学 位 論 文 の 要 旨

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学位論文名	Association of Bone Mineral Density, Bone Turnover Markers, and Vertebral Fractures With All-Cause Mortality in Type 2 Diabetes Mellitus.
発表雑誌名	Calcified Tissue International
(巻, 初項～終項等, 年)	(in press)
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論 文 内 容 の 要 旨

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become an important problem worldwide due to the rapidly increasing number of patients and its association with high mortality. Accumulating evidence has shown that patients with T2DM have an increased risk of osteoporotic fracture independent of bone mineral density (BMD). Because osteoporotic fractures such as hip and vertebral fractures (VF) increase mortality in the general population, diabetes-related bone fragility may also be associated with mortality in patients with diabetes mellitus. However, no studies have investigated whether bone metabolism or the prevalence of osteoporotic fractures is involved in the mortality of patients with T2DM.

Osteoporosis is generally associated with accelerated bone turnover. Several previous studies showed bone turnover markers to be associated with mortality. However, there have been no reports on the association between bone turnover markers and mortality in T2DM patients. Several meta-analyses showed lower serum levels of osteocalcin, a bone formation marker, in patients with T2DM compared to those in non-diabetic subjects. It has been shown that osteocalcin has an endocrine function regulating glucose homeostasis and atherogenesis. We previously showed that serum osteocalcin was associated with insulin sensitivity and secretion and negatively associated with glucose levels, atherosclerosis parameters, and vascular calcification in patients with T2DM. Therefore, we hypothesized that lower serum osteocalcin levels may be associated with increased mortality in patients with T2DM.

In the present study, we thus examined the association of bone turnover markers, BMD, and the presence of VF with all-cause mortality in patients with T2DM.

MATERIALS AND METHODS

This is a historical cohort study investigating the association between bone parameters and the endpoint of all-cause mortality in patients with T2DM. Patients admitted to Shimane University Hospital for T2DM education and treatment from 1997 to 2009 were screened. According to the hospital records, 843 men and 667 women were admitted. Among them, the bone parameters of 441 men and 356 postmenopausal women were evaluated by measurements of bone turnover markers and BMD as well as lateral X-ray examination of the thoracic and lumbar spine (LS) to assess the presence of VF on admission. We excluded 58 men and 20 women because of diseases affecting bone metabolism. Then, we investigated patient survival or death by medical records and telephone surveys from 2013 to 2014. Unfortunately, we could not contact 161 men and 147 women. Finally, 411 patients (222 men and 189 postmenopausal women) were included in this study. To investigate the association of bone turnover markers with mortality, patients who received medication for osteoporosis (a man and 18 women) were omitted.

This study was approved by the institutional review board of Shimane University Faculty of Medicine (Study number 1814), and the requirement for informed patients consent was waived because no intervention and further examinations were performed.

RESULTS AND DISCUSSION

At the baseline, means of patients' age, duration of diabetes, and HbA1c were 66.6 years old, 11.1 years, and 8.7%, respectively. Means of T score at LS, femoral neck (FN), and one-third of the radius (1/3R) were -0.63, -1.06, and -2.07, respectively. Means of bone-specific alkaline phosphatase (BAP), osteocalcin, and urinary N-terminal cross-linked telopeptide of type-I collagen (uNTX) were 27.5 U/L, 5.8 ng/mL, and 40.8 nMBCE/mM/Cr, respectively. The numbers of patients with single and multiple VF were 88 and 55, respectively. The numbers of patients with grade 1, 2, and 3 VF were 68, 60, and 15, respectively. During the follow-up period of almost 7 years, we observed 37 and 19 deaths in men and women, respectively.

High and low levels of bone turnover markers were established according to the median levels of each marker. Unadjusted survival analyses indicated that women with lower osteocalcin levels had higher mortality than those with higher levels of osteocalcin (p=0.011), but the association was not significant in the overall population and men. In contrast, neither BAP nor uNTX was associated with mortality. In the Cox regression analysis adjusted for age, HbA1c, body mass index, duration of diabetes, and serum creatinine, systolic blood pressure, and

LDL-cholesterol, serum osteocalcin was significantly associated with mortality in women [hazard ratio (HR) 3.82, 95% confidence interval (CI) 1.01-14.46 per SD decrease, p=0.048]. The association remained significant even after adjustment for L-BMD. To our knowledge, the present study is the first to show that lower serum osteocalcin was associated with higher risk of mortality in patients with T2DM. Therefore, osteocalcin may play important roles in postmenopausal women with T2DM independently of BMD.

In the overall population, Cox regression analyses adjusted for confounding factors described above showed that absolute LS-BMD and FN-BMD, but not 1/3R-BMD, were significantly associated with mortality (HR 1.72, 95%CI 1.21-2.45 per SD decrease, p=0.002 and HR 1.53, 95%CI 1.03-2.27 per SD decrease, p=0.04). Furthermore, we categorized subjects into normal (1.0 $\leq$ T score), osteopenia (-2.5 < T score <-1.0), and osteoporosis (T score $\leq$-2.5). The adjusted Cox regression analysis revealed that T score $\leq$-2.5 at LS and FN was significantly and positively associated with mortality (HR 3.25, 95%CI 1.48-7.16, p=0.003 and HR 5.19, 95%CI 1.83-14.75, p=0.002). In men, the adjusted Cox regression analyses showed that T score $\leq$-2.5 at FN was significantly associated with mortality (HR 7.15, 95%CI 1.95-26.18, p=0.003). These findings suggest that reduction in BMD can predict the risk of mortality, especially in men with T2DM. Because previous studies showed that increased mortality after osteoporotic fracture is more prominent in men than in women, the significant association between FN-BMD and mortality might be observed in men in this study.

Finally, unadjusted survival and the adjusted Cox regression analyses showed that multiple VF and grade 3 VF were significantly associated with higher mortality (HR 2.93, 95%CI 1.42-6.02, p=0.004 and HR 7.64, 95%CI 2.13-27.42, p=0.002). In addition, the association between grade 3 VF and mortality remained significant after additional adjustment for BMD. Therefore, severe VF independent of diabetic status and reduced BMD may be involved in the increased mortality observed in patients with T2DM.

CONCLUSION

The present study is the first to show the association of reduced BMD and severe VF with increased all-cause mortality in patients with T2DM. Moreover, higher serum osteocalcin was significantly associated with decreased mortality in postmenopausal women with T2DM.