Tzu Chi Medical Journal 2023; 35 (2): 165-170

Original Article

# Inverse association of serum osteocalcin and bone mineral density in renal transplant recipients

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**Submission** : 12-Mar-2022
**Revision** : 01-Apr-2022
**Acceptance** : 04-May-2022
**Web Publication** : 11-Jul-2022

## Abstract

**Objectives:** Osteocalcin, a protein from osteoblasts, affects bone mineralization and turnover. This study evaluates the association between fasting serum osteocalcin and bone mineral density (BMD) in renal transplant recipients. **Materials and Methods:** This study recruited 66 renal transplant recipients. We analyzed blood biochemistry studies from fasting blood samples. The serum osteocalcin levels were measured using a commercial enzyme immunoassay kit. We measure BMD by dual-energy X-ray absorptiometry in lumbar vertebrae (L2–L4). By the World Health Organization classification, we group recipients into three groups: normal, osteopenia, and osteoporosis. **Results:** Of the renal transplant recipients, 8 patients (12.1%) were osteoporosis, and 28 patients (42.4%) were osteopenia. From normal to osteoporosis groups, the osteoporosis group has highest serum osteocalcin ($P < 0.001$), alkaline phosphatase ($P = 0.005$), lowest body mass index ($P = 0.015$), and body weight ($P = 0.008$). Females had lower lumbar BMD than males among recruited renal transplant recipients ($P = 0.023$). In the multivariate forward stepwise linear regression analysis, body weight (adjusted $R^2$ change = 0.138; $P = 0.010$), and logarithmically transformed osteocalcin (log-osteocalcin; adjusted $R^2$ change = 0.131; $P = 0.012$) can predict lumbar BMD in the renal transplant recipients. **Conclusion:** Our study showed that fasting serum osteocalcin concentration was negatively correlated with the lumbar BMD in renal transplant recipients.

**Keywords:** *Bone mineral density, Dual-energy X-ray absorptiometry, Kidney transplantation, Osteocalcin, Osteoporosis*

## Introduction

Maintaining good physical health has been known to prevent or delay chronic diseases and aging [1]. Despite the substantial improvement in the treatment methods for cardiovascular diseases and cancer, fractures, especially hip fractures, have been associated with a short life expectancy between 1998 and 2017 [2]. Moreover, maintaining good bone and muscle strength is essential to achieve a longer life expectancy in older adults [3]. The risk factors for osteoporosis include various chronic diseases, nutrition deficiencies, endocrinopathy, and medications [4]. Of them, chronic kidney disease (CKD) and end-stage renal disease (ESRD) affect bone mineral density (BMD) through multiple pathways [5,6]. Furthermore, patients who undergo kidney transplantation (KT) have a higher risk for hip fracture than dialysis patients in the first 3 years' postoperative [7].

Dual-energy X-ray absorptiometry is the gold standard for diagnosing osteoporosis [6]. Since we cannot arrange dual-energy X-ray absorptiometry frequently, several biomarkers for diagnosing and following patients with osteoporosis have been investigated [8]. Osteocalcin, a Vitamin K-dependent protein from osteoblast, has been positively correlated with BMD and bone turnover in the normal population [9]. However, this correlation has become less evident in CKD, ESRD, and KT patients. To assess bone health after KT, we examined the correlation between serum osteocalcin level and BMD through dual-energy X-ray absorptiometry in KT patients.

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_55_22

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**How to cite this article:** Lin WC, Lee MC, Chen YC, Hsu BG. Inverse association of serum osteocalcin and bone mineral density in renal transplant recipients. Tzu Chi Med J 2023;35(2):165-70.

## Materials and methods

### Participants

Sixty-six KT patients from a medical center in Hualien, Taiwan, were enrolled in May 2016. This group comprised 41 males and 25 females. Among the 25 female KT patients, 13 patients had menopause. Our trained staff measure blood pressure (BP) by standard mercury sphygmomanometers with appropriate cuff sizes. After patients sat in a quiet room for 10 min, we took systolic BP (SBP) and diastolic BP (DBP) three times at 5-min intervals and averaged them. Hypertension was defined as taking antihypertensive medications or having SBP ≥140 mmHg or DBP ≥90 mmHg. We excluded the patients with acute infection, malignancy, acute rejection, acute myocardial infarction, pulmonary edema, and heart failure at blood sampling. The previous history of lumbar fracture, lumbar surgery, or currently using calcium, active Vitamin D metabolites, bisphosphonates, teriparatide, warfarin, or estrogen was also excluded. All enrolled patients should provide informed consent before entering our study. The Research Ethics Committee in Hualien Tzu Chi hospital approved our study (IRB104-69-B).

### Anthropometric analysis

Before measuring body weight and height, all patients were in light clothes without shoes. We recorded body weight and height in the nearest half-kilogram and nearest half-centimeter. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters squared) [10,11].

### Biochemical determinations

Approximately 5 mL of fasting blood samples were collected from all participants. After immediate centrifuged at 3000 g for 10 min, we used an autoanalyzer (Siemens Advia 1800, Siemens Healthcare GmbH, Henkestr, Germany) [12,13] to check serum levels of blood urea nitrogen (BUN), creatinine, fasting glucose, total cholesterol, triglycerides, total calcium, and phosphorus. We use commercial enzyme-linked immunosorbent assays to measure serum osteocalcin (eBioscience Inc., San Diego, CA, USA) [14] and intact parathyroid hormone (iPTH) (Abcam, Cambridge, MA, USA).

### Bone mineral density measurements

We measured lumbar vertebrae BMD through a dual-energy X-ray absorptiometry scan (QDR 4500, Hologic Inc., Marlborough, MA, USA) [10-13]. BMD was expressed in absolute values (g/cm$^2$). *Z*-scores were numbers of standard deviation from mean BMD of the same age, weight, and ethnic norms. *T*-scores were numbers of standard deviation from the mean BMD of gender-matched young controls. The diagnosis of osteoporosis and osteopenia was according to the World Health Organization criteria [15]. Osteoporosis was defined by *T*-scores −2.5 or lower. Osteopenia was defined by *T*-scores between 1.0 to −2.5.

### Statistical analysis

After we grouped data into three groups (normal, osteopenia, and osteoporosis), data have expressed as means ± standard deviation and tested for normal distribution using the Kolmogorov–Smirnov statistic. To detect inter-group differences, we analyzed nonnormal distributed data (fasting glucose, BUN, and osteocalcin) through Kruskal–Wallis analysis and normally distributed data through one-way analysis of variance and Fisher's protected *t*-test. We examine clinical variables associated with lumbar BMD or serum logarithmically transformed osteocalcin (log-osteocalcin) through simple linear regression analyses. The significant variables in simple linear regression analyses would be adapted in the multivariate forward stepwise regression analysis. We analyzed data using SPSS for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

## Results

Table 1 shows the clinical characteristics of normal, osteopenia, and osteoporosis group. The comorbidities include diabetes mellitus ($n$ = 11; 16.7%) and hypertension ($n$ = 37; 56.1%). The prescribed immunosuppressants include tacrolimus ($n$ = 50; 75.8%), mycophenolate mofetil ($n$ = 23; 34.8%), mycophenolate sodium ($n$ = 39; 59.1%), steroid ($n$ = 64; 97.0%), rapamycin ($n$ = 3; 4.4%), and cyclosporine ($n$ = 14; 21.2%). Of the renal transplant recipients, 8 (12.1%) were osteoporosis and 28 (42.4%) were osteopenia. The female patients had lower lumbar BMD than the male KT patients ($P$ = 0.023). From normal to osteoporosis groups, the osteoporosis group has highest serum osteocalcin ($P < 0.001$), alkaline phosphatase ($P$ = 0.005), lowest BMI ($P$ = 0.015), and body weight ($P$ = 0.008). The lumbar *T*-score values between the groups did not differ statistically in relation to diabetes, hypertension, transplantation model, or the use of different immunosuppressants.

Table 2 shows the results of the simple linear analysis and multivariate forward stepwise linear regression analysis of the clinical variables affecting the lumbar BMD. Height ($r$ = 0.251; $P$ = 0.042), body weight ($r$ = 0.389; $P$ = 0.001), and BMI ($r$ = 0.331; $P$ = 0.007) were positively associated with the lumbar BMD values, while log-osteocalcin ($r$ = −0.385; $P$ = 0.001) was negatively associated with lumbar BMD values among the KT patients. After adapting female, age, body weight, height, BMI, and log-osteocalcin in the multivariate forward stepwise linear regression analysis, body weight (adjusted $R^2$ change = 0.138; $P$ = 0.010) and log-osteocalcin (adjusted $R^2$ change = 0.131; $P$ = 0.012) predicted lumbar BMD values independently in KT patients.

Table 3 shows the simple and multivariable linear analyses between the serum log-osteocalcin levels and clinical variables in KT patients. Serum iPTH ($r$ = 0.271, $P$ = 0.028) and alkaline phosphatase ($r$ = 0.293, $P$ = 0.017) had positive associations, while height ($r$ = −0.322, $P$ = 0.008), and body weight ($r$ = −0.281, $P$ = 0.022) had negative associations with the serum log-osteocalcin levels of KT patients. After we adapted body weight, height, iPTH, and alkaline phosphatase in multivariate stepwise linear regression analysis, serum iPTH (β = 0.239; adjusted $R^2$ change = 0.046, $P$ = 0.035), alkaline phosphatase values (β = 0.283; adjusted $R^2$ change = 0.070, $P$ = 0.013), and height (β = −0.296; adjusted $R^2$ change = 0.090, $P$ = 0.010) predicts log-osteocalcin independently in KT patients.

**Table 1: Clinical characteristics of normal, osteopenia, and osteoporosis groups of the 66 kidney transplantation patients by World Health Organization classification**

| Characteristics | All patients (*n*=66) | Normal (*n*=32) | Osteopenia (*n*=26) | Osteoporosis (*n*=8) | *P* |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Female, *n* (%) | 25 (37.9) | 10 (31.3) | 9 (34.6) | 6 (75.0) | 0.067 |
| Age (years) | 51.86±8.94 | 50.81±7.73 | 51.12±9.70 | 58.50±9.20 | 0.079 |
| Kidney transplantation duration (months) | 49.52±39.41 | 49.05±34.58 | 49.94±47.10 | 50.03±34.66 | 0.996 |
| Cadaveric transplantation model, *n* (%) | 50 (75.8) | 24 (75.0) | 19 (73.1) | 7 (87.5) | 0.700 |
| Comorbidities, *n* (%) | | | | | |
| Diabetes mellitus | 11 (16.7) | 7 (21.9) | 4 (15.4) | 0 | 0.324 |
| Menopause | 13 (52.0) | 1 (10.0) | 6 (66.7) | 6 (100.0) | 0.001* |
| Hypertension | 37 (56.1) | 18 (56.3) | 15 (57.7) | 4 (50.0) | 0.929 |
| Examination | | | | | |
| SBP (mmHg) | 146.18±22.02 | 145.56±21.29 | 149.38±23.26 | 138.25±21.24 | 0.453 |
| DBP (mmHg) | 90.92±13.84 | 90.47±14.22 | 93.38±13.98 | 84.75±10.89 | 0.299 |
| Height (cm) | 161.79±8.35 | 163.13±8.94 | 161.31±8.05 | 158.00±6.09 | 0.283 |
| Body weight (kg) | 60.94±12.17 | 65.31±12.76 | 58.10±10.73 | 52.75±6.90 | 0.008* |
| BMI (kg/m$^2$) | 23.19±3.76 | 24.50±4.24 | 22.21±2.94 | 21.10±2.12 | 0.015* |
| Laboratory data | | | | | |
| BUN (mg/dL) | 21.00 (16.00-32.50) | 21.00 (16.00-34.75) | 19.00 (16.00-26.00) | 29.50 (19.25-34.38) | 0.316 |
| Creatinine (mg/dL) | 1.40±0.60 | 1.43±0.66 | 1.33±0.56 | 1.53±0.50 | 0.671 |
| Fasting glucose (mg/dL) | 96.50 (88.00-110.00) | 96.50 (88.00-121.25) | 91.00 (87.50-104.25) | 101.00 (87.25-115.25) | 0.556 |
| Total cholesterol (mg/dL) | 191.48±51.78 | 194.97±47.20 | 190.65±55.86 | 180.25±60.70 | 0.773 |
| Triglycerides (mg/dL) | 130.82±61.91 | 137.56±72.30 | 116.81±46.30 | 149.38±58.84 | 0.301 |
| Total calcium (mg/dL) | 9.60±0.90 | 9.71±0.84 | 9.46±0.88 | 9.55±1.19 | 0.576 |
| Phosphorus (mg/dL) | 3.26±0.70 | 3.32±0.67 | 3.30±0.80 | 2.88±0.38 | 0.259 |
| Intact parathyroid hormone (pg/mL) | 109.61±71.70 | 104.03±62.26 | 116.82±83.74 | 108.50±71.98 | 0.800 |
| Alkaline phosphatase (U/L) | 63.26±14.98 | 59.72±10.42 | 62.92±17.32 | 78.50±14.45 | 0.005* |
| Osteocalcin (ng/mL) | 8.09 (4.26-18.93) | 4.79 (2.23-100.48) | 9.65 (5.47-16.45) | 31.30 (26.48-47.05) | <0.001* |
| BMD results | | | | | |
| Lumbar BMD (g/cm$^2$) | 0.71±0.13 | 0.80±0.11 | 0.65±0.08 | 0.55±0.10 | <0.001* |
| Lumbar T-score | −1.03±1.17 | −0.04±0.73 | −1.74±0.42 | −2.71±0.17 | <0.001* |
| Lumbar Z-score | −0.46±1.17 | 0.25±0.49 | −0.89±0.46 | −1.89±0.40 | <0.001* |
| Kidney transplantation medications, *n* (%) | | | | | |
| Tacrolimus use | 50 (75.8) | 23 (71.9) | 20 (76.9) | 7 (87.5) | 0.643 |
| Mycophenolate mofetil use | 23 (34.8) | 9 (28.1) | 10 (38.5) | 4 (50.0) | 0.450 |
| Mycophenolate sodium use | 39 (59.1) | 22 (68.8) | 13 (50.0) | 4 (50.0) | 0.302 |
| Steroid use | 64 (97.0) | 32 (100.0) | 24 (92.3) | 8 (100.0) | 0.205 |
| Rapamycin use | 3 (4.5) | 1 (3.1) | 2 (7.7) | 0 | 0.570 |
| Cyclosporine use | 14 (21.2) | 8 (25.0) | 5 (19.2) | 1 (12.5) | 0.705 |

Values for continuous variables given as means±SD and test by one-way analysis of variance; variables not normally distributed given as medians and interquartile range and test by Kruskal-Wallis analysis; values are presented as number (%) and analysis was done using the Chi-square test. *$P$<0.05 was considered statistically significant after Kruskal-Wallis analysis or one-way analysis of variance. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, BMI: Body mass index, BMD: Bone mineral density, SD: Standard deviation

## Discussion

In this cross-sectional analysis of 66 KT patients, female menopause, lower body weight, and higher serum osteocalcin levels were observed in patients with osteopenia or osteoporosis compared with those with normal BMD. Furthermore, the serum log-osteocalcin level was negatively correlated, while body weight was positively correlated with lumbar BMD in KT patients.

Since advanced kidney disease, bone health is affected by CKD mineral and bone disease. Calcium, phosphate, parathyroid hormone, and Vitamin D play complex roles in bone metabolism [5,6]. Both CKD and ESRD patients are more vulnerable to fracture and osteoporosis [5]. Although KT returns our kidney function, some disease risk persists. Within the first 18 months after KT, BMD is 6%–8% lower than before KT [16]. Various studies pointed out that steroids affected bone health in KT patients [17]. When we prescribed fewer steroids for newer and stable KT patients, BMD stabilized, and facture lessened [17]. However, in one recent cohort study, 24% and 15% of KT patients still suffered from osteopenia and osteoporosis [18]. In this study, 42.4% had osteopenia and 12.1% had osteoporosis in our renal transplant recipients.

Osteoporosis is an imbalance between the activities of osteoclasts and osteoblasts. Current treatments are based on rebalancing both activities through medications, diet, and exercise [5]. In exercise, bone density strengthens by weight-bearing moves. Weight-bearing movements include

**Table 2: Correlation of lumbar bone mineral density levels and clinical variables among the 66 kidney transplantation patients**

| Variables | Lumbar BMD (g/cm²) | | | | |
|---|---|---|---|---|---|
| | Simple linear regression | | Multivariate linear regression | | |
| | *r* | *P* | β | Adjusted $R^2$ change | *P* |
| Female | −0.279 | 0.023 | — | — | — |
| Diabetes mellitus | 0.213 | 0.086 | — | — | — |
| Hypertension | 0.100 | 0.424 | — | — | — |
| Age (years) | −0.237 | 0.055 | — | — | — |
| KT duration (months) | −0.087 | 0.488 | — | — | — |
| Height (cm) | 0.251 | 0.042 | — | — | — |
| Body weight (kg) | 0.389 | 0.001 | 0.305 | 0.138 | 0.010 |
| BMI (kg/m²) | 0.331 | 0.007 | — | — | — |
| SBP (mmHg) | 0.030 | 0.813 | — | — | — |
| DBP (mmHg) | 0.060 | 0.630 | — | — | — |
| Log-BUN (mg/dL) | 0.052 | 0.678 | — | — | — |
| Creatinine (mg/dL) | 0.057 | 0.651 | — | — | — |
| Log-Glucose (mg/dL) | 0.052 | 0.679 | — | — | — |
| Total cholesterol (mg/dL) | 0.098 | 0.435 | — | — | — |
| Triglycerides (mg/dL) | 0.034 | 0.789 | — | — | — |
| Total calcium (mg/dL) | 0.078 | 0.536 | — | — | — |
| Phosphorus (mg/dL) | 0.025 | 0.844 | — | — | — |
| Intact parathyroid hormone (pg/mL) | −0.060 | 0.634 | — | — | — |
| Alkaline phosphatase (U/L) | −0.185 | 0.136 | — | — | — |
| Log-Osteocalcin (ng/mL) | −0.385 | 0.001 | −0.299 | 0.131 | 0.012 |

Data of BUN, glucose, and osteocalcin level showed skewed distribution and therefore were log-transformed before analysis. Analysis of data was done using the simple linear regression analyses or multivariate stepwise linear regression analysis (adapted factors were female, age, height, body weight, body mass index, and log-osteocalcin). BMD: Bone mineral density, KT: Kidney transplantation, BUN: Blood urea nitrogen, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index



lifting extra weight (e.g., dumbbells) and bearing one's own weight, such as dancing or jogging. Moreover, several studies have indicated that obesity protects people from osteoporosis [19,20]. In premenopausal and postmenopausal females and males, higher body weight and BMI indicate a higher BMD [21,22]. In people with CKD, the correlation between BMI and osteoporosis is constant [23]. A recent study in Taiwan showed that BMI was associated with higher BMD, but the percentage of body fat was in the opposite direction [24]. Many serum markers have been investigated to determine bone activity. Alkaline phosphatase is an enzyme in the liver, bone, intestines, and kidney. In osteoporosis, elevated alkaline phosphatase is an indicator of disease activity [25]. Alkaline phosphatase increases during osteoporosis which can be reduced through treatment [26,27]. The findings of the present study indicated that compared with the normal group, the osteopenia and osteoporosis groups presented with increased serum alkaline phosphatase and decreased BMI and body weight.

The role of osteocalcin, a Vitamin K-dependent protein from osteoblasts, in bone and energy metabolism have been investigated [9,28]. After osteoblast forms osteocalcin, most osteocalcin stays in bone and participates in bone matrix formation. It binds hydroxyapatite and calcium in the bone matrix and modulates bone mineralization and hydroxyapatite [9]. Only a small fraction of osteocalcin is released into circulation. In circulation, osteocalcin degrades quickly and is eliminated by the kidney. When osteoporosis happens, bone formation and resorption imbalance increase osteocalcin in serum [9]. Many clinical studies showed correlations between BMD and osteocalcin in post-menopausal women [29,30] and men with type 2 diabetes [31]. Uncarboxylated osteocalcin was also negatively associated with lumbar BMD in healthy women [32]. However, osteocalcin failed to correspond with BMD in ESRD patients [33]. In the present study, we found that the serum osteocalcin level was negatively associated with lumbar BMD in KT patients and could be a significant predictor of the development of osteoporosis in KT patients.

Osteocalcin is correlated with iPTH and alkaline phosphatase levels in CKD patients [34]. Moreover, osteocalcin is correlated with alkaline phosphatase levels at 3 and 6 months after KT [35]. One study that examined the results of bone biopsy before and after KT has indicated that early osteoblast apoptosis plays a critical role in posttransplant osteodystrophy and osteocalcin is significantly higher in the nonapoptosis group [36]. Similar to previous studies, the present study has also observed a positive correlation between serum log-osteocalcin level and serum iPTH and alkaline phosphatase levels in KT patients.

However, this study has several limitations. First, our data are a single-center cross-sectional study and the total sample size was relatively small. The analysis from 66 KT patients may be hard to apply to all KT patients. More patients and serial measurements are needed to evaluate the effect of osteocalcin on bone metabolism in KT patients. Second, uncarboxylated osteocalcin was converted into carboxylated osteocalcin due to the catalytic activity of the glutamate γ-carboxylase enzyme and Vitamin K as a coenzyme [28]. In

**Table 3: Correlation of serum logarithmically transformed osteocalcin levels and clinical variables among the 66 kidney transplantation patients**

| Variables | Log-Osteocalcin (ng/mL) | | | | |
|---|---|---|---|---|---|
| | Simple linear regression | | Multivariate linear regression | | |
| | *r* | *P* | β | Adjusted $R^2$ change | *P* |
| Female | 0.112 | 0.371 | — | — | — |
| Diabetes mellitus | −0.046 | 0.712 | — | — | — |
| Hypertension | 0.139 | 0.265 | — | — | — |
| Age (years) | 0.118 | 0.347 | — | — | — |
| KT duration (months) | −0.149 | 0.234 | — | — | — |
| Height (cm) | −0.322 | 0.008 | −0.296 | 0.090 | 0.010 |
| Body weight (kg) | −0.281 | 0.022 | — | — | — |
| BMI (kg/m$^2$) | 0.158 | 0.204 | — | — | — |
| SBP (mmHg) | 0.100 | 0.425 | — | — | — |
| DBP (mmHg) | 0.027 | 0.830 | — | — | — |
| Log-BUN (mg/dL) | −0.035 | 0.778 | — | — | — |
| Creatinine (mg/dL) | −0.038 | 0.760 | — | — | — |
| Log-glucose (mg/dL) | −0.077 | 0.537 | — | — | — |
| Total cholesterol (mg/dL) | −0.097 | 0.437 | — | — | — |
| Triglycerides (mg/dL) | 0.104 | 0.408 | — | — | — |
| Total calcium (mg/dL) | −0.020 | 0.871 | — | — | — |
| Phosphorus (mg/dL) | −0.002 | 0.989 | — | — | — |
| Intact parathyroid hormone (pg/mL) | 0.271 | 0.028 | 0.239 | 0.046 | 0.035 |
| Alkaline phosphatase (U/L) | 0.293 | 0.017 | 0.283 | 0.070 | 0.013 |

Data of BUN, glucose, and osteocalcin level showed skewed distribution and therefore were log-transformed before analysis. Analysis of data was done using the simple linear regression analyses or multivariate stepwise linear regression analysis (adapted factors were height, body weight, intact parathyroid hormone, and alkaline phosphatase). KT: Kidney transplantation, BUN: Blood urea nitrogen, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index



a systematic review and meta-analysis study, menatetrenone has been found to significantly decrease uncarboxylated osteocalcin and improve lumbar BMD in osteoporosis [37]. In the present study, we only measured intact osteocalcin and did not measure uncarboxylated osteocalcin. Thus, the causal relationship between serum osteocalcin or uncarboxylated osteocalcin levels and BMD should be confirmed by a longitudinal study with more KT patients.

## Conclusions

Together with body weight, serum osteocalcin level was independently associated with BMD in KT patients. Serum iPTH and alkaline phosphatase levels were positively associated, while height was negatively associated with the log-osteocalcin levels in KT patients.

### Financial support and sponsorship

This study was supported by a grant from Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan (TCRD108-53).

### Conflicts of interest

Dr. Ming-Che Lee and Bang-Gee Hsu, the editorial board members at *Tzu Chi Medical Journal*, had no roles in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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