middle-aged male patients with type 2 diabetes mellitus were administrated insulin secretagogues. The measurements of BMD of lumbar vertebra (L2-4), collum femoris and total body were conducted with dual-energy X-raya bsorptiometry, followed by the determination of glycosylated hemoglobin, plasma insulin concentration (fasting and postprandial), and fasting C-peptide. Our results revealed that there was no statistical difference of BMD ($P>0.05$) between patients in Group A_1or A_3andpatients in Group B (B_1, B_2 or B_3), while the BMD in Group A2 increased significantly ($P<0.05$). And the fracture risk in Group A3 increased significantly ($P<0.05$) compared with Group B (B_1, B_2 or B_3), Taken together, exogenetic insulin significantly increased BMD and fracture risk of middle-aged male patients with type 2 diabetes mellitus.

Keywords: Exogenetic insulin; type 2 diabetes mellitus; bone mineral density; fracture risk.

INTRODUCTION

At present, the bone mineral density (BMD) change in patients with type 2 diabetes mellitus (T_2DM) is still contentious. Recombinant human insulin therapy has been suggested as an important part of type 2 diabetes mellitus treatment according to recent guidelines and textbooks (Ahn *et al.,* 2013). Most of the studies indicated that the patients with T_2DMmay suffer from osteoporosis due to the decreasing BMD (Abdulameer *et al.,* 2012, Wang *et al.,* 2011). However, recent studies provided opposite results and believed that the BMD of patients with T_2DM was increasing (Arikan *et al.,* 2012, Srikanthan, Crandall *et al.,* 2014). We hereby investigated the BMD of the male patients with T_2DM who were administrated exogenetic insulin and performed a regression analysis on the progression of disease, pancreatic functions, etc. Additionally, our study assessed fracture risk for exploring BMD change and relevant influence factors, to provide more evidence for wider range of epidemiological analysis.

MATERIALS AND METHODS

Patients

Our study randomly recruited 240 male patients (40-50 year old) who get medical treatment in Department of Internal Medicine, Shantou Affiliated Hospital in Guangzhou University of Chinese Medicine from January 2010 to January 2015, who meet the T_2DM diagnostic criteria. These patients shall be well-distributed in Shantou city according to the population density and only one case of each family could be involved. The study was approved by the Hospital Scientific Committee "Committee of Shantou Affiliated Hospital in Guangzhou University of Chinese Medicine" and written informed consent was obtained from all patients included in the study.

Inclusive criteria

Male patients in accord with the T_2DM diagnostic criteria in *China Guideline for Type 2 Diabetes Mellitus of* 2013 were accepted. Group A included 120 patients who were administrated the recombinant human insulin to conduct intensive in sulintherapy, premixed insulin therapy, long-acting insulin therapy or other related therapies; Group B included 120 patients who were administrated insulin secretagogues, like sulphonylurea, meglitinide, or inhibitors like dipeptidyl peptidase-4 to control blood glucose. No other medicines, like hypoglycemic agent, were administrated to those enrolled patients. Moreover, diseases, such as hyperthyroidism and hyperparathyroidism, rheumatic disease or renal disease that may induce secondary osteoporosis, should be excluded. No diabetic ketoacidosis, diabetic hyperosmolar or other acute complications were found. These patients were not bed-ridden and never take glucocorticoid, VD, calcium fortifier, or used agents affecting bone metabolism like carbonated beverage. The body mass index of those 240 patients was (25.7±3.1) kg/m^2; the blood glucose control should be up to general standard, exactly, the fasting blood glucose or pre-prandial blood

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glucose was 6-8mmol/L; 2-hour post-meal blood glucose was 8-10mmol/LL.

Grouping

Patients in Group A were divided into groups by the medication time of insulin: those with less than one year were classified into Group A_1; those with one to three years were classified into Group A_2 and those with three to five years were classified into Group A_3. Patients in Group B were divided into groups by the categories of insulin secretagogues: Patients being administrated with sulphonylurea compounds were in Group B_1, patients being administrated with meglitinide were in Group B_2 and patients being administrated with inhibitors like dipeptidyl peptidase-4 were in Group B_3.

BMD measurement

The BMD of assigned patients was measured by bone densitometry in our hospital with medix-90 dual-energy X-ray bone sonometers (MEDILINK). The parts to be measured were lumbar vertebra (L2-L4), collum femoris and the total body (in g/cm2). If the BMD of one or more parts was lower than the peak BMD of healthy adult at the same gender and race about 1.0 standard deviation, it shall be deemed to be of low bone mass (Mohammadi *et al.*, 2014, Wang *et al.*, 2013).

Monitoring method for glycemic Index and insulin level

Glycosylated hemoglobin (HbA_1C), fasting blood glucose and 2-hour post-meal blood glucose, C-peptide and insulin of the assigned patients should be measured on the same day of bone densitometry measurement.

Fracture risk

Only fracture incidents happening after hypoglycemic therapy were inquired in Group A and B; accidental fracture is excluded.

STATISTICAL ANALYSIS

Statistical analysis with SPSS 21.0 was performed. The data should be presented by mean± standard deviation (x±s); comparison among groups was conducted with independentt-test or non-parametric test; enumeration data was tested by chi-square; and $P<0.05$ was regarded as significant.

RESULTS

For HbA1C and FINS, there was no significant difference between A_1 or A_3 group with B groups (B_1, B_2 or B_3) ($p>0.05$), while there was significant difference of 2h post-meal insulin between A_2group with B group (B_1, B_2 or B_3) ($p<0.05$) (table 1). The BMD of patients in group A_2increased significantly ($p<0.05$) compared with that in group B. Additionally, there was no significant difference of BMD between patients in group A_1or $A_3$with patients in B groups (B_1, B_2 or B_3) ($p>0.05$) (table 2). Fracture risk of patients in-group A_3 increased significantly ($p<0.05$) compared with B groups (B_1, B_2 or B_3). And group A_1or A_2 compared with group B, their fracture risks have no statistical significance ($p>0.05$).

DISCUSSION

According to more and more studies of epidemiology, the research results about the BMD changes of type 2 diabetes mellitus were reported worldwide (Oei *et al.*, 2013). There were different opinions about the influence of type 1 diabetes mellitus and type 2 diabetes mellitus on bone metabolism, and the mechanism remained unclear (Armas *et al.*, 2012, Ma *et al.*, 2012). The results showed that the BMD of lumbar vertebra, collum femoris and other bones increased or remained unchanged in middle-aged male patients with type 2 diabetes mellitus treated with exogenetic insulin, compared with healthy people. However, fracture risk increased significantly after 3 years of exogenetic insulin administration. Recently, Oei *et al.* suggested that hyperinsulinemia and BMD increased among patients with type 2 diabetes mellitus and at the same time, the mechanical structure of bone changed and fracture risk would increase (Oei *et al.*, 2013, Wang *et al.*, 2015). And Looker *et al.* got similar results, BMD of T_2DM is 4%-5% higher than that of normal control and there was no significant difference of BMD change between different genders or races (Looker *et al.*, 2013). Dobnig *et al.* suggested that BDM of T_2DM patients increased significantly than non-diabetic patients using quantitative calcaneus ultrasound method, wherein they investigated the bone metabolism difference of old-aged diabetic patient after age, weight and movement ability corrected (Yamaguchi *et al.*, 2011). These high BMD changes mentioned above might resulted from T_2DM patients' hyperinsulinemia after taken insulin and secretagogues antidiabetes drug in the treatment process. According to *Guidelines for Osteoporosis Prevention* made by America NOF and American National Medical Association in 2008, BMD was closely related to osteoporosis. Furthermore, osteoporosis was related to fracture.

In a word, the BMD of type 2 diabetic patients may be influenced by many factors, among which exogenetic insulin protects BMD or increases BMD of type 2 diabetic patients, but also increased fracture risk. More mechanisms remained to be identified.

CONCLUSION

Exogenetic insulin treatment increased insulin in patients' blood and may increase the BMD of middle-aged male patients with type 2 diabetes mellitus who have taken insulin for 1-3 year and consequently their fracture risks would increase after 3 year of exogenetic insulin treatment.

Table 1: Comparison of blood glucose level and fasting insulin level between patients in group A and group B

Item	A			B		
	A_1	A_2	A_3	B_1	B_2	B_3
HbA1c (%)	8.800±1.265	8.799±1.265	8.804±1.265	8.804±1.258	8.823±1.277	8.814±1.274
FINS (μIU/mL)	14.347±4.600	14.377±4.600	14.354±4.470	14.338±4.675	13.758±4.507	14.424±4.880
2h post-meal insulin (μIU/mL)	23.145±8.115	27.639±9.786*	23.154±7.970	23.129±8.409	23.050±9.696	23.115±10.386

Table 2: Comparison of BMDin different partsbetween group A and group B

Item	A			B		
	A_1	A_2	A_3	B_1	B_2	B_3
Lumbar vertebra	0.907±0.046	0.936±0.075*	0.907±0.046	0.904±0.045	0.904±0.040	0.904±0.037
Collum femoris	0.725±0.028	0.755±0.085*	0.726±0.033	0.717±0.044	0.718±0.032	0.716±0.038
Total body	0.855±0.062	0.908±0.073*	0.865±0.051	0.866±0.046	0.871±0.046	0.875±0.040

Table 3: Comparison of Fracture risk in patients being given hypoglycemic drugs between group A and group B

Group	Cases	Fracture cases	Fracture rate (%)
A_1	40	2	5
A_2	40	2	5
A_3	40	4	10*
B_1	40	0	0
B_2	40	1	2.5
B_3	40	0	0

Note *P<0.05 was presented as significant difference compared with B groups (B_1, B_2 or B_3).

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