Association of bone mineral density, bone turnover markers, and vertebral fractures with all-cause mortality in type 2 diabetes mellitus

Short title: Osteoporosis and mortality in type 2 diabetes

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Abstract

Purpose: Patients with type 2 diabetes mellitus (T2DM) have an increased risk of fragility fracture. However, the association between diabetes-related osteoporosis and mortality in T2DM remains unknown. **Methods:** This historical cohort study assessed the endpoint of all-cause mortality in patients with T2DM. According to our hospital record, bone parameters were examined in 797 patients from 1997-2009. We excluded 78 because of diseases affecting bone metabolism and couldn't follow up 308 patients. Finally, in 411 patients, the associations of bone turnover markers, bone mineral density (BMD), and the prevalence of vertebral fractures with mortality were investigated by Cox regression analyses adjusted for confounding factors. **Results:** Of 411 patients, 56 died during the follow-up period of almost seven years. Cox regression analyses showed that reduced BMD at the lumbar spine (LS) and femoral neck (FN) (T-score ≤-2.5) and severe vertebral fractures were associated with higher mortality (hazard ratio [HR]=3.25, 95% confidence interval [CI] 1.48-7.16, p=0.003 for LS-T score ≤-2.5; HR=5.19, 95% CI 1.83-14.75, p=0.002 for FN-T score ≤-2.5; HR=2.93, 95% CI 1.42-6.02, p=0.004 for multiple vertebral fractures; HR=7.64, 95% CI 2.13-27.42, p=0.002 for grade 3 vertebral fracture). Separate analysis in men and women showed that decreased serum osteocalcin was associated with mortality in women (HR=3.82, 95% CI 1.01-14.46 per SD decrease, p=0.048). **Conclusions:** The present study is the first to show the association of reduced BMD and severe vertebral fractures with increased all-cause mortality in patients with T2DM. Moreover, higher serum osteocalcin was significantly associated with decreased mortality in women with T2DM.

Key words: type 2 diabetes mellitus, osteoporosis, osteocalcin, mortality, bone mineral density, vertebral fracture

Abbreviations:

T2DM, type 2 diabetes mellitus; BMD, bone mineral density; CTX, carboxyterminal telopeptide of type 1 collagen; P1NP, aminoterminal propeptide of type 1 collagen; BAP, bone-specific alkaline phosphatase; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen; CV, coefficients of variation; HbA1c, Hemoglobin A1c; L, lumbar spine; FN, femoral neck; 1/3R, one third of the radius; SD, standard deviation; HR, hazard ratio, 95% CI, 95% confidence interval; BMI, body mass index

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. Previous studies have shown that the presence of T2DM increases the risks of cardiovascular diseases [1], infection [2], and cancer [3], all of which are associated with increased mortality. Indeed, the adjusted relative risk of death was almost twice that in patients with diabetes mellitus compared to that of age-matched controls [4]. On the other hand, accumulating evidence has shown that patients with T2DM have an increased risk of osteoporotic fracture independent of bone mineral density (BMD) [5-7]. Because osteoporotic fractures such as hip and vertebral fractures increase mortality in the general population [8,9], 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 [10-14]. In patients with hip fractures, higher serum levels of carboxyterminal telopeptide of type 1 collagen (CTX), a marker of bone resorption, were associated with increased all-cause mortality, although a marker of bone formation, serum osteocalcin, was not [13]. Elderly patients with the highest quartiles of both serum CTX and aminoterminal propeptide of type 1 collagen (P1NP), another marker of bone formation, were significantly and independently more likely to die compared with other patients [10]. In contrast, several studies showed a U-shaped association of osteocalcin and CTX with mortality in elderly men aged 79-89 years [14] and patients at high cardiovascular risk referred for coronary angiography [11,12]. However, there have been no reports on the association between bone turnover markers and mortality in T2DM

patients.

Inhibited bone formation and low turnover of bone remodeling have also been suggested to be involved in diabetes-related bone fragility [15]. Several meta-analyses showed significantly lower serum levels of osteocalcin in patients with T2DM compared to those in nondiabetic subjects [16]. Osteocalcin is expressed and produced specifically in osteoblasts and is an endocrine hormone secreted by bone. Previous studies showed that osteocalcin knockout mice displayed obesity and impaired glucose tolerance due to decreased insulin secretion and sensitivity as well as inhibited adipocyte differentiation and adiponectin secretion [17]. In addition, several studies showed that the osteocalcin receptor is expressed in vascular cells [18] and that osteocalcin has beneficial anti-atherogenic effects on endothelial and vascular smooth muscle cells [19,20]. Indeed, we previously showed that serum osteocalcin levels were associated with insulin sensitivity and secretion [21] and negatively associated with glucose levels, atherosclerosis parameters, and vascular calcification in patients with T2DM [22-24]. Therefore, we hypothesized that lower serum osteocalcin levels may be associated with increased mortality in patients with T2DM.

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

Subjects and methods

Subjects

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 1997-2009 were screened. According to the hospital records, 843 men and 667 women were admitted. We consecutively examined bone parameters in patients with T2DM who admitted to our hospital for the treatment of T2DM except for having malignant diseases, infection, necessity of operation, and other special purposes. 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 to assess for the presence of vertebral fracture on admission. We excluded 58 men and 20 women with diseases including hyperthyroidism, hyperparathyroidism, hepatic dysfunction, growth hormone deficiency, and acromegaly because these diseases influence bone metabolism. We investigated patient survival or mortality by medical records and telephone surveys from 2013 to 2014, a median follow-up period of 80 and 83 months in men and women, respectively. Unfortunately, we were unable to contact 161 men and 147 women. Finally, 222 men and 189 postmenopausal women with T2DM were included in this study. This study was approved by the institutional review board of Shimane University Faculty of Medicine; the requirement for informed patient consent was waived because no intervention and further examinations were performed.

Biochemical measurements

After overnight fasting, blood and urine samples were collected on the second day after admission. Hemoglobin A1c (HbA1c) and serum creatinine levels were measured by standard biochemical methods as

previously reported [21-26]. HbA1c was determined by high-performance liquid chromatography. HbA1c values were estimated as NGSP (National Glycohemoglobin Standardization Program) equivalent values calculated by the formula: HbA1c (%) = HbA1c (JDS) (Japan Diabetes Society) (%) + 0.4%. Serum total osteocalcin and bone-specific alkaline phosphatase (BAP) levels were measured by radioimmunoassay and enzyme immune assay, respectively. The coefficients of variation (CV) of osteocalcin and BAP measurements were 5.5% and 6.9%, respectively. Urinary N-terminal cross-linked telopeptide of type-I collagen (uNTX) was measured by enzyme-linked immunosorbent assay with CV of 5.7%.

Radiography

Lateral X-ray films of the thoracic and lumbar spine were taken at the time of admission. The anterior, central, and posterior heights of each of the 13 vertebral bodies from Th4-L4 were measured. A patient was diagnosed with a vertebral fracture when at least one of the three vertebral height measurements decreased by >20% when compared to the height of the nearest uncompressed vertebral body. Grading of vertebral fracture was performed using Genant semiquantitative criteria [27]. VFs were classified as follows; grade 1, a reduction of 20-25%; grade 2, 25-40%; and grade 3, more than 40%.

BMD of the lumbar spine 2-4 (L), femoral neck (FN), and one-third of the radius (1/3R) were measured by dual-energy X-ray absorptiometry (QDR-4500; Hologic, Waltham, MA, USA). The CV (precision) of measurements of L-, FN-, and 1/3R-BMD by our methods were 0.9%, 1.7%, and 1.9%, respectively. T-scores indicate a deviation from the averaged BMD in sex-matched young Japanese normal reference mean, and Z-scores indicate a deviation from the averaged BMD in normal age- and sex-matched Japanese subjects in the standardized normal distribution.

137 Statistical analysis

138 Data were expressed as means ± standard deviation (SD). When bone turnover markers were
139 examined, we omitted the patients with treatments for osteoporosis. The statistical significance between
140 two groups was determined using Student's *t* and χ^2 tests. Kaplan-Meier curves, log-rank tests, and Cox
141 proportional hazard regression analyses were used to estimate the association between bone parameters
142 and the risk of mortality after adjusting for confounding factors. All analyses were performed using
143 StatView (Abacus Concepts, Berkeley, CA, USA). A $p < 0.05$ was considered statistically significant.

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Results

Subject baseline characteristics

The patient background characteristics are shown in Table 1; these parameters were compared between male and female subjects. Age, body mass index (BMI), Z-score at FN and 1/3R, and bone turnover markers were significantly lower in men than in women. Serum creatinine levels, absolute BMD, and T score at all sites, as well as the ratio of the presence of grades 1 and 2 vertebral fractures, were significantly higher in men than in women. We observed 37 and 19 deaths in men and women (cumulative mortality; 16.7% and 10.0%, respectively). The numbers of patients who had been taking insulin, sulfonylurea, metformin, and thiazolidines, respectively, were 41, 83, 32, and 24 men, and 59, 65, 37, and 17 women. A man took bisphosphonate, and 13 and 5 women took bisphosphonate and selective estrogen receptor modulator.

We then compared various parameters between dead and surviving patients (Table 2). In total, male, and female subjects, the dead patients were significantly older; the BMD, and LS and FN T scores were significantly lower in dead patients compared with survivors. In the overall subject population, the duration of diabetes, serum creatinine level, and the ratio of multiple and grade 3 vertebral fractures were significantly higher in dead patients than in survivors, while BMI, FN-Z score, and osteocalcin level were significantly lower in dead patients than in survivors. Among male subjects, serum creatinine levels were significantly higher in dead patients than in survivors, while 1/3R-T score was significantly lower in dead patients than in survivors. Among female subjects, the duration of diabetes, HbA1c level, and the ratio of multiple and grade 3 vertebral fractures were significantly higher in dead patients than in survivors, while 1/3R-BMD and 1/3R-T scores and serum osteocalcin level were significantly lower in dead patients than in survivors.

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168 Association between bone turnover markers and all-cause mortality

169 We examined the association between bone turnover markers and mortality risk only in those
170 patients who were not treated for osteoporosis (221 men and 171 women). High and low levels of bone
171 turnover markers were established according to the median levels of each marker. The median levels of
172 osteocalcin were 5.3 ng/mL for all subjects, 4.7 ng/mL for men, and 6.5 ng/mL for women. Unadjusted
173 survival analyses indicated that female patients with lower osteocalcin levels had higher mortality than
174 those with higher levels of osteocalcin ($p = 0.011$) (Fig. 1C), but the association was not significant in the
175 overall population and male subjects (Fig. 1A and B). In contrast, neither BAP nor uNTX was associated
176 with mortality in the total subject population, male, or female subjects (data not shown).

177 In the Cox regression analysis adjusted for age, HbA1c level, BMI, duration of diabetes, and serum
178 creatinine level, systolic blood pressure, and LDL-cholesterol, serum osteocalcin levels were significantly
179 associated with mortality in female subjects (hazard ratio [HR] = 3.82, 95% confidence interval [CI] =
180 1.01-14.46 per SD decrease, $p = 0.048$), but not the total population or male subjects (Table 3). The
181 association remained significant even after adjusting for LS-BMD (HR = 5.84, 95% CI 1.04-32.78, $p =$
182 0.045). In contrast, neither BAP nor uNTX were associated with mortality in the total population, male, or
183 female subjects.

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185 Association between BMD and all-cause mortality

186 In the total subject population, Cox regression analysis adjusted for age, gender, HbA1c level, BMI,
187 duration of diabetes, serum creatinine level, systolic blood pressure, LDL-cholesterol, and treatment for
188 osteoporosis showed that absolute LS-BMD and FN-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 = 0.040) (Table 4). Then, we divided the subjects into three categories, normal (1.0 ≤ T-score), osteopenia (-2.5 < T-score < -1.0), and osteoporosis (T-score ≤ -2.5), according to World Health Organization (WHO) osteoporosis categorization (28). Unadjusted survival analyses indicated that the total population and female subjects with LS-T scores ≤ -2.5 had higher mortality compared with those with normal LS-T scores in ($p<0.001$ and $p<0.001$), and that the total population, male, and female subjects with FN-T scores ≤ -2.5 had higher mortality compared with those with normal FN-T scores ($p < 0.001$, $p < 0.001$, and $p = 0.033$, respectively) (Fig. 2). Moreover, Cox regression analysis adjusted for age, gender, HbA1c level, BMI, duration of diabetes, and serum creatinine level, systolic blood pressure, LDL-cholesterol, and treatment for osteoporosis revealed that LS-T score ≤ -2.5 or FN-T score ≤ -2.5 were significantly and positively associated with mortality in the total subjects (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, respectively). In contrast, 1/3R-BMD was not associated with mortality in the unadjusted survival analyses (data not shown) and adjusted Cox regression.

In men, the adjusted Cox regression analyses showed that FN-T score ≤ -2.5 was significantly associated with mortality (HR = 7.15, 95% CI 1.95-26.18, p = 0.003), and absolute FN-BMD was tended to be associated with mortality (HR = 1.50, 95% CI = 0.97-2.32 per SD decrease, p = 0.069). In contrast, neither BMD nor T-score at LS, FN, and 1/3R categories were associated with mortality in women in adjusted Cox regression analyses.

Association between vertebral fractures and all-cause mortality

Finally, we examined the association between the severity of vertebral fracture and mortality. Unadjusted survival analyses indicated that patients with multiple vertebral fractures had higher mortality compared with those without vertebral fractures in the total population and female subjects ($p < 0.001$ and $p < 0.001$, respectively) (Fig. 3A and C), but not male subjects (Fig. 3B). Moreover, patients with grade 3 vertebral fracture had higher mortality compared with those without vertebral fractures in the total population and female subjects ($p = 0.002$ and $p < 0.001$, respectively) (Fig. 3D and F). In Cox regression analysis adjusted for age, gender, HbA1c level, BMI, duration of diabetes, serum creatinine level, systolic blood pressure, LDL-cholesterol, and treatment for osteoporosis, multiple vertebral fractures were significantly and positively associated with mortality in the total population (HR = 2.93, 95% CI = 1.42-6.02, $p = 0.004$) (Table 5). Cox regression analysis adjusted for the confounding factors described above revealed grade 3 vertebral fracture to be significantly and positively associated with mortality in the total subjects (HR = 7.64, 95% CI = 2.13-27.42, $p = 0.002$) (Table 5). Furthermore, the association remained significant even after adjusting for L-BMD, FN-BMD, and 1/3R-BMD (HR = 6.89, 95% CI = 1.93-24.54, $p = 0.003$, HR = 5.39, 95% CI = 1.43-20.33, $p = 0.013$, and HR = 6.87, 95% CI = 1.82-26.01, $p = 0.005$, respectively).

Discussion

Several studies have examined the association of serum osteocalcin levels with mortality. Gulin et al. showed that serum osteocalcin levels were not associated with one-year all-cause mortality in 236 patients (59 males) with hip fracture, although high levels of a bone resorption marker were significantly associated with mortality [13]. However, Lerchbaum et al. showed a U-shaped association of serum osteocalcin with all-cause mortality in men and women referred for coronary angiography [11,12]. Yeap et al. also reported that the highest and lowest quintiles of serum osteocalcin levels showed a significant increase in all-cause mortality in older men aged 70-89 years [14]. These findings suggest that higher and lower levels of serum osteocalcin may be associated with mortality in elderly subjects at high cardiovascular risk. Although the underlying mechanism of the association between osteocalcin and mortality risk is unclear, the association appears to depend on the background characteristics. However, no studies have examined the effects of serum osteocalcin level on mortality risk in patients with T2DM. To our knowledge, the present study is the first to show that lower serum osteocalcin levels were associated with higher risk of all-cause mortality in postmenopausal women with T2DM. Moreover, the association between osteocalcin level and the mortality rate was significant even after adjusting for BMD, suggesting that the effects of osteocalcin on mortality risk are independent of bone mass.

Although we tested the association of osteocalcin tertile with mortality in female subjects, we did not observe a U-shaped association of serum osteocalcin with mortality (data not shown). As previous studies have shown lower serum osteocalcin levels in T2DM than in persons without T2DM [16], the serum osteocalcin levels of the participants in the current study were lower compared with those in previous studies [11,12,14]. This may explain the differences in association curves between previous studies and ours. Furthermore, the previous studies did not examine bone formation markers other than

serum osteocalcin. The present study observed no association between BAP or uNTX and mortality; therefore, osteocalcin may play important roles in T2DM independently of bone formation and turnover.

Since previous studies have reported different effects of osteocalcin on sex hormones [29,30], analysis of the results of clinical studies on osteocalcin and mortality should separately consider men and women in order to avoid such sex-related differences. The findings of the current study suggest that serum osteocalcin may play important roles in the prognosis of women with T2DM. In contrast, serum osteocalcin was not associated with mortality risk in men with T2DM. Thus, there may be sex differences in the association in patients with T2DM. There are no clear reasons why serum osteocalcin was not associated with the risk of mortality in men with T2DM in this study. Other researchers and we previously showed serum osteocalcin to be positively associated with serum adiponectin in women, but not men [26,31,32]. As adiponectin has anti-diabetic, anti-atherogenic, and anti-tumor effects [31-35], the effects of osteocalcin on adiponectin expression may be more significant in female patients with T2DM. Moreover, previous studies have shown that osteocalcin enhances testosterone secretion from Leydig cells in men [29]. Indeed, we previously reported a significant positive association between serum osteocalcin and free testosterone levels in men with T2DM [36]. However, it has no effect on estrogen expression because ovaries lack its receptor. Differences in the effects of osteocalcin on sex hormones may be another possible explanation. However, to determine the association between osteocalcin and mortality in patients with T2DM, it is necessary to perform further large-scale studies.

On the other hand, we found that the reduction in BMD was a significant predictor of the risk of mortality in patients with T2DM, especially in men. Although patients with T2DM show no BMD reduction, there is an increased risk of hip fracture [6,7]. These findings suggest that deterioration of bone quality is an important factor in the etiology of diabetes-related bone fragility. Therefore, T2DM patients

with both impaired bone quality as well as decreased BMD may be at extremely high risk of fracture. FN-BMD may be more accurate, especially in elderly patients compared to L-BMD because of the lack of accuracy in systematic measurements due to irregularities in the spinal elements. In addition, a higher frequency of arterial calcification in the aorta could directly interfere with BMD acquisition in the lumbar spine, especially in patients at high risk of cardiovascular diseases such as those with T2DM. Indeed, atherosclerosis parameters are negatively associated with FN-BMD, but not L-BMD, in men with T2DM [37]. Therefore, the WHO did not recommend the measurement of L-BMD when developing the absolute risk score for osteoporotic fractures [38]. The results of the present study suggest that measurement of FN-BMD may be more accurate than that of L-BMD for assessing mortality risk in patients with T2DM. Although it is unknown why the association between FN-BMD and mortality is more pronounced in men, there may exist sex differences. Because previous studies have shown that the increased mortality after hip fractures is more prominent in men than in women [39,40], lower FN-BMD was significantly associated with mortality in men in this study. However, further studies are needed to clarify the sex differences.

Previous studies have shown that vertebral fracture increases mortality [39]. We previously demonstrated an increased risk of vertebral fracture in patients with T2DM [7]. The present study revealed that the presence of severe vertebral fractures such as multiple and grade 3 fractures is associated with increased mortality in patients with T2DM independent of age, duration of diabetes, HbA1c levels, BMI, and renal function. In addition, the association between grade 3 vertebral fracture and mortality remained significant after additional adjustment for BMD. Therefore, vertebral fracture independent of diabetic status and associated with impaired bone quality may be involved in the increased mortality observed in patients with T2DM.

The present study had several limitations. First, the sample size was not large enough to make definite conclusions. Second, we analyzed only those subjects who visited Shimane University Hospital, a tertiary center for evaluation or treatment of T2DM. Therefore, the patients enrolled in this study might have relatively severe disease. Third, we could not follow up several patients. Therefore, some patients lost to follow-up may have died. Fourth, non-diabetic control subjects were not examined in this study. Therefore, we can't compare the contribution of BMD reduction, low osteocalcin level, and the presence of vertebral fracture to the mortality between T2DM and non-diabetics. Fifth, the information regarding the treatments for osteoporosis and diabetes were not available in this study. Sixth, we diagnosed vertebral fracture according to height-based criteria [27] in this study. Therefore, grade 1 deformities might be non-fractural in their etiology. Therefore, we performed subgroup analysis about the association between the number of grade 1 fractures and mortality after excluding the patients with grade 2 and 3. Cox proportional hazard regression analyses adjusting for confounding factors (model 5) showed a significant association of multiple grade 1 fractures with all-cause mortality in total subjects (HR = 5.65, 95% CI = 1.51-21.19, p = 0.010). Finally, we could not analyze the causes of death such as cardiovascular, infection, and malignant diseases. In conclusion, we found for the first time that lower serum osteocalcin levels, reduced BMD, and severe vertebral fractures were associated with increased all-cause mortality in patients with T2DM. Moreover, higher serum osteocalcin was significantly associated with decreased mortality in women with T2DM. Because this is a historical cohort study, there are several limitations such as the sample size was limited and loss to follow-up. Thus, further large-scale longitudinal studies are necessary.

Author contributions

H.M. researched data and wrote manuscript. I.K. researched data and wrote/reviewed/edited manuscript. T.S. contributed to discussion and reviewed/edited manuscript.

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Disclosure Summary

Hitomi Miyake, Ippei Kanazawa, and Toshitsugu Sugimoto declare that they have no conflicts of interest.

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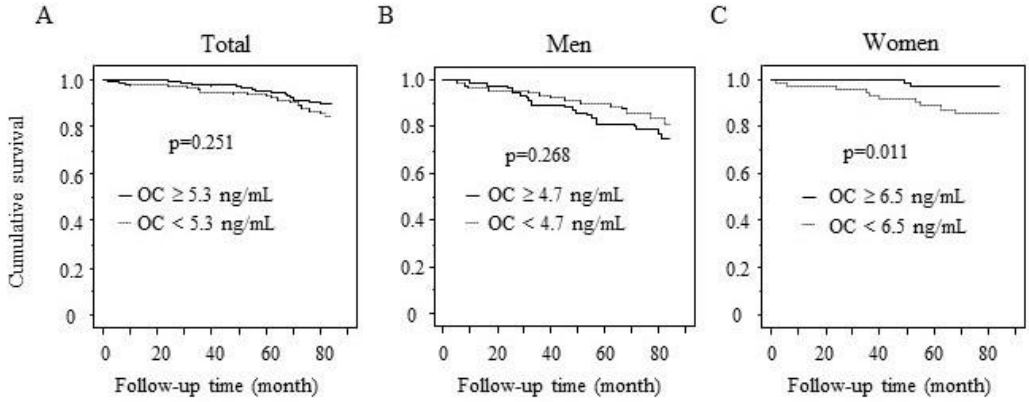
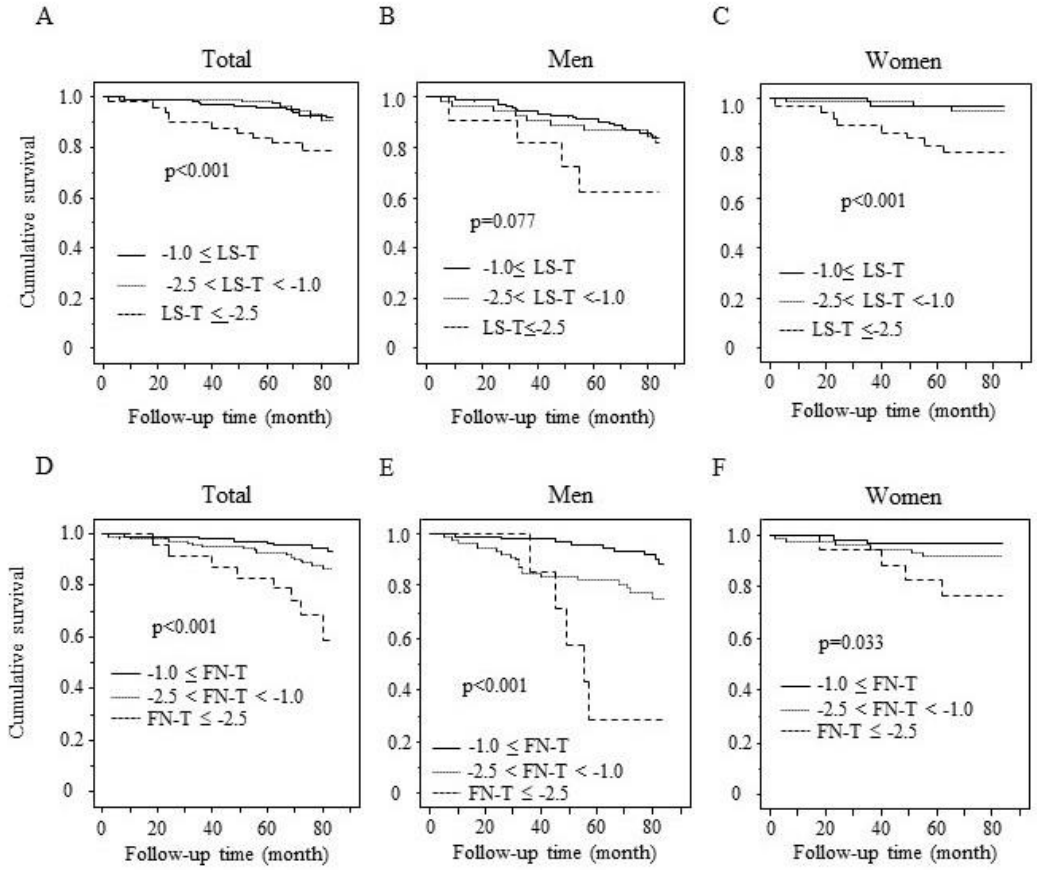
Supplemental Figure 1



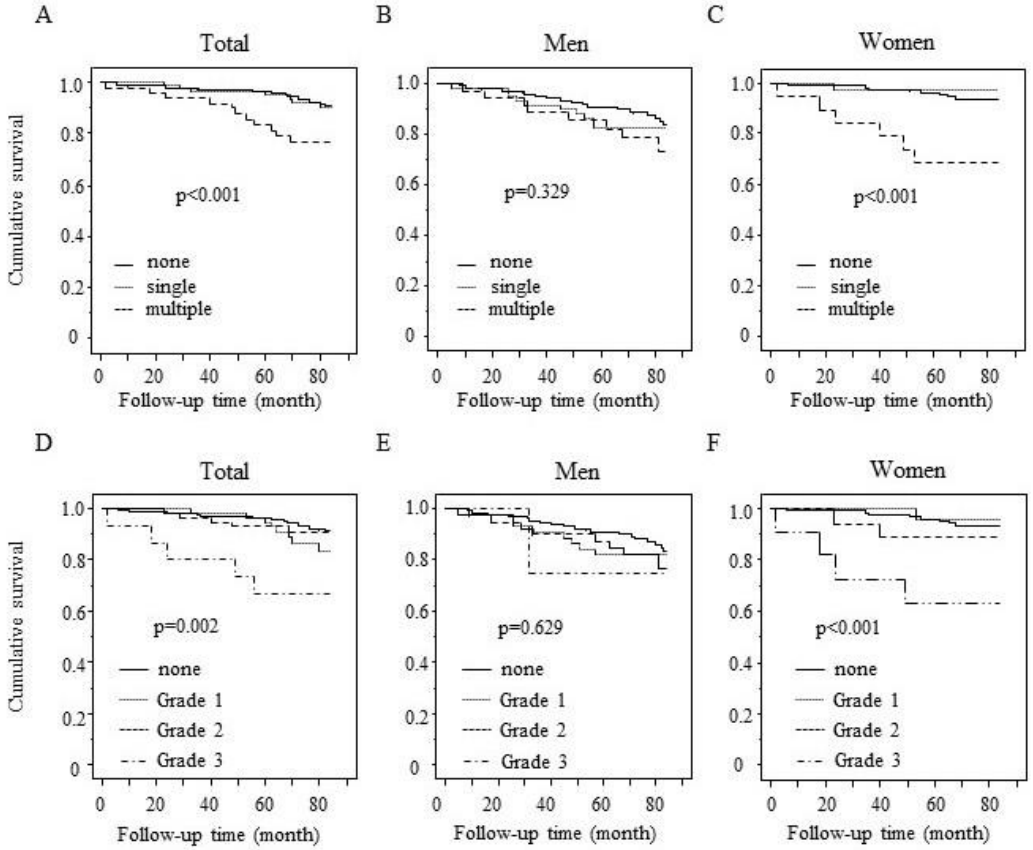
Survival curves of higher and lower serum osteocalcin levels in the total population (A) and male (B) and female subjects (C) with type 2 diabetes mellitus

Supplemental Figure 2



Survival curves by T score at LS in the total population (A) and male (B) and female subjects (C) as well as at FN in total (D), male (E), and female subjects (F) with type 2 diabetes mellitus

Supplemental Figure 3



Survival curves by the number and grade of vertebral fractures in the total population (A and D) and male (B and E) and female subjects (C and F) with type 2 diabetes mellitus

Table 1 Baseline characteristics

	Total	Men	Women	p value
Number of subjects	411	222	189	
Age (years)	66.6 ± 9.5	64.7 ± 9.4	67.6 ± 9.4	0.002
Duration of diabetes (years)	11.1 ± 10.0	10.4 ± 10.0	12.2 ± 10.0	0.057
BMI (kg/m^2)	23.9 ± 4.2	23.4 ± 4.1	24.6 ± 4.3	0.005
HbA1c (%)	8.7 ± 2.1	8.7 ± 2.1	8.7 ± 2.2	0.826
Serum creatinine (mg/dL)	0.73 ± 0.22	0.82 ± 0.23	0.62 ± 0.17	<0.001
LS BMD (g/cm^2)	0.96 ± 0.20	1.03 ± 0.19	0.88 ± 0.19	<0.001
T score	-0.63 ± 1.72	-0.14 ± 1.55	-1.21 ± 1.73	<0.001
Z score	0.53 ± 1.16	0.45 ± 1.09	1.25 ± 0.09	0.151
FN BMD (g/cm^2)	0.71 ± 0.13	0.76 ± 0.12	0.64 ± 0.12	<0.001
T score	-1.06 ± 1.03	-0.85 ± 0.95	-1.33 ± 1.08	<0.001
Z score	0.37 ± 1.05	0.25 ± 1.00	1.10 ± 0.09	0.018
1/3R BMD (g/cm^2)	0.62 ± 0.11	0.70 ± 0.07	0.53 ± 0.09	<0.001
T score	-2.07 ± 1.57	0.07 ± 1.38	-2.59 ± 1.65	<0.001
Z score	0.01 ± 1.46	-0.51 ± 1.33	0.67 ± 1.36	<0.001
BAP (U/L)	27.5 ± 9.7	25.0 ± 7.8	30.8 ± 11.0	<0.001
Osteocalcin (ng/mL)	5.8 ± 2.7	5.0 ± 2.6	6.8 ± 2.6	<0.001
uNTx (nMBCE/mM/Cr)	40.8 ± 24.7	33.2 ± 16.8	50.8 ± 29.5	<0.001
Number of vertebral fractures				
none	268 (65.2%)	133 (59.9%)	135 (71.4%)	
single	88 (21.4%)	54 (24.3%)	34 (18.0%)	0.056
multiple	55 (13.4%)	35 (15.8%)	20 (10.6%)	0.058
Grade of vertebral fracture				
grade1	68 (16.5%)	44 (19.8%)	24 (12.7%)	0.026
grade2	60 (14.6%)	41 (18.5%)	19 (10.1%)	0.009
grade3	15 (3.6%)	4 (1.8%)	11 (5.8%)	0.083
Death	56 (13.6%)	37 (16.7%)	19 (10.1%)	0.051

BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; 1/3R, one-third of the radius; BAP, bone-specific alkaline phosphatase; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen

Table 2 Comparison of demographic and biochemical parameters between dead patients and survivors

	Total		Men		Women	
	Alive	Dead	Alive	Dead	Alive	Dead
Number of subjects	355	56	185	37	170	19
Men	187 (52.7%)	37 (66.1%)				
Age (years)	64.9 ±9.2	73.4 ± 7.7 ***	63.4 ± 9.3	71.2 ± 6.9 ***	66.5 ± 9.0	77.2 ± 7.9 ***
Duration of diabetes (years)	10.7 ±9.7	13.7 ± 11.6 *	10.2 ± 9.7	11.6 ± 11.3	11.6 ± 9.6	17.9 ± 11.7 *
BMI (kg/m²)	24.2 ±4.3	22.5 ± 3.6 **	23.7 ± 4.2	22.3 ± 3.3	24.7 ± 4.3	23.2 ± 4.3
HbA1c (%)	8.6 ±2.1	9.2 ± 2.4	8.6 ± 2.0	8.8 ± 2.3	8.5 ± 2.1	10.0 ± 2.6 **
Serum creatinine (mg/dL)	0.72 ±0.21	0.80 ± 0.30 *	0.80 ± 0.21	0.92 ± 0.31 **	0.63 ± 0.17	0.60 ± 0.12
LS BMD (g/cm²)	0.97 ±0.20	0.91 ± 0.21 *	1.04 ± 0.19	0.97 ± 0.17 *	0.89 ± 0.19	0.77 ± 0.22 *
T score	-0.55 ±1.70	-1.15 ± 1.77 *	-0.04 ± 1.56	-0.64 ± 1.42 *	-1.11 ± 1.68	-2.19 ± 1.99 *
Z score	0.57 ±1.17	0.26 ± 1.09	0.49 ± 1.11	0.27 ± 0.96	0.66 ± 1.23	0.23 ± 1.35
FN BMD (g/cm²)	0.71 ±0.13	0.65 ± 0.15 **	0.77 ± 0.12	0.70 ± 0.11 ***	0.65 ± 0.11	0.56 ± 0.17 **
T score	-0.98 ±0.98	-1.58 ± 1.22 ***	-0.74 ± 0.91	-1.36 ± 0.97 ***	-1.25 ± 0.99	-2.08 ± 1.59 **
Z score	0.43 ±1.00	0.00 ± 1.27 **	0.31 ± 0.99	-0.03 ± 1.02	0.57 ± 1.00	0.07 ± 1.75
1/3R BMD (g/cm²)	0.62 ±0.11	0.62 ± 0.11	0.70 ± 0.06	0.67 ± 0.08 *	0.53 ± 0.09	0.48 ± 0.06 *
T score	-2.00 ±1.54	-2.49 ± 1.70	-1.57 ± 1.28	-2.11 ± 1.73 *	-2.50 ± 1.67	-3.45 ± 1.21 *
Z score	0.05 ±1.40	-0.26 ± 1.78	-0.49 ± 1.19	-0.60 ± 1.83	0.67 ± 1.36	0.62 ± 1.33
BAP (U/L)	27.7 ±9.5	26.4 ± 11.2	24.9 ± 7.4	25.3 ± 9.8	31.0 ± 10.6	29.4 ± 14.4
Osteocalcin (ng/mL)	5.9 ±2.8	5.1 ± 2.4	4.9 ± 2.5	5.2 ± 2.6	7.0 ± 2.6	5.1 ± 2.0 *
uNTx (nMBCE/mM/Cr)	40.2 ±24.1	44.3 ± 28.0	32.1 ± 16.9	38.4 ± 15.8	50.0 ± 27.8	58.7 ± 43.7
Number of vertebral fracture						
none	238 (67.0%)	30 (53.6%)	114 (61.6%)	19 (51.4%)	124 (72.9%)	11 (57.9%)
single	78 (22.0%)	10 (17.9%)	45 (24.3%)	9 (24.3%)	33 (19.4%)	1 (5.3%)
multiple	39 (11.0%)	16 (28.6%) ***	26 (14.1%)	9 (24.3%)	13 (7.6%)	7 (36.8%) ***
Grade of vertebral fracture						
grade1	59 (16.6%)	9 (16.1%)	36 (19.5%)	8 (21.6%)	23 (13.5%)	1 (5.3%)
grade2	48 (13.5%)	12 (21.4%)	32 (17.3%)	9 (24.3%)	16 (9.4%)	3 (15.8%)
grade3	10 (2.8%)	5 (8.9%) *	3 (1.6%)	1 (2.7%)	7 (4.1%)	4 (21.1%) **

BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; 1/3R, one-third of the radius; BAP, bone-specific alkaline phosphatase; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen

*; $p<0.05$, **; $p<0.01$, ***; $p<0.001$

Table 3 Hazard ratios stratified by bone turnover markers

	Total			Men			Women		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
BAP									
Model 1	0.96	0.70-1.33	0.793	0.92	0.64-1.31	0.630	1.00	0.56-1.81	0.988
Model 2	0.98	0.71-1.36	0.893	0.92	0.64-1.31	0.631	1.18	0.62-2.24	0.621
Model 3	1.04	0.74-1.45	0.854	0.89	0.63-1.27	0.526	1.70	1.07-1.31	0.216
Model 4	1.03	0.74-1.43	0.883	0.88	0.63-1.24	0.468	1.54	0.63-3.78	0.343
Osteocalcin									
Model 1	1.21	0.85-1.70	0.293	1.02	0.72-1.46	0.895	**3.13**	**1.13-8.66**	**0.028**
Model 2	1.13	0.79-1.60	0.511	1.00	0.70-1.43	0.999	**3.13**	**1.09-9.00**	**0.034**
Model 3	1.19	0.82-1.73	0.366	1.15	0.77-1.73	0.497	3.00	0.96-9.39	0.059
Model 4	1.19	0.82-1.73	0.370	1.15	0.76-1.74	0.496	**3.82**	**1.01-14.46**	**0.048**
uNTx									
Model 1	0.81	0.62-1.04	0.104	0.76	0.56-1.03	0.080	0.89	0.58-1.36	0.581
Model 2	0.80	0.62-1.05	0.109	0.75	0.55-1.03	0.074	1.05	0.65-1.70	0.844
Model 3	0.83	0.63-1.10	0.208	0.79	0.55-1.14	0.211	1.30	0.69-2.45	0.420
Model 4	0.83	0.99-1.03	0.203	0.81	0.55-1.19	0.283	1.57	0.83-2.98	0.164

Cox proportional hazard regression models were performed with all-cause mortality as a dependent variable.
Model 1; adjusted for age (plus gender for total subjects)
Model 2; adjusted for model 1 plus HbA1c
Model 3; adjusted for model 2 plus BMI, duration of diabetes, and serum creatinine
Model 4: adjusted for model 3 plus systolic blood pressure and LDL-C

Unit of change; Standard deviation per decrease.
HR, hazard ratio; CI, confidential interval; BAP, bone-specific alkaline phosphatase; uNTX, urinary N-terminal cross-linked telopeptide of type-I collagen

Table 4 Hazard ratios stratified by bone mineral density

		Total			Men			Women		
		HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
LS BMD	Model 1	**1.75**	**1.27-2.40**	**<0.001**	**1.45**	**1.02-2.07**	**0.039**	**2.17**	**1.18-4.01**	**0.013**
	Model 2	**1.72**	**1.25-2.36**	**<0.001**	**1.46**	**1.02-2.09**	**0.038**	**1.89**	**1.01-3.51**	**0.046**
	Model 3	**1.59**	**1.14-2.20**	**0.005**	1.29	0.89-1.86	0.178	1.45	0.68-3.12	0.337
	Model 4	**1.65**	**1.17-2.32**	**0.004**	1.28	0.88-1.85	0.196	1.29	0.59-2.80	0.521
	Model 5	**1.72**	**1.21-2.45**	**0.002**	1.31	0.90-1.90	0.165	1.63	0.67-3.99	0.264
FN BMD	Model 1	**1.70**	**1.17-2.38**	**0.005**	**1.64**	**1.12-2.41**	**0.011**	1.43	0.76-2.69	0.271
	Model 2	**1.61**	**1.13-2.30**	**0.009**	**1.67**	**1.13-2.47**	**0.011**	1.12	0.58-2.17	0.727
	Model 3	**1.50**	**1.02-2.21**	**0.044**	**1.56**	**1.01-2.40**	**0.045**	0.78	0.36-1.69	0.531
	Model 4	**1.52**	**1.03-2.25**	**0.040**	1.52	0.99-2.34	0.058	0.79	0.37-1.66	0.529
	Model 5	**1.53**	**1.03-2.27**	**0.040**	1.50	0.97-2.32	0.069	0.82	0.38-1.73	0.507
1/3R BMD	Model 1	1.02	0.64-1.64	0.912	1.05	0.73-1.53	0.789	1.18	1.03-1.22	0.645
	Model 2	0.99	0.98-1.61	0.983	1.06	0.73-1.55	0.744	1.11	0.53-2.35	0.778
	Model 3	0.93	0.53-1.62	0.800	1.07	0.70-1.63	0.769	1.16	0.47-2.85	0.750
	Model 4	0.92	0.53-1.59	0.763	1.02	0.67-1.56	0.933	1.00	0.38-2.60	0.999
	Model 5	0.90	0.52-1.56	0.710	0.99	0.64-1.53	0.968	0.99	0.38-2.58	0.826
LS-T score										
-1.0 ≤		1.00			1.00			1.00		
< -1.0, -2.5 <	Model 1	1.39	0.68-2.83	0.363	1.41	0.64-3.14	0.394	1.54	0.26-9.34	0.636
	Model 2	1.47	0.72-2.99	0.287	1.42	0.64-3.16	0.385	1.72	0.28-10.42	0.555
	Model 3	1.31	0.63-2.70	0.473	1.11	0.48-2.55	0.814	0.95	0.13-6.95	0.963
	Model 4	1.33	0.64-2.78	0.449	1.11	0.47-2.62	0.803	1.00	0.14-7.32	0.997
	Model 5	1.33	0.64-2.79	0.448	1.19	0.50-2.83	0.687	1.45	0.16-13.18	0.740
≤ -2.5	Model 1	**2.95**	**1.46-5.95**	**0.003**	2.42	0.82-7.10	0.108	5.96	1.26-28.27	0.025
	Model 2	**2.99**	**1.44-6.17**	**0.003**	2.54	0.86-7.56	0.093	5.08	1.04-24.90	0.045
	Model 3	**2.66**	**1.25-5.66**	**0.011**	1.70	0.54-5.40	0.367	4.11	0.68-24.68	0.122
	Model 4	**2.97**	**1.36-6.47**	**0.006**	1.68	0.52-5.45	0.386	3.38	0.56-20.42	0.185
	Model 5	**3.25**	**1.48-7.16**	**0.003**	1.81	0.56-5.91	0.323	4.97	0.69-35.70	0.111
FN-T score										
-1.0 ≤		1.00			1.00			1.00		
< -1.0, -2.5 <	Model 1	2.04	0.99-4.22	0.054	2.16	0.96-4.85	0.063	0.84	0.16-4.55	0.842
	Model 2	**2.11**	**1.02-4.35**	**0.043**	2.10	0.93-4.72	0.073	0.94	0.17-5.25	0948
	Model 3	1.64	0.77-3.51	0.200	1.71	0.72-4.07	0.222	0.90	0.16-4.93	0.903
	Model 4	1.66	0.78-3.54	0.191	1.71	0.72-4.05	0.225	1.53	0.22-10.52	0.667
	Model 5	1.55	0.72-3.33	0.267	1.62	0.68-3.89	0.278	1.01	0.14-7.15	0.989
≤ -2.5	Model 1	**5.66**	**2.20-14.56**	**<0.001**	**7.15**	**2.27-22.51**	**<0.001**	2.16	0.36-12.90	0.400
	Model 2	**5.38**	**2.01-14.37**	**<0.001**	**8.03**	**2.48-25.93**	**0.001**	1.49	0.21-10.35	0.688
	Model 3	**4.92**	**1.74-13.86**	**0.003**	**7.19**	**2.03-25.50**	**0.002**	0.54	0.05-5.94	0.618
	Model 4	**4.94**	**1.74-13.99**	**0.003**	**6.85**	**1.88-24.86**	**0.004**	0.59	0.05-7.28	0.682
	Model 5	**5.19**	**1.83-14.75**	**0.002**	**7.15**	**1.95-26.18**	**0.003**	0.53	0.05-6.18	0.611

Cox proportional hazard regression models were performed with all-cause mortality as a dependent variable.
Model 1; adjusted for age (plus gender for total subjects)
Model 2; adjusted for model 1 plus HbA1c
Model 3; adjusted for model 2 plus BMI, duration of diabetes, and serum creatinine
Model 4; adjusted for model 3 plus systolic blood pressure and LDL-C
Model 5; adjusted for model 4 plus treatment for osteoporosis
Unit of change; Standard deviation per decrease for BMD
HR, hazard ratio; CI, confidential interval; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; 1/3R, one-third of the radius

Table 5 Hazard ratios stratified by number or grade of vertebral fractures

		Total			Men			Women		
		HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
Non VF		1.00			1.00			1.00		
Single VF	Model 1	0.81	0.40-1.64	0.562	0.87	0.40-1.88	0.725	0.31	0.04-2.48	0.267
	Model 2	0.82	0.40-1.66	0.573	0.87	0.40-1.88	0.714	0.33	0.04-2.74	0.307
	Model 3	0.90	0.44-1.87	0.784	0.93	0.42-2.03	0.852	0.32	0.04-2.77	0.301
	Model 4	0.94	0.45-1.94	0.861	0.99	0.45-2.18	0.973	0.26	0.03-2.38	0.233
	Model 5	0.93	0.45-1.92	0.844	0.97	0.44-2.15	0.947	0.08	0.01-1.22	0.069
Multiple VFs	Model 1	**2.57**	**1.36-4.85**	**0.004**	1.33	0.58-3.06	0.500	2.79	0.90-8.65	0.076
	Model 2	**2.51**	**1.32-4.79**	**0.005**	1.32	0.57-3.04	0.519	2.64	0.75-9.30	0.131
	Model 3	**2.74**	**1.39-5.37**	**0.003**	1.31	0.56-3.03	0.531	2.16	0.49-9.54	0.308
	Model 4	**3.05**	**1.51-6.16**	**0.002**	1.52	0.63-3.66	0.352	2.62	0.55-12.52	0.229
	Model 5	**2.93**	**1.42-6.02**	**0.004**	1.32	0.53-3.32	0.552	3.49	0.76-16.06	0.109
Non VF		1.00			1.00			1.00		
Grade 1	Model 1	1.06	0.50-2.25	0.884	0.98	0.43-2.26	0.969	0.42	0.05-3.40	0.414
	Model 2	1.06	0.50-2.27	0.877	0.96	0.42-2.22	0.926	0.44	0.05-3.61	0.441
	Model 3	1.19	0.55-2.61	0.657	1.01	0.43-2.34	0.986	0.35	0.04-3.21	0.353
	Model 4	1.20	0.55-2.62	0.651	1.10	0.47-2.61	0.822	0.34	0.04-3.21	0.347
	Model 5	1.19	0.54-2.61	0.660	1.08	0.46-2.57	0.855	0.32	0.03-3.10	0.323
Grade 2	Model 1	1.25	0.62-2.52	0.533	1.01	0.44-2.31	0.988	0.95	0.20-4.59	0.946
	Model 2	1.24	0.61-2.53	0.546	1.01	0.44-2.32	0.987	0.96	0.19-4.96	0.959
	Model 3	1.39	0.67-2.89	0.379	1.10	0.47-2.58	0.824	0.56	0.08-4.21	0.574
	Model 4	1.43	0.68-3.00	0.346	1.29	0.54-3.12	0.567	0.26	0.02-3.06	0.281
	Model 5	1.45	0.69-3.05	0.333	1.13	0.45-2.83	0.800	0.22	0.02-3.03	0.261
Grade 3	Model 1	**5.37**	**1.97-14.67**	**0.001**	2.36	0.32-17.68	0.402	**3.70**	**1.06-12.93**	**0.041**
	Model 2	**5.38**	**1.92-15.08**	**0.001**	2.61	0.34-20.00	0.356	3.18	0.80-12.60	0.100
	Model 3	**6.16**	**2.12-17.94**	**<0.001**	3.06	0.38-24.35	0.291	2.52	0.56-11.26	0.227
	Model 4	**6.48**	**2.23-18.86**	**0.001**	2.88	0.36-23.21	0.321	2.25	0.51-9.88	0.283
	Model 5	**7.64**	**2.13-27.42**	**0.002**	2.89	0.36-23.36	0.319	2.90	0.47-18.05	0.254

Cox proportional hazard regression models were performed with all-cause mortality as a dependent variable.
Model 1; adjusted for age (plus gender for total subjects)
Model 2; adjusted for model 1 plus HbA1c
Model 3; adjusted for model 2 plus BMI, duration of diabetes, and serum creatinine
Model 4; adjusted for model 3 plus systolic blood pressure and LDL-C
Model 5; adjusted for model 4 plus treatment for osteoporosis
HR, hazard ratio; CI, confidential interval