

# Research on the correlation of diabetes mellitus complicated with osteoporosis with lipid metabolism, adipokines and inflammatory factors and its regression analysis

Z. CHEN<sup>1</sup>, G.-H. ZHAO<sup>1</sup>, Y.-K. ZHANG<sup>1</sup>, G.-S. SHEN<sup>2</sup>, Y.-J. XU<sup>2</sup>, N.-W. XU<sup>1</sup>

<sup>1</sup>Department of Orthopedics, Changzhou 2<sup>nd</sup> People's Hospital Affiliated to Nanjing Medical University, Nanjing, Jiangsu Province, China

<sup>2</sup>Department of Orthopedics, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu Province, China

*Zi Chen and Guohui Zhao contributed equally*

**Abstract.** – **OBJECTIVE:** To investigate the correlation of type 2 diabetes mellitus (DM) complicated with osteoporosis with lipid metabolism, adipokines and inflammatory factors, and to define the risk factors via the multivariate regression analysis.

**PATIENTS AND METHODS:** A total of 80 patients with DM admitted into our hospital from November 2015 to November 2016 were enrolled, including 40 patients complicated with osteoporosis and 40 patients not complicated with osteoporosis. The levels of blood lipid, adipokines and inflammatory factors were compared; the correlations between bone mineral density (BMD) and total cholesterol (TC), adiponectin and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were analyzed; and multivariate Logistic regression analysis was performed for osteoporosis, hyperlipidemia, abnormal adipokine levels and body's inflammatory response.

**RESULTS:** The levels of serum lipid indexes, total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C), in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis. The level of high-density lipoprotein cholesterol (HDL-C) was significantly higher than that in patients complicated with osteoporosis. The levels of adipokines, adiponectin and visfatin, in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis. The levels of inflammatory factors, TNF- $\alpha$ , interleukin-6 (IL-6) and C-reactive protein (CRP), in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis. There were negative correlations between BMD and TC, adiponectin and TNF- $\alpha$ . Abnormal blood lipid, abnormal adipokine levels and elevated inflammatory factor levels were independent risk factors for osteoporosis.

**CONCLUSIONS:** Enhanced inflammatory response, abnormal blood lipid metabolism and abnormal changes in adipokines may increase the risk of osteoporosis in patients with diabetes mellitus.

Key Words:

Type 2 diabetes mellitus, Osteoporosis, Lipid metabolism, Adipokines, Inflammatory factors.

## Introduction

Type 2 diabetes mellitus (DM) is the most clinically common chronic disease at present<sup>1</sup>, whose intervention priority is the first- and second-level prevention, so the long-acting management and control measures should be combined to reduce the relevant risk factors, decrease the incidence, morbidity and death rates of diabetes mellitus<sup>2</sup>, and improve the prognosis of patients<sup>3</sup>. Osteoporosis is the most common orthopedic complicating disease in the middle-aged and aged people<sup>4</sup>, and its main clinical manifestations are chronic pain, pathological fractures, loss of height and spinal deformity<sup>5</sup>, which is mainly caused by the decreased bone tissue cell content in unit volume and the metabolic disorder of bone tissues. Osteoporosis often occurs in the elderly women<sup>6</sup>. With the social aging in China, the incidence rate of osteoporosis has been increased significantly, and the fracture is the most common and the most serious complication in osteoporosis patients<sup>7</sup>. Once the patients are complicated with diabetes mellitus, it is bound to seriously affect the recovery of patients and increase the likelihood of se-

rious complications<sup>8</sup>. To better clarify the related risk factors of diabetes mellitus complicated with osteoporosis and guide the clinical treatment, this study mainly investigated the influences of inflammatory factors, lipid metabolism and adipokines on patients.

## Patients and Methods

### Patients

A total of 80 patients with DM admitted into our hospital from November 2015 to November 2016 were enrolled, including 40 patients complicated with osteoporosis and 40 patients without complicating osteoporosis. All patients were diagnosed as DM via the clinical manifestation, blood glucose assay and glucose tolerance test, and diagnosed as osteoporosis via the detection of bone mineral density (BMD). Our work was approved by the Ethics Committee of Changzhou 2<sup>nd</sup> People's Hospital Affiliated to Nanjing Medical University (Nanjing, Jiangsu Province, China) and all patients signed the informed consent when enrolled. Patients with severe dysfunction of heart, lung, liver or kidney, complicated with mental disorders, coagulation dysfunction, malignant tumors, autoimmune diseases or defined infection, or those who refused to be enrolled, were excluded. According to whether patients were complicated with osteoporosis, they were divided into two groups with 40 cases in each group. In observation group, there were 17 males and 23 females aged 55-80 years old ( $68.9 \pm 1.8$ ) with the duration of DM of 11-40 years ( $25.4 \pm 2.7$ ) and standard deviation (SD) value of BMD of  $-2.3$ - $2.5$  ( $-1.3 \pm 0.1$ ). In the control group, there were 16 males and 24 females aged 55-80 years old ( $68.8 \pm 1.7$ ) with the duration of DM of 11-40 years ( $25.5 \pm 2.7$ ) and SD value of BMD of  $-2.3$ - $2.5$  ( $-1.4 \pm 0.1$ ). There were no statistically significant differences in gender, age, duration of DM and SD value of BMD between the two groups ( $p > 0.05$ ).

### Research Methods and Observation Indexes

After fasting for 8 h, 5 mL fasting elbow venous blood was taken from all subjects in the morning, and submitted for inspection. The levels of blood lipid, adipokines and inflammatory factors in patients with and without complicating osteoporosis were compared. The correlation between BMD and total cholesterol (TC), adiponectin and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were analyzed

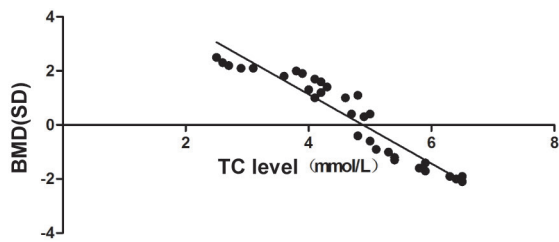
and multivariate Logistic regression analysis was performed for osteoporosis, hyperlipidemia, abnormal adipokine levels, and body's inflammatory response.

### Evaluation Methods

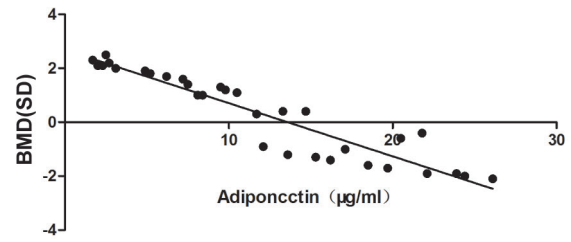
Diagnostic criteria of osteoporosis: it was mainly based on BMD value combined with the constitutional characteristics of Chinese population. Generally, BMD of the third lumbar vertebra that was 2 SD below the mean peak bone mass was deemed as osteoporosis, and the reference value of BMD of the third lumbar vertebra  $SD = 1.228 \text{ g/cm}^3$ . Detection of inflammatory cytokine levels: after fasting for 8 h, 5 mL fasting elbow venous blood was collected in the morning and submitted for inspection. TNF- $\alpha$  and IL-6 were measured via the double-antibody single-step sandwich assay. C-reactive protein (CRP) was detected via the turbidimetric immunoassay. The normal reference range of TNF- $\alpha$  in adults is 5-100 ng/L, the normal reference range of IL-6 in adults is 56.4-150.3 ng/L and the normal reference range of CRP in adults is  $\leq 10 \text{ mg/L}$ . Measurement of blood lipid levels: after fasting for 8 h, 5 mL fasting elbow venous blood was collected in the morning and submitted for inspection, followed by centrifugation at 3000 r/min for 5 min to obtain the upper serum. The levels of TC, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were detected via the electrochemiluminescence using the full-automatic biochemical detector (Beckmann, Brea, CA, USA). The normal reference range of TC in adults is below 3-5.2 mmol/L, that of TG is below 1.7 mmol/L, that of LDL-C is below 3.12 mmol/L and that of HDL-C is above 1.04 mmol/L. Detection of adipokine levels: after fasting for 8 h, 5 mL fasting elbow venous blood was collected in the morning and submitted for inspection, followed by detection via the enzyme linked immunosorbent assay (ELISA) using the full-automatic biochemical detector (Beckmann, Brea, CA, USA). The normal reference range of adiponectin in adults is 3.62-13.06  $\mu\text{g/mL}$  and that of visfatin is 65 pg/mL-103 pg/mL.

### Statistical Analysis

Statistical Product and Service Solutions 13.0 (SPSS Inc., Chicago, IL, USA) was used. Measurement data were presented as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ );  $t$ -test was used for the comparison of means between the two groups, and chi-square test was used for the comparison of



**Figure 1.** Analysis of correlation between BMD and TC: there was a negative correlation between BMD and TC ( $r = -0.9480, p < 0.0001$ ).



**Figure 2.** Analysis of correlation between BMD and adiponectin: there was a negative correlation between BMD and adiponectin ( $r = -0.9369, p < 0.0001$ ).

**Table I.** Comparisons of blood lipid levels in patients with and without complicating osteoporosis (mmol/L,  $\bar{x} \pm s$ ).

|  | TC      | TG      | LDL-C     | HDL-C     |
|--|---------|---------|-----------|-----------|
| Patients without complicating osteoporosis | 4.8±0.3 | 1.6±0.1 | 3.03±0.02 | 1.34±0.10 |
| Patients complicated with osteoporosis     | 6.2±0.2 | 2.3±0.2 | 3.98±0.11 | 0.98±0.08 |
| <i>t</i>                                   | 24.558  | 19.799  | 53.740    | 17.779    |
| <i>p</i>                                   | 0.000   | 0.000   | 0.000     | 0.000     |

ratios between the two groups.  $p < 0.05$  suggested that the difference was statistically significant.

## Results

### Comparisons of Blood Lipid, Adipokine and Inflammatory Factor Levels in Patients with and Without Complicating Osteoporosis

The levels of serum lipid indexes, TC, TG, and LDL-C, in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis ( $p < 0.05$ ); the level of HDL-C was significantly higher than that in patients complicated with osteoporosis ( $p < 0.05$ ) (Table I). The levels of adipokines, adiponectin and visfatin in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis ( $p < 0.05$ ) (Table II). The levels of inflammatory

factors, TNF- $\alpha$ , IL-6 and CRP, in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis ( $p < 0.05$ ) (Table III). Analysis of correlation between BMD and TC: there was a negative correlation between BMD and TC ( $r = -0.9480, p < 0.0001$ ) (Figure 1). Analysis of correlation between BMD and adiponectin: there was a negative correlation between BMD and adiponectin ( $r = -0.9369, p < 0.0001$ ) (Figure 2). Analysis of correlation between BMD and TNF- $\alpha$ : there was a negative correlation between BMD and TNF- $\alpha$  ( $r = -0.9383, p < 0.0001$ ) (Figure 3).

### Multivariate Logistic Regression Analysis of Osteoporosis, Hyperlipidemia, Abnormal Adipokine Levels and Body's Inflammatory Response

Multivariate Logistic regression analysis, with whether osteoporosis occurred as the dependent variable, and with the abnormal blood lipid, abnormal adipokine levels and elevated inflamma-

**Table II.** Comparisons of adipokine levels in patients with and without complicating osteoporosis ( $\bar{x} \pm s$ ).

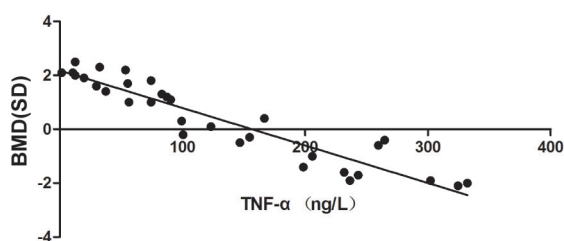
|  | Adiponectin ( $\mu\text{g/mL}$ ) | Visfatin ( $\text{pg/mL}$ ) |
|--|----------------------------------|-----------------------------|
| Patients without complicating osteoporosis | 10.6±0.9                         | 87.9±5.9                    |
| Patients complicated with osteoporosis     | 23.8±3.6                         | 133.1±12.4                  |
| <i>t</i>                                   | 22.498                           | 20.818                      |
| <i>p</i>                                   | 0.000                            | 0.000                       |

**Table III.** Comparisons of inflammatory factor levels in patients with and without complicating osteoporosis ( $\bar{x} \pm s$ ).

|  | TNF- $\alpha$ (ng/L) | IL-6 (ng/L)     | CRP (mg/L)     |
|--|----------------------|-----------------|----------------|
| Patients without complicating osteoporosis | 100.3 $\pm$ 5.1      | 79.0 $\pm$ 3.1  | 6.1 $\pm$ 0.2  |
| Patients complicated with osteoporosis     | 251.6 $\pm$ 11.0     | 125.0 $\pm$ 5.0 | 11.1 $\pm$ 1.5 |
| <i>t</i>                                   | 78.923               | 49.452          | 20.897         |
| <i>p</i>                                   | 0.000                | 0.000           | 0.000          |

**Table IV.** Multivariate Logistic regression analysis of osteoporosis, hyperlipidemia, abnormal adipokine level and body's inflammatory response.

|                               | B     | SE    | OR    | <i>p</i> |
|-------------------------------|-------|-------|-------|----------|
| Abnormal blood glucose        | 0.781 | 0.034 | 2.031 | 0.030    |
| Insulin resistance            | 0.685 | 0.025 | 1.824 | 0.023    |
| Elevated inflammatory factors | 0.719 | 0.031 | 1.992 | 0.036    |

**Figure 3.** Analysis of correlation between BMD and TNF- $\alpha$ : there was a negative correlation between BMD and TNF- $\alpha$  ( $r=-0.9383$ ,  $p<0.0001$ ).

tory factor levels as the independent variables, showed that the abnormal blood lipid, abnormal adipokine levels and elevated inflammatory factor levels were independent risk factors for osteoporosis (Table IV).

## Discussion

Fracture caused by the osteoporosis is one of the most serious complications of osteoporosis<sup>9</sup>, which belongs to the brittle fracture that causes severe fractures and even spontaneous fractures due to the minor injuries in daily life and activities<sup>10</sup>. In particular, the risk of fractures due to violence is significantly increased when the body falls from high levels<sup>11</sup>. The occurrence of this disease is often due to the less cortical bone and decreased bone density. In case of fracture, the internal fixation treatment has poor firmness, so internal fixation will be loose, thus leading to delayed fracture healing and even nonunion of fracture<sup>12</sup>. The recurrence rate of fracture in pa-

tients complicated with osteoporosis will be increased significantly. So osteoporotic fracture, as a serious threat to the physical and mental health of the elderly<sup>13</sup>, needs the clinical attention. Long-term increase in blood sugar in patients with diabetes mellitus will lead to the fat metabolism disorder, vascular endothelial cell damage, decreased sensitivity to insulin, fibrinolytic system dysfunction, increased inflammatory response and a series of other changes<sup>14</sup>. At the same time, it will also increase the osteolytic effect, further aggravating osteoporosis<sup>15</sup>. In this work, the correlation between the inflammatory response, blood lipid metabolism, adipokines and the diabetic patient complicated with osteoporosis, were investigated, and it was found that the levels of serum lipid indexes, TC, TG, and LDL-C, in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis, and the level of HDL-C was significantly higher than that in patients complicated with osteoporosis, suggesting that the blood lipid metabolism of diabetic patients complicated with osteoporosis is significantly abnormal. Also, the levels of adipokines, adiponectin and visfatin, in patients without complicating osteoporosis were significantly lower than those in patients complicated with osteoporosis, indicating that the levels of adipokines in diabetic patients complicated with osteoporosis are also significantly abnormal. At the same time, it was found that the levels of inflammatory factors, TNF- $\alpha$ , IL-6 and CRP, in patients without complicating osteoporosis, were significantly lower than those in patients complicated with osteoporosis, suggesting that the aseptic inflammatory response in diabetic pa-

tients complicated with osteoporosis is more significant. Moreover, research on the correlations between BMD and TC, adiponectin and TNF- $\alpha$ , showed that there were negative correlations between BMD and TC, adiponectin and TNF- $\alpha$ . Finally, multivariate logistic regression analysis of inflammatory response, blood lipid metabolism and adipokines suggested that the abnormal blood lipid, abnormal adipokine levels and elevated inflammatory factor levels are independent risk factors for osteoporosis. A large number of inflammatory cytokines will be produced in the body of patients with type 2 diabetes mellitus, and the levels of inflammatory factors in the body will be further increased if the osteoporosis is complicated<sup>16</sup>, maybe because increased inflammatory factor levels in the body of patients with diabetes mellitus<sup>17</sup> affect the process of bone metabolism, lower the blood calcium level and reduce the deposition of calcium salts in bone<sup>18</sup>, thus reducing BMD and increasing the risk of osteoporosis in patients<sup>19</sup>. Moreover, the long-term increase in blood glucose in patients with type 2 diabetes mellitus will also affect the fat metabolism in the body, leading to the dysfunction of adipocytes and abnormal adipokine levels, thus causing the bone metabolic disequilibrium and aggravating osteoporosis<sup>20</sup>.

## Conclusions

Enhanced inflammatory response, abnormal blood lipid metabolism, and abnormal changes in adipokines, may increase the risk of osteoporosis in patients with type 2 diabetes mellitus.

## Conflict of interest

The authors declare no conflicts of interest.

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