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Correlation of serum testosterone with insulin resistance in elderly male type 2 diabetes mellitus patients with osteoporosis

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ABSTRACT

Aims/Introduction: The present study was designed to investigate the correlations between the serum testosterone level and insulin sensitivity in elderly male type 2 diabetes patients with osteoporosis.

Materials and Methods: A total of 35 elderly male patients with type 2 diabetes (type 2 diabetes group), 30 elderly male type 2 diabetes patients combined with osteoporosis (DO group) and 30 healthy elderly men (normal control group) participated in the present study. The fasting plasma glucose, fasting insulin, testosterone (T) and estradiol (E_2) were measured. The insulin sensitivity index (ISI), homeostasis model assessment of insulin resistance (HOMA-IR) and E_2/T were calculated. Then, the correlations of serum testosterone level with ISI and HOMA-IR were analyzed by statistical methods.

Results: The HOMA-IR, E_2 and E_2/T of the type 2 diabetes group and DO group were significantly increased, whereas the bone mineral density, ISI, T and sex hormone binding globulin were decreased compared with those of the normal control group. Serum testosterone levels of the type 2 diabetes group and DO group were negatively correlated to the HOMA-IR (r = –0.496, –0.506; $P < 0.05$), whereas they were positively correlated to the fasting insulin (r = 0.281, 0.292; $P < 0.05$) and ISI (r = 0.364, 0.403; $P < 0.05$).

Conclusions: The reduced level of serum testosterone in elderly male type 2 diabetes patients with osteoporosis might promote insulin resistance.

INTRODUCTION

The incidences of type 2 diabetes mellitus and osteoporosis appear to rise year by year, along with the improvement of living standards and the aging of the population. Type 2 diabetes mellitus and osteoporosis are common diseases that occur simultaneously or successively in elderly people. It is estimated that approximately 1% of bone mineral density is lost in men every year, and the morbidity of osteoporosis increases with lengthening of the lifespan and course extension[1]. Diabetes mellitus is a pandemic metabolic disease with substantial morbidity and mortality. Patients with diabetes mellitus have various skeletal disorders, including osteopenia or osteoporosis, Charcot's arthropathy, and diabetic foot syndrome[2]. As for osteoporosis, it is a metabolic disease of the skeletal system. The essential characteristics of osteoporosis are low bone content and destroyed micro-framework, which could lead to the loss of bone strength, increased bone brittleness and fracture. It has been reported that osteoporosis is a common and severe complication of the skeletal system ii patients with type 2 diabetes[3].

Testosterone plays a significant role in obesity, glucose homeostasis and lipid metabolism. It has been reported that elderly male patients with type 2 diabetes have obviously reduced serum testosterone levels, which might promote insulin resistance, whereas elderly male patients with type 1 diabetes have normal serum testosterone level[4]. Population studies have shown that the reduced level of serum testosterone is an independent risk factor for diabetes and metabolic syndrome in men[5–7]. The role of sex hormones in diabetes mellitus and diabetes mellitus combined with osteoporosis is attracting more and more attention. The relationship between low bone mineral density (BMD) and type 1 diabetes has obtained consistently reliable results, whereas it remains controversial in type 2 diabetes[8–10].

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In order to further explore the correlation of serum testosterone level with insulin resistance, and to investigate the possible mechanisms of elderly male patients with type 2 diabetes, we investigated 65 patients diagnosed with type 2 diabetes at Department of Geriatrics, the First Affiliated Hospital of Suzhou University, Suzhou, Jiangsu, China.

MATERIALS AND METHODS

Study Participants

All the study participants were Han Chinese without osteoporosis and had no history of fracture. No patients were taking other medications that could affect bone metabolism.

The normal control (NC) group consisted of 30 healthy elderly male patients (age 75.12 ± 10.60 years) with no history of diabetes mellitus, thrombus, hemorrhagic disease, tumor, endocrine disease, cardiovascular disease, liver diseases or kidney diseases from the physical examination center of the First Affiliated Hospital of Suzhou University, Suzhou, Jiangsu, China. Furthermore, these selected patients had not used any sex hormones in the past 3 months. The type 2 diabetes group consisted of 35 elderly male patients (75.47 ± 12.10 years) from our inpatients who were diagnosed with type 2 diabetes for 5 years from June 2011 to November 2012. The patients in the present study conformed to the diagnostic criteria of diabetes mellitus that was established by the World Health Organization in 1999. All of these selected patients had no endocrine or metabolic disease, no history of cardiac-cerebral vascular disease or tumors, and did not use any sex hormones within 1 year. No patients with type 2 diabetes (without osteoporosis) had kidney or liver failure.

The type 2 diabetes combined with osteoporosis (DO) group consisted of 30 elderly male patients (age 76.32 ± 11.4 years) with no history of endocrine disease, myocardial infarction, cerebral infarction, liver dysfunctions or renal insufficiency from our inpatients and outpatients with type 2 diabetes and osteoporosis. These patients did not use any sex hormones within 1 year. The sites of fracture suffered by the patients in the DO group were ankle, lumbar, hip, limbs and so on. Some fractures were recent fractures, such as hip and ankle fractures. The present study was approved by hospital medical ethics committees, and all participants gave written informed consent.

METHODS

The fasting blood of all study participants was collected within 5 min of waking up in the morning. The serum was immediately separated after the blood had coagulated to measure the fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), fasting insulin (FINS) and high-density lipoprotein cholesterol (HDL-C). The remaining serum was preserved to measure the sex hormone binding globulin (SHBG), and the levels of hormones including testosterone (T) and estradiol (E_2). T and E_2 assays were carried out using the Bechman Coulter Access automated chemiluminometric immunoassay system (Beckman Coulter Inc, Miami, FL, USA). The inter-assay coefficient of variation was 5%, and the intra-assay coefficient of variation was 5% for T and E_2. The reference range for T and E_2 was 0.1–16 ng/mL and 20–3,600 pg/mL, respectively. The ratio of testosterone to estradiol (E_2/T) was also calculated. The level of the postprandial plasma glucose (PPG) was detected 2 h after the meal. The FPG and PPG were determined by the hexokinase method using an automatic biochemical analyzer (BakermanCX-9, Coulter Inc., Miami, FL, USA), and the HbA1c was detected by using D-10 analyzer (BIO-RAD Laboratories, Richmond, CA, USA). The levels of T and E_2 were detected by the method of chemiluminescence. The FINS was measured by radioimmunoassay. All kits were provided by Roche (Roche Diagnostics, Mannheim, Germany).

The Prodigy Dual-energy X-ray absorptiometry (GE Medical Lunar, Madison, WI, USA) was used to measure the BMD at the L1–L4 lumbar spine (L1–4), left femoral neck (Neck), greater trochanter (Troch), internal trochanter (Inter), total hip (Htot) and Wards. The instrument accuracy was 1%, and the repeated measurement error was less than 5%. The instrument calibration was carried out using the modules provided by the manufacturer after start-up every day, and the measuring processes were carried out by the specific operator.

Height and weight were measured with standardized protocols and calibrated equipment during a physical examination in the examination center of our hospital. The body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). The insulin sensitivity index (ISI) was calculated by the formula: $ISI = In\ (FPG \times FINS)^{-1}$. The homeostasis model assessment of insulin resistance (HOMA-IR) was evaluated by the homeostasis model assessment and calculated by the following formula: $HOMA\text{-}IR = FINS \times FPG / 22.5$.

In the present study, the diagnostic criteria of osteoporosis was that BMD of any measured site was 2.5 standard deviations below peak BMD of same-sex people or 1–2.5 standard deviations below peak BMD, but at least one brittle fracture.

Statistical Analysis

Statistical analysis was carried out using SPSS version 13.0 statistical software (SPSS Inc., Chicago, IL, USA), and the results were expressed as mean ± standard deviation. All of the measurement data were analyzed by the *t*-test and ANOVA. Pearson's correlation coefficient was used to show the correlation. Multiple-factor analysis was carried out by using multiple stepwise regression and non-conditional logistic regression analysis. There was a statistically significant difference when $P < 0.05$, and highly significant difference when $P < 0.01$.

RESULTS

There was no significant difference in the duration of type 2 diabetes, ethnicity, smoking status, alcohol intake, case number, age and HDL-C among the three groups. Compared with the NC group, the BMI of the type 2 diabetes group was obviously increased (23.70 ± 3.22 kg/m^2 vs 22.9 ± 2.51 kg/m^2, $P < 0.05$), and the FPG, FINS and HbA1c of the type 2 diabetes and DO group were significantly increased ($P < 0.01$), which is shown

Table 1 | Comparisons of the clinical data among the normal control, type 2 diabetes and type 2 diabetes combined with osteoporosis groups

Group	Age (years)	BMI (kg/m^2)	HDL-C (mmol/L)	FPG (mmol/L)	PPG (mmol/L)	FINS (mIU/L)	HbA1c (%)
NC (n = 30)	76.12 ± 10.6	22.9 ± 2.51	1.35 ± 0.16	5.47 ± 0.71	7.02 ± 0.41	11.35 ± 6.17	5.42 ± 0.81
Type 2 diabetes (n = 35)	75.47 ± 12.1	23.7 ± 3.22*	1.27 ± 0.24	8.19 ± 3.03**	8.13 ± 1.32*	15.02 ± 9.06**	7.05 ± 1.04**
DO (n = 30)	76.32 ± 11.4	23.1 ± 2.74	1.31 ± 0.21	9.04 ± 3.12**	9.24 ± 1.07**	16.230 ± 8.2**	8.12 ± 1.28**

Data presented as mean ± standard deviation. *P < 0.05, compared with the normal control (NC) group; **P < 0.01, compared with NC group; BMI, body mass index; DO, type 2 diabetes combined with osteoporosis; FINS, fasting insulin; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; PPG, postprandial plasma glucose.

in Table 1. There was no significant difference in the BMI, FPG, PPG, FINS and HbA1c between the type 2 diabetes group and DO group (P > 0.05).

The differences in the BMD at the L1–4, Neck, Troch, Inter, Htot and Wards among the NC, type 2 diabetes and DO groups are shown in Table 2. The BMD at the L1-4, Neck, Troch, Inter, Htot and Wards for patients in the type 2 diabetes (P < 0.05) and DO groups (P < 0.01) were obviously decreased. Furthermore, the BMD at the L1–4, Neck, Troch, Inter and Htot for patients in the DO group were significantly lower than those in the type 2 diabetes group (P < 0.05).

Compared with the NC group, the HOMA-IR, E_2 and E_2/T of the type 2 diabetes group and the DO group were significantly increased (P < 0.05), whereas the ISI, T and SHBG were decreased very obviously compared with the NC group (P < 0.05). The HOMA-IR of the DO group was higher, whereas the ISI, T and SHBG were lower than those of the type 2 diabetes group (P < 0.05; Table 3). Furthermore, Pearson's correlation analysis was carried out with the level of serum testosterone as the dependent variable, and the age, BMI, HbA1c, FPG, FINS, ISI and HOMA-IR as independent variables. The analysis results showed that whether combined with osteoporosis or not, the level of serum testosterone was negatively correlated to the age, BMI, HbA1c, FPG and HOMA-IR (P < 0.05), whereas the level of serum testosterone was positively correlated to the FINS and ISI (P < 0.05). Furthermore, the level of serum testosterone was negatively correlated to the HOMA-IR (r = –0.496, –0.506; P < 0.05), and positively correlated to the FINS (r = 0.281, 0.292; P < 0.05) and ISI (r = 0.364, 0.403; P < 0.05) after adjusting the age and BMI (Table 4).

Multiple stepwise regression analysis was carried out using the REG procedure of the SPSS system with BMD as dependent variable, and the age, course, BMI, HDL-C, HbA1c, testosterone, FPG and HOMA-IR as independent variables. The analysis results showed that the age (r = 0.347, P < 0.05), BMI (r = 0.226, P < 0.05), FPG (r = 0.143, P < 0.05), HOMA-IR (r = 0.284, P < 0.05) and testosterone level (r = 0.277, P < 0.05) were the independent risk factors for BMD.

Table 2 | Comparisons of the bone mineral density at the L1–L4 lumbar spine, left femoral neck, greater trochanter, internal trochanter, total hip and Wards among the normal control, type 2 diabetes and type 2 diabetes combined with osteoporosis groups

Group	BMD (Neck; g/cm^2)	BMD (Troch; g/cm^2)	BMD (Inter; g/cm^2)	BMD (Htot; g/cm^2)	BMD (Ward; g/cm^2)	BMD (L1–4; g/cm^2)
NC	1.04 ± 0.23	0.79 ± 0.16	1.12 ± 0.23	1.08 ± 0.15	0.76 ± 0.16	1.29 ± 0.24
Type 2 diabetes	0.97 ± 0.22*	0.69 ± 0.14*	1.03 ± 0.19*	0.97 ± 0.17*	0.64 ± 0.23*	0.85 ± 0.37*
DO	0.84 ± 0.18**#	0.56 ± 0.18**#	0.96 ± 0.21**#	0.85 ± 0.14**#	0.62 ± 0.19**	0.74 ± 0.21**#

Data presented as mean ± standard deviation. *P < 0.05, compared with the normal control (NC) group; **P < 0.01, compared with the NC group; #P < 0.05, compared with the type 2 diabetes group; BMD, bone mineral density; Htot, total hip; Inter, internal trochanter; L1–4, L1–L4 lumbar spinal; Neck, left femoral neck; Troch, greater trochanter.

Table 3 | Comparisons of the homeostasis model assessment of insulin resistance and insulin sensitivity index among the normal control, type 2 diabetes and type 2 diabetes combined with osteoporosis groups

Group	HOMA-IR	ISI	E_2 (pg/mL)	T (ng/mL)	SHBG (ng/L)	E_2/T
NC	1.06 ± 0.51	–0.41 ± 0.48	41.43 ± 12.5	4.14 ± 0.92	11.24 ± 4.25	10.65 ± 4.26
Type 2 diabetes	1.48 ± 0.52**	–4.79 ± 0.76**	45.72 ± 13.1*	3.40 ± 0.84*	10.82 ± 4.62*	15.06 ± 6.03*
DO	1.82 ± 0.46**#	–5.32 ± 0.61**#	48.23 ± 11.8**	3.02 ± 0.91**#	9.03 ± 3.12**#	16.21 ± 5.49**

Data presented as mean ± standard deviation. *P < 0.05, compared with the normal control (NC) group; **P < 0.01, compared with the NC group; #P < 0.05, compared with the type 2 diabetes group; DO, type 2 diabetes combined with osteoporosis; E_2, estradiol; E_2/T, ratio of testosterone to estradiol; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; SHBG, sex hormone binding globulin; T, testosterone.

Table 4 | Correlations between the serum testosterone level and the fasting insulin, insulin sensitivity index, homeostasis model assessment of insulin resistance of the type 2 diabetes and type 2 diabetes combined with osteoporosis groups

	Type 2 diabetes group (n = 35)	DO group (n = 30)
FINS (mU/L)		
r-value	0.281	0.292
P-value	<0.05	<0.05
ISI		
r-value	0.364	0.403
P-value	<0.05	<0.05
HOMA-IR		
r-value	–0.496	–0.506
P-value	<0.05	<0.05

DO, type 2 diabetes combined with osteoporosis; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, insulin sensitivity index; *r*, correlation coefficients; T, testosterone.

DISCUSSION

In the previous study, we found that the BMD was negatively related to the age and course of patients, which indicated that the bone formation and bone transformation were reduced along with the age and course of patients. Therefore, elderly patients with long-term diabetes should pay particular attention to osteoporosis, and early prevention and treatment should be emphasized. Duarte *et al.*[11] found that hyperglycemic status is related to the bone turnover, and will eventually lead to osteoporosis.

Majima *et al.*[12] found that HbAlc is negatively related to the peripheral tissue BMD in the first 2 years of diabetes mellitus, which indicates that the morbidity of osteoporosis could be reduced by early control of hyperglycemia. In this current study, the HbA1c of the type 2 diabetes and DO groups was significantly increased, whereas the BMD was obviously decreased ($P < 0.01$), which was in accordance with the report of Majima *et al.*

Insulin resistance is defined as a state that requires more insulin to obtain the biological effects achieved by a lower amount of insulin in the normal state[13,14]. Insulin resistance is a key feature of some diseases, including type 2 diabetes, coronary artery disease and hypertension. Testosterone is the main male hormone, and could be gradually reduced with age. Over the past three decades, it has become apparent that testosterone plays a significant role in the maintenance of bone and muscle mass, in erythropoiesis, and in mental functions. However, testosterone is also a key player in glucose homeostasis and lipid metabolism[15]. Clinical studies suggest that low serum levels of testosterone in men are often associated with obesity, insulin resistance and metabolic compromise[16,17]. Reduced testosterone will lead to cardiovascular disease, such as diabetes mellitus, hypertension, metabolic disorder of serum lipids and atherosclerosis. It has been generally recognized that reduced testosterone is an independent risk factor for these diseases[18]. Pitteloud *et al.*[19] have found that reduced testosterone is related to the adverse metabolism condition, and could reduce mitochondrial function and insulin sensitivity, thus promoting the occurrence of the metabolic syndrome. In the present study, the HOMA-IR, E_2 and E_2/T of the type 2 diabetes group and DO group were significantly increased, whereas the ISI and T were decreased very obviously compared with the NC group.

Research on the clinical models constructed for androgen deprivation therapy of prostatic cancer have established the roles of testosterone in the regulation of glucose metabolism[20,21]. The results showed that insulin resistance occurred a few months after androgen deprivation therapy, and the incidence rates of hyperinsulinemia, hyperglycemia and metabolic syndrome were increased after long-term androgen deprivation therapy[22,23]. It has been reported that the reduced level of sex hormones was related to hyperglycemia, though the age, BMI and relevant factors were adjusted. The degree of hyperglycemia was directly associated with the duration of sex hormone suppression[24]. Studies have confirmed that the glycemic control, insulin resistance, obesity and osteoporosis of male type 2 diabetes patients with hypogonadism were improved after hormone replacement therapy[25]. Although testosterone replacement treatment has advantages for obesity, it could also obviously decrease insulin resistance according to randomized control trials[26]. Similarly, we found that the serum testosterone level of the type 2 diabetes group and DO group was negatively related to HOMA-IR. Some studies have shown that a low serum testosterone level might increase the development of cardiovascular disease, such as atherosclerosis, which might be partly as a result of low testosterone levels being associated with insulin resistance[26,27]. Furthermore, the serum testosterone level of the type 2 diabetes group and DO group was observed to be positively related to ISI in the present study. Migliaccio *et al.*[28] have reported that testosterone level was directly correlated with BMD at the lumbar and neck, whereas we found many factors including age, BMI, FPG, HOMA-IR and testosterone level were independent risk factors for BMD. However, there were some limitations to the present study. The correlations between the drugs used for the treatment of diabetes and BMD or testosterone levels were not considered. Furthermore, the diagnosis of osteoporosis was based on BMD in the present study, whereas it has recently been reported that patients with diabetes might develop fragility fractures regardless of BMD values or asymptomatic fractures[29,30]. In addition, the sample size of the collected cases in the present study was relatively small.

In conclusion, the reduced level of serum testosterone in elderly male type 2 diabetes patients with osteoporosis is responsible for insulin resistance, which might provide a novel therapeutic strategy for elderly male type 2 diabetes patients with complications. However, the problem of whether the changes in the level of serum testosterone could be used as an index of diabetic intervention treatment is worthy of attention, and needs to be further studied with a larger sample size.

DISCLOSURE

The authors declare no conflict of interest.

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