International Journal of Diabetes in Developing Countries (January–March 2024) 44(1):48–52
https://doi.org/10.1007/s13410-023-01185-5

ORIGINAL ARTICLE

# Bone mineral density and its predictors in a cohort of adults with type 1 diabetes attending a tertiary care institute in North India

**Soham Mukherjee[1] · Rimesh Pal[1] · Sanjay Kumar Bhadada[1] · Amanpreet Kaur[1] · Ashu Rastogi[1]**

Received: 3 November 2021 / Accepted: 24 February 2023 / Published online: 10 March 2023


## Abstract

**Background** The incidence of type 1 diabetes (T1D) is showing a rising trend all over the world, and these patients are living longer than before. With increasing longevity, they are at increased risk of chronic complications including fractures. However, the bone mineral density (BMD) data in T1D patients are conflicting and variable across the studies. Here, we aimed to study the BMD in adult patients with T1D and delineate its predictors.

**Material and methods** We recruited 40 T1D patients and equal number of age- and sex-matched control subjects. Clinical, biochemical, hormonal, and densitometric assessments were performed for each of the participants and compared between the two groups.

**Results** The median age of T1D and control subjects was 23.5 (21–27.75) years and 24 (22–26) years, respectively. The median duration of diabetes in T1D patients was 12.5 (9–15.75) years with a mean HbA1C of $8.7 \pm 1.9\%$. The serum corrected calcium, phosphorous, alkaline phosphatase, creatinine, and plasma 25-hydroxyvitamin D and iPTH levels were comparable between the groups. In T1D subjects, the mean lumbar spine and left hip BMD were $0.876 \pm 0.154$ gm/cm$^2$ and $0.780 \pm 0.112$ gm/cm$^2$, respectively, which corresponded to mean *Z*-scores of $-1.5 \pm 1.4$ and $-1.4 \pm 0.9$, respectively, which were significantly lower compared to control group. Multiple linear regression analyses showed that BMI and serum albumin were significant determinant of lumbar spine and hip BMD, respectively, in patients with T1D.

**Conclusion** Patients of T1D have apparently reduced BMD, which is being influenced by BMI and serum albumin level.

**Keywords** Type 1 diabetes · Bone mineral density · Body mass index · Albumin

## Introduction

Type 1 diabetes mellitus (T1D) is characterized by autoimmune destruction of pancreatic β-cells with consequent absolute insulin deficiency and hyperglycemia. It affects more than one million children and adolescents worldwide, and the incidence is progressively rising [1, 2]. Since the discovery of insulin, there has been a sharp decline in the acute complication-related mortality associated with T1D. Further, with the advent of newer form of insulin analogs having better pharmacokinetic and pharmacodynamic profile and development of newer technology in this field, patients with T1D are living longer and hence inadvertently are at an increased risk of long-term complications [2].

Adult patients with T1D have a six-fold increased fracture risk [3]. Recent studies where dual X-ray absorptiometry (DXA) had been used revealed lower bone mineral density in adolescents and adults with T1D as compared to control population [4, 5]. However, data is not consistent across all the studies in this regard [6]. In a meta-analysis, Vestergaard et al. observed that the increased risk of hip fracture in T1D patients could not be explained by BMD alone [7]. In a more recent study on patients with long standing T1D, the authors did not find any substantial differences in *T*-score between cases and matched controls [8]. Despite having higher BMD at lumbar spine, the female patients of T1D in the same study cohort showed higher rate of fragility fractures compared to controls. Hence, there must be additional factors, which might be contributing to the fracture risk in T1D.

Consistent with the international trend, the prevalence of T1D in India is also rising and the current prevalence reported in various studies varies from 3.7 to 10.2 per 100,000 populations [6]. There is paucity of data regarding

✉ Sanjay Kumar Bhadada
bhadadask@rediffmail.com

[1] Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

bone health in patients of T1D from India. Here, we aimed to study the bone mineral density in adult patients with T1D in India and tried to find out its determinants in the same cohort.

## Material and methods

This prospective study was conducted in Endocrinology department of Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh. Consecutive patients of T1D of age ≥ 18 years of either sex, visiting Endocrinology OPD of PGIMER, Chandigarh, during the year 2017 were included. Patients who had concurrent hypothyroidism were on stable doses of L-thyroxine therapy for at least 3 months with $T_4$ level within normal range at the time of recruitment. Patients with all other comorbidities such as celiac disease, malignancy, chronic kidney disease (eGFR < 60 ml/min), and pregnant women were excluded. Patients who had received glucocorticoids, complementary and alternative medications, bisphosphonate, teriparatide, or any other medicines that may affect bone turnover were excluded. All the patients were examined for pubertal development, and those with less than Tanner stage 5 were also not included in the study. All the female patients included in the study were eumenorrheic. We also included equal number of age- and sex-matched healthy adult controls from the Chandigarh Urban Bone Epidemiological Study (CUBES) [9–12].

Clinical and demographic details of these patients were evaluated by detailed interviews. Past and family history of fragility fractures was inquired of. The patients were thoroughly examined, and details including height, weight, pubertal staging, and bony deformities were documented. Height was estimated thrice by a stadiometer, and the mean was considered as the final height. Weight was also measured thrice with a digital weighing machine, and the mean value was taken. The formula, weight (in kg)/height (in meter$^2$), was used to calculate body mass index (BMI).

### Laboratory parameters

Blood samples were drawn from the study participants after an overnight fast. These samples were processed for hemoglobin, creatinine, total calcium, inorganic phosphorous, alkaline phosphatase, glycated hemoglobin (HbA1C), triiodothyronine ($T_3$), tetraiodothyronine ($T_4$), thyroid stimulating hormone (TSH), 25-hydroxyvitamin D (25(OH)vitamin D), intact parathyroid hormone (iPTH), and IgA tissue transglutaminase (IgA TTg) antibody. Serum total calcium level was corrected for albumin level. Hemoglobin level was measured with Coulter LH 780 Automated Analyzer (Beckman Coulter, Inc., Brea, CA, USA). Serum creatinine, albumin, total calcium, and inorganic phosphorous were estimated by Modular P800 Analyzer (Roche Diagnostics, Mannheim, Germany). HbA1c was estimated by Bio-Rad D10 analyzer (DCCT standardized). Plasma $T_3$, $T_4$, TSH, 25(OH) vitamin D, and iPTH were estimated using electrochemiluminescence (ECLIA) using Elecsys 2010 Analyzer (Roche Diagnostics, Mannheim, Germany). IgA-tTg antibody was estimated by using fluoroenzyme assay.

### DXA

All the T1D and control subjects underwent dual energy X-ray absorptiometry (DXA) scan using the HOLOGIC Discovery A (QDR 4500; Hologic Inc., Bedford, MA) scanner for assessment of bone mineral density and *Z*-scores at the lumbar spine (L1-L4) and left hip. All DXA scans were performed by a dedicated, International Society of Clinical Densitometry (ISCD)-certified technician. Quality control procedures were carried out in accordance with the manufacturer's recommendations.

### Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 23. The normality of data was checked using the Shapiro–Wilk test. Normally, distributed data were expressed as mean ± standard deviation (SD), and non-normally distributed data were expressed as median (interquartile range, IQR). The comparison between two normally distributed data was performed using Independent Samples *t*-test, and for non-parametric data, Mann–Whitney *U* test was used. Correlations between BMD and demographic/biochemical variables (continuous) were performed using Pearson/Spearman correlation based on the normality of data. Following univariate analysis, the continuous variables were considered for multiple linear regression analysis. A $p$ value < 0.05 was considered significant.

## Results

We recruited 40 T1D and equal number of age- and sex-matched healthy adult controls. The median age of T1D subjects was 23.5 (21–27.75) years and 18 were male. The median age of control subjects was 24 (22–26) years with equal male to female ratio. The demographic, clinical, and biochemical data of these patients are described in Table 1. Although T1D group had comparable mean height compared to control group (158.82 ± 12.19 cm and 159.84 ± 10.54 cm, respectively, $p = 0.693$), the mean weight and BMI were more in the latter group (50.97 ± 9.90 kg

**Table 1** Clinical and biochemical parameters of T1D and control group

| Parameters | T1D ($N=40$) | Control ($N=40$) | $p$ value |
|---|---|---|---|
| Age (year) | 23.5 (21–27.75) | 24 (22–26) | 0.946 |
| Height (cm) | 158.82 ± 12.19 | 159.84 ± 10.54 | 0.693 |
| Weight (kg) | 50.97 ± 9.90 | 59.73 ± 11.88 | 0.001 |
| BMI (kg/m$^2$) | 20.10 ± 3.07 | 23.29 ± 3.56 | 0.000 |
| Duration of DM (years) | 12.5 (9–15.75) | - | |
| Urea (mg/dl) | 24.2 (19.3–29.49) | 23.0 (18.0–31.0) | 0.764 |
| Creatinine (mg/dl) | 0.69 ± 0.16 | 0.72 ± 0.15 | 0.361 |
| Ca (mg/dl) | 9.09 ± 0.47 | 9.18 ± 0.40 | 0.377 |
| Corrected Ca (mg/dl) | 8.89 ± 0.52 | 8.83 ± 0.48 | 0.611 |
| P (mg/dl) | 3.57 ± 0.51 | 3.67 ± 0.53 | 0.398 |
| ALP (U/L) | 136.96 ± 92.28 | 105.18 ± 36.93 | 0.054 |
| Albumin (mg/dl) | 4.23 ± 0.39 | 4.43 ± 0.41 | 0.029 |
| PTH (pg/ml) | 66.20 ± 98.46 | 52.44 ± 22.54 | 0.466 |
| 25(OH)vitamin D (ng/ml) | 13.5 (8.99–23.11) | 11.46 (6.7–20.6) | 0.259 |
| HbA1c (%) | 8.67 ± 1.94 | 5.34 ± 0.39 | 0.000 |
| T3 (ng/ml) | 1.20 ± 0.27 | 1.32 ± 0.24 | 0.049 |
| T4 (μg/dl) | 7.65 ± 1.14 | 7.80 ± 1.68 | 0.644 |
| TSH (mIU/ml) | 2.51 (1.49–3.98) | 2.76 (2.13–4.47) | 0.268 |

vs. 59.73 ± 11.88 kg, $p=0.001$ and 20.10 ± 3.07 kg/m$^2$ vs. 23.29 ± 3.56 kg/m$^2$, $p=0.000$; respectively).

The median duration of diabetes in the T1D patients was 12.5 (9–15.75) years with a mean HbA1C of 8.7 ± 1.9%. Among the T1D patients, two had fragility fracture, while none of the subjects in the control group had similar history. Among these two patients, one had fracture at right 4th and 5th metacarpal, and the remaining one sustained fracture at supracondylar region of left humerus. None of the siblings of T1D patients had history of fragility fracture. Six T1D patients had hypothyroidism for which they were receiving stable dose of L-thyroxine. The serum corrected calcium, phosphorous, alkaline phosphatase, creatinine, and plasma 25(OH) vitamin D and iPTH level were comparable between the two groups (Table 1). Although serum albumin and plasma T3 level were significantly lower in T1D group compared to control (4.23 ± 0.39 mg/dl vs. 4.43 ± 0.41 mg/dl, $p=0.029$ and 1.20 ± 0.27 ng/ml vs. 1.32 ± 0.24 ng/ml, $p=0.049$, respectively), T4 and TSH level were comparable between both the groups. In T1D subjects, the mean lumbar spine and left hip BMD were 0.876 ± 0.154 gm/cm$^2$ and 0.780 ± 0.112 gm/cm$^2$, respectively, which corresponded to mean *Z*-scores of -1.5 ± 1.4 and -1.4 ± 0.9, respectively. The BMD and *Z*-scores at lumbar spine and left hip in T1D subjects were significantly lower as compared to those in the control group (Table 2).

In patients with T1D, there were no gender differences in BMD at the lumbar spine ($p=0.996$) or at the hip ($p=0.981$). In this subgroup of subjects, there were significant positive correlations between lumbar spine BMD and BMI ($r=0.480$ and $p=0.002$) and serum albumin ($r=0.427$ and $p=0.006$). Similarly, there were significant positive correlations between hip BMD and BMI ($r=0.440$ and $p=0.005$) and serum albumin ($r=0.416$ and $p=0.008$). Notably, there were no significant correlations between lumbar spine and hip BMD with age, T1D duration, HbA1c, serum calcium, phosphate, or 25(OH) vitamin D. Multiple linear regression analyses showed that BMI (unstandardized coefficient $\beta=0.019$ and $p=0.014$) was significant determinant, while serum albumin (unstandardized coefficient $\beta=0.119$ and $p=0.050$) was trending to be significant determinant of lumbar spine BMD. On the contrary, albumin (unstandardized coefficient $\beta=0.110$ and $p=0.029$) was found to be a significant determinant of hip BMD, while BMI was trending to be significant for the same (unstandardized coefficient $\beta=0.011$ and $p=0.073$) in patients with T1D.

**Table 2** DXA parameters in T1D and control group at lumbar spine and left hip

| Parameters | T1D ($N=40$) | Control ($N=40$) | $p$ value |
|---|---|---|---|
| Lumber spine BMD (gm/cm$^2$) | 0.876 ± 0.154 | 0.945 ± 0.107 | 0.022 |
| Lumber spine *Z*-score | -1.5 ± 1.4 | -0.9 ± 0.9 | 0.019 |
| Left hip BMD (gm/cm$^2$) | 0.780 ± 0.112 | 0.902 ± 0.108 | 0.000 |
| Left hip *Z*-score | -1.4 ± 0.9 | -0.5 ± 0.8 | 0.000 |

## Discussion

In this prospective cohort study, we observed apparently lower BMD and *Z*-scores at both lumbar spine and hip in T1D subjects as compared to control. The BMI and serum albumin were also lower in the former group. In patients with T1D, there were no gender differences as far as the BMD is concerned. In the same subgroup of patients, BMI and serum albumin were significant determinant of lumbar spine and hip BMD, respectively.

Although fracture risk increases in long standing T1D patients by almost four to six folds, BMD in these patients is variable with inconsistent results across the studies. In a meta-analysis, Shah et al. reported that spine and femoral BMD was modestly lower in T1D adults as compared to controls [13]. Similarly in another meta-analysis, Vestergaard and colleagues observed lower BMD at the hip and spine in patients with T1D as compared to controls [7]. On the contrary, Pan and colleagues noted that the pooled differences in the lumbar spine BMD were not different between T1D subjects and controls [14]. Similarly, Leidig-Bruckner

et al. did not observe any difference in femoral neck BMD between T1D subjects and controls [15]. These were further reinforced by observation of Novak D and colleagues, who reported comparable femoral and lumbar spine areal BMD between T1D and control subjects [16]. In a lone study reported from India, Joshi et al. found lower BMD of total body and at lumbar spine in patients with T1D as compared to the control population [17]. Similar to most of these studies, we also noted apparently lower BMD and *Z*-score in patients with T1D compared to healthy controls.

Although HbA1C was significantly higher in T1D group compared to control, it did not show any correlation with lumbar spine and hip BMD. Duration of diabetes also did not appear to have significant influence on BMD. Similar to our finding, Leidig-Bruckner et al. also reported diabetes-specific variables including HbA1C and duration of diabetes were not significant predictors of the corresponding BMD [15]. Roggen et al. noted the absence of correlation between HbA1C and duration of diabetes with forearm volumetric apparent mineral density in T1D patients [18]. Karaguzel and colleagues also did not observe any correlation of BMD with duration of diabetes and HbA1C level [19]. However, Joshi et al. from India had shown that lower BMD at total body and at lumbar spine was associated with higher HbA1C [17].

We observed lower serum $T_3$ level in patients with T1D as compared to control. Six of our T1D patients had hypothyroidism, and all of them were on stable doses of L-thyroxine. Isolated low $T_3$ in T1D subjects had been documented in the literature. Völzke and colleagues reported lower serum free T3 levels in T1D cohort compared to control subjects suggestive of a possible low $T_3$ syndrome in the former group [20]. Tahirović et al. noted existence of euthyroid sick syndrome in children and adolescents with T1D having poor glycemic control with lower T3 and elevated rT3 level compared to control group [21]. Radetti and colleagues observed higher serum cortisol along with lower $T_3$ level in T1D subjects as compared to controls [22]. Stress models demonstrating an interplay between the hypothalamus-pituitary-thyroid and -adrenal axes provide a possible explanation of low $T_3$ syndrome in T1D subjects [23, 24].

In our T1D study cohort, BMI and serum albumin were significant determinants of lumbar spine and hip BMD, respectively. Further, BMI and serum albumin were trending to be significant predictors for hip and lumbar spine BMD, respectively. Similar to our finding, Leidig-Bruckner et al. noted that BMI was significantly associated with lumbar spine and femoral neck BMD [15]. Roggen et al. found a correlation between trabecular BMD and BMI *z*-score in female patients of T1D [18]. It is an established fact that lower BMI may be associated with increased risk of osteoporosis due to lesser quantity of mechanical loading produced thereof [6]. Apart from this, the adipose tissue, through the secretion of various adipocytokines, also increases BMD. Patients of T1D usually have low BMI, and hence, they are at increased risk of developing osteoporosis [25].

We observed lower serum albumin level in T1D subjects compared to control group. Insulin is an important hormone involved in regulation of albumin synthesis. The correlation of insulin reserve and serum albumin level is evident from animal models of insulin deficiency where three days of insulin therapy normalized serum albumin level [26]. This had been further established by Feo et al. who observed impaired hepatic production of albumin in insulin deficient state with a 10% rise in albumin synthesis daily following insulin infusion in individuals with diabetes mellitus [27]. Afshinnia et al. in a large retrospective analysis of data of 21 121 patients observed an independent association of lower serum albumin level with frequency of osteoporosis [28]. Although, the exact pathophysiological mechanism that correlate low albumin values with a decreased BMD is not clear, hypoalbuminemia may be directly or indirectly related to nuclear factor-κB (NF-κB). NF-κB can induce osteoclastic activity and may suppress osteogenesis [29–31]. Other proposed mechanism includes reduced albumin deposition and enhanced efflux from spongiosal components of bone, given the fact that albumin is present throughout the bony matrix [28].

Our study is limited by a relatively small sample size. A prospective study with a larger population of T1D may be more useful in delineating significant correlation between individual variables. We took single HbA1C value of individual T1D patient during the study. However, we know that glycemic adverse effects on any organ are cumulative in nature. Hence, an average HbA1C value over a prolong period may be reflective of a true glycemic burden in an individual rather than single point of time measurement and ideally should have been done in these kinds of studies. We did not evaluate the bone microarchitecture, which may be altered in patients with T1D. A further study detailing the bony microarchitecture by HRpQCT or bone histomorphometry may be more informative in this regard.

## Conclusion

To conclude, patients of T1D have apparently reduced BMD and BMD *Z*-score as compared to control population. While BMI was a significant predictor of lumbar spine BMD, serum albumin was appeared to influence hip BMD. Further, long-term follow-up is required to delineate whether these findings would translate into increased fracture risk in the same group of patients.

## Declarations

**Competing interests** The authors declare no competing interests.

## References


1. International Diabetes Federation. IDF diabetes atlas. 8th ed. Brussels: International Diabetes Federation; 2017.
2. Onkamo P, Vaananen S, Karvonen M, Tuomilehto J. Worldwide increase in incidence of type I diabetes–the analysis of the data on published incidence trends. Diabetologia. 1999;42:1395–403.
3. Hough FS, Pierroz DD, Cooper C, Ferrari SL. Mechanisms in endocrinology: mechanisms and evaluation of bone fragility in type 1 diabetes mellitus. Eur J Endocrinol. 2016;174:R127–38.
4. Saha MT, Sievanen H, Salo MK, Tulokas S, Saha HH. Bone mass and structure in adolescents with type 1 diabetes compared to healthy peers. Osteoporos Int. 2009;20:1401–6.
5. Hadjidakis DJ, Raptis AE, Sfakianakis M, Mylonakis A, Raptis SA. Bone mineral density of both genders in type 1 diabetes according to bone composition. J Diabetes Complicat. 2006;20:302–7.
6. Dhaon P, Shah VN. Type 1 diabetes and osteoporosis: a review of literature. Ind J Endocrinol Metab. 2014;18:159–65.
7. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes: a meta-analysis. Osteoporos Int. 2007;18:427–44.
8. Alhuzaim ON, Lewis EJ, Lovblom LE, Cardinez M, Scarr D, Boulet G, Weisman A, Lovshin JA, Lytvyn Y, Keenan HA, Brent MH. Bone mineral density in patients with longstanding type 1 diabetes: results from the Canadian study of longevity in type 1 diabetes. J Diabetes Complicat. 2019;33: 107324.
9. Aggarwal A, Ram S, Garg A, Pal R, Bhansali A, Singh P, Sharma S, Thakur JS, Sachdeva N, Bhadada SK. Metabolic bone profile of healthy adult North Indian population from Chandigarh Urban Bone Epidemiological Study (CUBES). Indian J Clin Biochem. 2019;28:1–7.
10. Pal R, Aggarwal A, Singh T, Sharma S, Khandelwal N, Garg A, Bhansali A, Kumar A, Yadav U, Singh P, Dhiman V. Diagnostic cut-offs, prevalence, and biochemical predictors of sarcopenia in healthy Indian adults: the Sarcopenia-Chandigarh Urban Bone Epidemiological Study (Sarco-CUBES). Eur Geriatr Med. 2020;11:725–36.
11. Aggarwal A, Pal R, Bhadada SK, Ram S, Garg A, Bhansali A, Singh P, Thakur JS, Singh T, Sachdeva N, Rao SD. Bone mineral density in healthy adult Indian population: the Chandigarh Urban Bone Epidemiological Study (CUBES). Arch Osteoporos. 2021;16:1–9.
12. Pal R, Bhadada SK, Aggarwal A, Singh T. The prevalence of sarcopenic obesity in community-dwelling healthy Indian adults-the Sarcopenic Obesity-Chandigarh Urban Bone Epidemiological Study (SO-CUBES). Osteoporosis and Sarcopenia. 2021;7:24–9.
13. Shah VN, Harrall KK, Shah CS, Gallo TL, Joshee P, Snell-Bergeon JK, Kohrt WM. Bone mineral density at femoral neck and lumbar spine in adults with type 1 diabetes: a meta-analysis and review of the literature. Osteoporos Int. 2017;28:2601–10.
14. Pan H, Wu N, Yang T, He W. Association between bone mineral density and type 1 diabetes mellitus: a meta-analysis of cross-sectional studies. Diabetes Metab Res Rev. 2014;7:531–42.
15. Leidig-Bruckner G, Grobholz S, Bruckner T, Scheidt-Nave C, Nawroth P, Schneider JG. Prevalence and determinants of osteoporosis in patients with type 1 and type 2 diabetes mellitus. BMC Endocr Disord. 2014;14:1–3.
16. Novak D, Forsander G, Kristiansen E, Svedlund A, Magnusson P, Swolin-Eide D. Altered cortical bone strength and lean mass in young women with long-duration (19 years) type 1 diabetes. Sci Rep. 2020;10:1–9.
17. Joshi A, Varthakavi P, Chadha M, Bhagwat N. A study of bone mineral density and its determinants in type 1 diabetes. J Osteoporos. 2013. https://doi.org/10.1155/2013/397814.
18. Roggen I, Gies I, Vanbesien J, Louis O, De Schepper J. Trabecular bone mineral density and bone geometry of the distal radius at completion of pubertal growth in childhood type 1 diabetes. Horm Res Paediatr. 2013;79:68–74.
19. Karagüzel G, Akçurin S, Özdem S, Boz A, Bircan I. Bone mineral density and alterations of bone metabolism in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2006;19:805–14.
20. Völzke H, Krohn U, Wallaschofski H, Lüdemann J, John U, Kerner W. The spectrum of thyroid disorders in adult type 1 diabetes mellitus. Diabetes Metab Res Rev. 2007;23:227–33.
21. Tahirović H, Dućić V, Smajić A. Euthyroid sick syndrome in type I diabetes mellitus in children and adolescents. Acta Paediatr Hung. 1991;31:67–73.
22. Radetti G, Paganini C, Gentili L, Barbin F, Pasquino B, Zachmann M. Altered adrenal and thyroid function in children with insulin-dependent diabetes mellitus. Acta Diabetol. 1994;31:138–40.
23. Helmreich DL, Parfitt DB, Lu XY, Akil H, Watson SJ. Relation between the hypothalamic-pituitary-thyroid (HPT) axis and the hypothalamic-pituitary-adrenal (HPA) axis during repeated stress. Neuroendocrinology. 2005;81:183–92.
24. Mastorakos G, Pavlatou M. Exercise as a stress model and the interplay between the hypothalamus-pituitary-adrenal and the hypothalamus-pituitary-thyroid axes. Horm Metab Res. 2005;37:577–84.
25. Hofbauer LC, Brueck CC, Singh SK, Dobnig H. Osteoporosis in patients with diabetes mellitus. J Bone Miner Res. 2007;22:1317–28.
26. Peavy DE, Taylor JM, Jefferson LS. Time course of changes in albumin synthesis and mRNA in diabetic and insulin-treated diabetic rats. Am J Physiol. 1985;248(6):E656–63.
27. Feo PD, Gaisano MG, Haymond MW. Differential effects of insulin deficiency on albumin and fibrinogen synthesis in humans. J Clin Investig. 1991;88:833–40.
28. Afshinnia F, Wong KK, Sundaram B, Ackermann RJ, Pennathur S. Hypoalbuminemia and osteoporosis: reappraisal of a controversy. J Clin Endocrinol Metab. 2016;101:167–75.
29. Abu-Amer Y. NF-κB signaling and bone resorption. Osteoporos Int. 2013;24:2377–86.
30. Cao X, Lin W, Liang C, et al. Naringin rescued the TNF-α-induced inhibition of osteogenesis of bone marrow-derived mesenchymal stem cells by depressing the activation of NF-κB signaling pathway. Immunol Res. 2015;62:357–67.
31. Jimi E, Aoki K, Saito H, et al. Selective inhibition of NF-κB blocks osteoclastogenesis and prevents inflammatory bone destruction in vivo. Nat Med. 2004;10:617–24.