Bone mineral density in Palestinian patients with end-stage renal disease and the related clinical and biochemical factors: Cross-sectional study

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Abstract

Introduction

End-Stage Renal Disease (ESRD) is the ultimate result of chronic kidney disease (CKD). In Palestine, the prevalence of ESRD was 240.3 PMP which is comparable with the nearby countries. Accelerated bone loss among ESRD patients is attributed to abnormal bone turn over that leads to osteoporosis and osteopenia. The risk of fractures is increased four-fold in men and women on hemodialysis, which explains the importance of assessing the bone mineral density among these population. The goals of this study were to find the prevalence of osteoporosis in ESRD patients as determined by bone mineral density (BMD) at different sites and to determine whether BMD correlates with many other clinical parameters.

Methods

A cross-sectional study of 194 ESRD patients were recruited from the dialysis unit in An-Najah National University Hospital, Nablus, Palestine. The patients were on regular hemodialysis or peritoneal dialysis. BMD was measured at the lumbar spine and the hip using the dual-energy X-Ray absorptiometry (DEXA) and the value is expressed as T-score. The data were analyzed using SPSS, version 26. The relationship between BMD and the clinical and biochemical parameters among the ESRD patients was assessed.

Results

We found that 42.8% of ESRD patient had osteoporosis and 40.2% had osteopenia. There were significantly higher proportions of osteoporosis and osteopenia among patients >60 years of age (p<0.005). Patients with osteoporosis and osteopenia had significantly higher
Introduction

End-Stage Renal Disease (ESRD) is the ultimate result of chronic kidney disease (CKD) [1]. CKD is defined as decreased kidney function, as shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m², or markers of kidney damage, or both, for at least 3 months, regardless of the underlying cause [2]. The normal level of GFR varies by age, sex and body size with the normal GFR in young adults is considered approximately 120 to 130 ml/min/1.73 m² and it normally declines with age [3].

According to KDOQI- Kidney Disease Outcomes Quality Initiative- guidelines [4], CKD stage 5 or end ESRD is defined as: GFR less than 15 ml/min/1.73 m², which is accompanied in most cases by signs and symptoms of uremia and, eventually, the need for kidney replacement therapy, dialysis or transplantation [2, 3–5].

In 2018, the measured ESRD prevalence in the Middle East is estimated to be 360 per million population (PMP) [6] compared with 2160 PMP in the US in 2016 [7]. In Palestine, the prevalence of ESRD was 240.3 PMP [8] which is comparable with the nearby countries.

Accelerated bone loss among ESRD patients is attributed to abnormal bone turnover that leads to the status of bone problems, osteoporosis and osteopenia [9].

Secondary hyperparathyroidism is a common complication of CKD and it is attributed to hyperphosphatemia, hypocalcemia, reduced vitamin D synthesis as well as PTH skeletal resistance [5, 10, 11]. The excessive secretion of PTH among renal failure patients results in increased bone turnover [11–13]. In addition to high PTH levels, other risk factors are linked to low bone density such as advanced age, low serum albumin level as well as high serum alkaline phosphatase levels [9, 10].

To examine the strength of the bones, there are qualitative (Bone Biopsy) and quantitative (densitometry) methods. DEXA scan is recognized as the best available method worldwide to assess bone density because of its high accuracy, short scan time and low radiation dose [9, 14].

The results of DEXA scans can be expressed as BMD (g/cm²), Z-score or T-score. The T-score is the number of standard deviations (SD) from the mean of a healthy young adult, while Z-score is the number of SD from the mean of healthy age and gender-matched populations [15].

DEXA scans can be performed at different parts of the body with the most common skeletal parts to be measured are lumbar spine (LS) and proximal femur [15]. The International Society for Clinical Densitometry (ISCD) recommends BMD measurement of the postero-anterior LS (L1–L4) and hip (total and neck) [16].
Prevalence of bone disorders, including osteoporosis, in hemodialysis patients is estimated to be between 33–66% [14]. The tendency to fracture is inversely correlated with BMD, confirming the importance of BMD measurement [17]. According to the WHO, the diagnosis of osteoporosis is applied when the T score on Bone-Mineral Density measurement using DEXA scan is -2.5 or lower [15, 18]. When the T score is between -1.0 and -2.5 the term is referred to as Osteopenia [19]. It has been demonstrated that the risk of fractures is increased four-fold in men and women on hemodialysis [5, 20].

Other studies have shown that the yearly incidence rate for fractures by site is approximately 1% for hip fractures and 2.5% for any fracture affecting ESRD patients [5]. Following a hip fracture, patients with ESRD have a 1-year mortality rate twice that of other hemodialysis patients [20].

The aim of this study is to assess the level of bone mass density in the hip and Lumbar Spine of patients undergoing dialysis and to find its correlation with some clinical and biochemical factors.

Materials and methods

Study design, setting and population

This cross-sectional correlation study was conducted between November 2018 and February 2019 at the dialysis center of An-Najah National University Hospital (NNUH), Nablus, Palestine. This unit is the largest dialysis center in the region with more than 350 patients receiving hemodialysis and peritoneal dialysis therapy.

All participants were ESRD patients on regular hemodialysis (three times weekly, 4 hours per session) or peritoneal dialysis (Continuous ambulatory peritoneal dialysis) from both genders. We excluded children and patients with a history of bone malignancy.

All participants were provided oral and written informed consents for participation in the study. The study was carried out with the approval of The Institutional Review Board of An-Najah National University. The principal investigator invited the eligible subjects to participate in the study and 194 of them approved their participation.

Date collection

Clinical and demographic characteristics were collected from the participants and their medical records. These included age, gender, number of years on dialysis, diabetic status (yes, no), Hypertension status (yes, no), Type of dialysis (Hemodialysis or Peritoneal dialysis), history of transplantation (yes, no), history of fractures (yes, no) in addition to the relevant medication history (Alfacalcidol, calcium supplements and phosphate binders, sevelamer). The biochemical parameters were: serum levels of albumin, calcium, phosphate, alkaline phosphatase (ALP) and parathyroid hormone (PTH). The biochemical measurements were conducted on a monthly basis with the exception of PTH which was measured every three months. All biochemical parameters were collected before the start of the dialysis session on all data collection occasions. All blood samples were sent to the laboratory for analysis immediately after collection and were analyzed on the same day. One set of blood sample was analyzed for every single patient. The measurement procedures and reports were validated by the Division of Biochemistry and Laboratory at NNUH.

Bone Mineral Density (BMD)

BMD was measured using dual-energy X-Ray absorptiometry (DEXA) scan (Hologicapparatus model Discovery WI S/N 82189). It was performed within the same month of all biomedical
parameters by trained technicians at Rahma Medical center, Nablus. We measured BMD at the LS and the hip. The LS was measured in posterior–anterior (PA at L1–L4) projection. The hip was measured in the area of the neck, the trochanter (Troch), the intertrochanteric (Inter), the total hip, and Ward’s Triangle. The results are expressed as BMD (g/cm²), a T-score.

**Statistical analyses**

The biochemical and demographic characteristics of the participants were summarized using the descriptive statistics. Means with standard deviation (SD) were used to summarize continuous variables and frequencies with percentages for categorical variables. We used ANOVA, Kruskal Wallis test, independent t-test and Chi-squared test to examine for any statistically significant differences between the different groups as appropriate. All outcome variables were normally distributed and no data transformation was needed. Ordinal logistic regression was used to control for gender, age, duration of dialysis and variables found to be significant in univariable analysis. Any p-value less than 0.05 is considered to be statistically significant and all analyses were conducted using the SPSS computer software version 26.0 (IBM Corp).

**Results**

**Baseline characteristics of the patients**

One hundred ninety four patients were enrolled and all of them completed the study. One hundred eighty four were on hemodialysis and the remaining ten patients were on peritoneal dialysis.

The mean age of participants was 57.0 years (SD = 14.5) and 114 patients (58.8%) were males. About 52.1% (n = 101) and 78.4% (n = 152) had diabetes and hypertension, respectively. The mean duration on hemodialysis was 48 months. Only sixteen patients (8.2%) had tried renal transplantation and 17.5% of the patients had experienced a prior fracture. The baseline demographic, biochemical and clinical characteristics of patients are summarized in Table 1.

**Bone densitometric data (BMD)**

The overall prevalence of osteoporosis among the participants was 42.8% whilst the proportion of people who had osteopenia was 40.2%. According to the site, 33.5% of patients had osteoporosis in the LS and 32.0% in the Hip. See Fig 1.

**BMD in relation to laboratory and clinical parameters**

Univariable analysis was conducted to assess the relationship between patients’ BMD status, and their background and clinical characteristics. Proportions of osteopenia and osteoporosis were significantly higher among patients ≥60 years of age relative to patients <60 years of age for LS and Hip BMD (p<0.05). For gender, females have significantly had higher LS osteoporosis compared to males (P = 0.033).

There was a significant relationship between BMD and PTH levels. Osteopenia and osteoporotic patients had higher serum levels of PTH, this was statistically significant for the Total BMD (P = 0.008) and Hip BMD (P = 0.019). This relation remains significant after controlling for gender, age and duration of dialysis. See Table 2. For the Hip BMD, Post hoc analysis showed that PTH is significantly higher among osteoporosis group compared to osteopenia group (P = 0.006) and compared to normal group (P = 0.034). For total BMD, the significant difference was observed between osteoporosis group compared to osteopenia group (P = 0.022). Serum calcium was on average higher among the osteoporotic and osteopenic patients in all BMD studies and the difference was statistically significant among the spine.
**Table 1.** Baseline clinical and biochemical characteristics of the participants (194).

| Variables                        | Frequency (%) | Mean±SD (Range) |
|----------------------------------|---------------|-----------------|
| **Age (years)**                  |               |                 |
| <60                              | 102 (52.6%)   |                 |
| ≥60                              | 92 (47.4%)    |                 |
| **Gender**                       |               |                 |
| Male                             | 114 (58.8%)   |                 |
| Female                           | 80 (41.2%)    |                 |
| **Duration of Dialysis (months)**|               | 48.0±45.0 (2.0–228.0) |
| **Type of Dialysis**             |               |                 |
| Hemodialysis                     | 184 (94.8%)   |                 |
| Peritoneal Dialysis              | 10 (5.2%)     |                 |
| **History of renal transplantation (yes)** | 16 (8.2%) |                   |
| **History of fractures (yes)**   | 34 (17.5%)    |                 |
| **Diabetes Mellitus (yes)**      | 101 (52.1%)   |                 |
| **Hypertension (yes)**           | 152 (78.4%)   |                 |
| Alpha D3 Supply (yes)            | 185 (92.5%)   |                 |
| Calcium Supplementation (yes)    | 169 (87.1%)   |                 |
| Sevelamer Supplementation (yes)  | 24 (12.0%)    |                 |
| Calcium Supplementation dose (mg/day) | 923.0±358.9 (177.4–2155) | |
| Alpha D3 Supplementation dose (mcg/day) | 0.700±0.48 (0.25–2.75) | |
| Sevelamer Supplementation dose (mg/day) | 2566.3±1112 (700–4200) | |
| Serum Calcium level (mg/dl)*     | 8.8±0.95 (3.9–11.5) | |
| Serum PTH level (pg/ml)          | 605.5±772.9 (25.9–6244.0) | |
| Serum Phosphorus level (mg/dl)   | 4.75±1.43 (1.7–11.1) | |
| Serum Albumin level (g/dl)       | 3.8±0.34 (2.7–4.6) | |

*Calcium is not corrected with albumin

https://doi.org/10.1371/journal.pone.0241201.t001

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**Fig 1.** Distribution of bone mass density among participants (n = 194).

https://doi.org/10.1371/journal.pone.0241201.g001
BMD (P<0.05). Post hoc analysis showed that this difference is mainly significant between the normal and osteopenia group (P = 0.041).

Duration of dialysis was inversely associated BMD. Total, LS and hip osteoporotic patients had significantly higher duration of dialysis compared to osteopenia and normal patients (P = <0.05). This relation remains significant after controlling for gender, age and duration of dialysis, see Table 2. Post hoc analysis showed that duration of dialysis was significantly higher among total osteoporotic patients compared to osteopenia patients (P = 0.04), hip osteoporotic patients compared to normal patients (P = 0.013), and LS osteoporotic patients compared to normal patients (P = 0.028). Serum albumin was lower among osteoporotic patients according to Spine and Hip BMD (P<0.05). On post hoc test, hip osteoporotic patients had significantly lower level of albumins compared to osteopenia group (P = 0.041) and compared to normal group (P = 0.021). For LS BMD, the difference in serum albumin level was significant between osteoporosis and normal groups (P = 0.02). Moreover, in the three occasions, osteoporotic patients used to ingest less calcium supplements than the osteopenia and the normal patients (P<0.05 in the Spine BMD).

There were no significant differences in BMD between patients on HD and PD although the percentage of HD patients with normal BMD is higher than in PD patients. Even though 50% of patients with renal transplantation had osteoporosis, the association between BMD and renal transplantation was not significant.

According to Spearman correlation, there was a significant negative correlation (p<0.05) between duration of dialysis and both LS BMD and hip BMD. BMD (t-score) decreases as the duration of dialysis increases and this increases the risk of osteoporosis. PTH was also negatively correlated with LS and hip BMD (p<0.01, p<0.05 respectively). There was no correlation between hip BMD and either blood albumin level or doses of calcium carbonate, but both variables were correlated with LS BMD. We found a significant positive correlation between age and LS BMD, but not with hip BMD. Furthermore, there was no statistically significant correlation between hip and LS BMD with blood calcium or phosphorus level (Table 3).

Discussion

The aim of this cross-sectional study was to assess the prevalence of BMD among ESRD patients who undergo regular dialysis and the relation with other clinical and biochemical factors.

This study showed that most of ESRD patients had significantly low BMD, including osteopenia and osteoporosis, with a percentage of 83%, 71.1% and 71.1% at the total, hip and spine, respectively. See Fig 1. This is close to the findings of previous studies [14, 15, 21].

Low BMD was found to be associated with increased total duration of dialysis, higher serum PTH level, higher serum calcium level and decreased intake of elemental calcium supplement which confirms the findings of previous studies [9, 14, 22–24].

The percentage of female with osteoporosis in our study was higher than men in the three sites but the difference was statistically significant in the spine BMD. This trend is similar to previous studies [15, 24]. Zayour et al reported a significantly higher prevalence of osteoporosis among women (55% in men and 87% in women undergoing HD); and suggested that sex, diabetes mellitus, and duration of HD were predictors of low BMD [21]. We attribute this difference to the lower population of this study (28 Vs. 194) and the difference among gender distribution (20 males vs. 8 females).

This study showed no significant difference in BMD between patients on HD and PD (p = 0.571), which is in line with the findings of Nybo M et al. [25].
| Parameters                  | Normal (n = 33) | Osteopenia (n = 78) | Osteoporosis (n = 83) | P value | Adjusted P value** |
|-----------------------------|-----------------|---------------------|-----------------------|---------|-------------------|
| **Age**                     |                 |                     |                       |         |                   |
| <60                         |                 |                     |                       |         |                   |
| Total                       | 21 (20.6%)      | 46 (45.1%)          | 35 (34.3%)            | 0.128   | 0.080             |
| Lumbar spine                | 30 (29.4%)      | 44 (43.1%)          | 28 (27.5%)            | 0.046   | 0.399             |
| Hip                         | 32 (31.4%)      | 45 (44.1%)          | 25 (24.5%)            | 0.039   | 0.002             |
| ≥60                         |                 |                     |                       |         |                   |
| Total                       | 12 (13.0%)      | 32 (34.2%)          | 48 (52.2%)            | 0.128   | 0.080             |
| Lumbar spine                | 26 (28.3%)      | 29 (31.5%)          | 37 (40.2%)            | 0.046   | 0.399             |
| Hip                         | 19 (20.7%)      | 36 (39.1%)          | 37 (40.2%)            | 0.039   | 0.002             |
| **Gender**                  |                 |                     |                       |         |                   |
| Male                        |                 |                     |                       |         |                   |
| Total                       | 22(19.3%)       | 46(40.4%)           | 46 (40.4%)            | 0.539   | 0.678             |
| Lumbar spine                | 41(36.0%)       | 38 (33.3%)          | 35 (30.7%)            | 0.033   | 0.173             |
| Hip                         | 31 (27.2%)      | 51 (44.7%)          | 32 (28.1%)            | 0.371   | 0.752             |
| Female                      |                 |                     |                       |         |                   |
| Total                       | 11(13.8%)       | 32(40.0%)           | 37 (40.2%)            | 0.539   | 0.678             |
| Lumbar spine                | 15(18.8%)       | 36 (43.8%)          | 30 (37.5%)            | 0.033   | 0.173             |
| Hip                         | 20 (25.0%)      | 30 (37.5%)          | 30 (37.5%)            | 0.371   | 0.752             |
| **Dialysis Type**           |                 |                     |                       |         |                   |
| Hemodialysis                |                 |                     |                       |         |                   |
| Total                       | 32(17.4%)       | 75 (40.8%)          | 77 (41.8%)            | 0.520   | —                 |
| Lumbar spine                | 54(29.3%)       | 70(38.0%)           | 60 (32.6%)            | 0.520   | —                 |
| Hip                         | 48(26.1%)       | 78(42.4%)           | 58(31.5%)             | 0.743   | —                 |
| Peritoneal Dialysis         |                 |                     |                       |         |                   |
| Total                       | 1(10.0%)        | 3(30.0%)            | 6(60.0%)              | 0.520   | —                 |
| Lumbar spine                | 2(20.0%)        | 3(30.0%)            | 5(50.0%)              | 0.520   | —                 |
| Hip                         | 3(30.0%)        | 3(30.0%)            | 4(40.0%)              | 0.571   | —                 |
| **Duration on Dialysis**    |                 |                     |                       |         |                   |
| (Months)                    |                 |                     |                       |         |                   |
| Total                       | 39±39.8         | 41.3±41.2           | 57.8±48.8             | 0.030*  | 0.021             |
| Lumbar Spine                | 34.8±36.0       | 51.1±47.3           | 55.8±46.8             | 0.028*  | 0.050             |
| Hip                         | 38.7±39.6       | 44.3±43.7           | 59.8±48.1             | 0.012*  | 0.005             |
| **History of Transplantation** (Yes) |         |                     |                       |         |                   |
| Yes                         |                 |                     |                       |         |                   |
| Total                       | 4(25.0%)        | 4(25.5%)            | 8(50.0%)              | 0.393*  | —                 |
| Lumbar Spine                | 5(31.3%)        | 2(12.5%)            | 9(56.3%)              | 0.059*  | —                 |
| Hip                         | 3(18.8%)        | 8(50.0%)            | 5 (31.3%)             | 0.718*  | —                 |
| No                          |                 |                     |                       |         |                   |
| **History of Fractures**    |                 |                     |                       |         |                   |
| Yes                         |                 |                     |                       |         |                   |
| Total                       | 3(8.8%)         | 11(32.4%)           | 20(58.8%)             | 0.094*  | —                 |
| Lumbar Spine                | 6(17.6%)        | 12(35.3%)           | 16(47.1%)             | 0.128*  | —                 |
| Hip                         | 6(17.6%)        | 12(35.3%)           | 16(47.1%)             | 0.104*  | —                 |
| No                          |                 |                     |                       |         |                   |
| **Diabetes Mellitus** (Yes) |                 |                     |                       |         |                   |
| Yes                         |                 |                     |                       |         |                   |
| Total                       | 16(15.8%)       | 46(45.4%)           | 39(38.6%)             | 0.284*  | —                 |
| Lumbar Spine                | 32(32.7%)       | 39(38.6%)           | 30(29.7%)             | 0.462*  | —                 |
| Hip                         | 25(24.8%)       | 44(43.6%)           | 32(31.7%)             | 0.538*  | —                 |
| No                          |                 |                     |                       |         |                   |
| **Hypertension** (Yes)      |                 |                     |                       |         |                   |
| Yes                         |                 |                     |                       |         |                   |
| Total                       | 26(17.1%)       | 63(41.4%)           | 63(41.4%)             | 0.754*  | —                 |
| Lumbar Spine                | 46(30.3%)       | 58(38.2%)           | 48(31.6%)             | 0.521*  | —                 |
| Hip                         | 29(17.0)        | 63(41.2)            | 64(41.8)              | 0.534*  | —                 |
| No                          |                 |                     |                       |         |                   |
| **Serum Calcium**           |                 |                     |                       |         |                   |
| Total                       | 8.7±1.40        | 8.8±0.84            | 8.9±0.81              | 0.053*  | 0.092             |
| Lumbar Spine                | 8.5±1.2         | 9.1±0.8             | 8.7±0.8              | 0.004*  | 0.921             |
| Hip                         | 8.7±1.2         | 8.8±0.8             | 8.9±0.8              | 0.568*  | —                 |
| **Serum PTH**               |                 |                     |                       |         |                   |
| Total                       | 454.8±378.9     | 469.7±478.3         | 792.9±1018.7          | 0.008** | 0.012             |

(Continued)
Table 2. (Continued)

| Parameters                     | Normal (n = 33)† | Osteopenia (n = 78)† | Osteoporosis (n = 83)† | P value | Adjusted P value** |
|--------------------------------|------------------|----------------------|------------------------|---------|--------------------|
| Lumbar Spine                   | 448.9±402        | 592±613              | 766.2±1113             | 0.083** | 0.554              |
| Hip                            | 507.3±391        | 465±465              | 869.2±1186             | 0.019** | 0.014              |
| Serum Phosphorus               |                  |                      |                        |         |                    |
| Total                          | 5.0±1.43         | 4.7±1.27             | 4.7±1.65               | 0.481†  | —                  |
| Lumbar Spine                   | 4.9±1.4          | 4.7±1.2              | 4.7±1.7               | 0.621†  | —                  |
| Hip                            | 5.1±1.5          | 4.7±1.4              | 4.6±1.3               | 0.126   | —                  |
| Serum Albumin                  |                  |                      |                        |         |                    |
| Total                          | 3.9±0.28         | 3.9±0.35             | 3.7±0.33              | 0.401†  | —                  |
| Lumbar Spine                   | 3.9±0.3          | 3.9±0.4              | 3.7±0.3              | 0.013†  | 0.025              |
| Hip                            | 3.9±0.32         | 3.8±0.33             | 3.7±0.3              | 0.019†  | 0.010              |
| Elemental Calcium supplement   |                  |                      |                        |         |                    |
| dose                           |                  |                      |                        |         |                    |
| Total                          | 1001±354         | 939.9±370            | 872.3±347             | 0.620†  | —                  |
| Lumbar Spine                   | 1055±373         | 906±369              | 830±328              | 0.005†  | 0.201              |
| Hip                            | 939±346          | 960±380              | 858±339              | 0.275†  | —                  |
| Alfacalcidol dose              |                  |                      |                        |         |                    |
| Total                          | 0.68±0.37        | 0.70±0.48            | 0.70±0.51             | 0.387†  | —                  |
| Lumbar Spine                   | 0.69±0.35        | 0.72±0.50            | 0.69±0.50             | 0.940†  | —                  |
| Hip                            | 0.66±0.39        | 0.70±0.49            | 0.72±0.51             | 0.750†  | —                  |
| Phosphorus binders dose        |                  |                      |                        |         |                    |
| Total                          | 2880±1073        | 2171±390             | 3200±1563             | 0.064†  | —                  |
| Lumbar Spine                   | 2628±1002        | 2666±1093            | 3054±155              | 0.751†  | —                  |
| Hip                            | 2800±979         | 2755±1702            | 2933±1058             | 0.958†  | —                  |

*ANOVA test ** Kruskal Wallis Test
# Chi-square test
†This represent the total numbers
** Adjusted for age, gender, duration of dialysis.

https://doi.org/10.1371/journal.pone.0241201.t002

Table 3. Spearman correlation of Spinal and Hip BMD with biochemical measurements.

| Characteristic                | Spine BMD r (p-value) | Hip BMD r (p-value) |
|------------------------------|-----------------------|---------------------|
| Age                          | 0.057 (0.412**)       | -0.121 (0.093)      |
| Duration of dialysis         | -0.199 (0.005*)       | -0.195 (0.006*)     |
| Serum Calcium Level          | 0.024 (0.736)         | 0.039 (0.736)       |
| Serum PTH Level              | -0.201 (0.005**)      | -0.195 (0.012*)     |
| Serum Phosphorous level      | 0.07 (0.341)          | 0.142 (0.48)        |
| Serum Albumin Level          | 0.24 (0.001**)        | 0.14 (0.089)        |
| CA Carbonate                 | 0.21 (0.009*)         | 0.096 (0.236)       |
| Ca Acetate                   | 0.08 (0.761)          | -0.03 (0.923)       |
| AlphaD3                      | -0.03 (0.758)         | 0.02 (0.822)        |
| Sevelamer                    | 0.584                 | 0.794               |
| Calcium supplementation dose | 0.191(0.016*)        | 0.073 (0.365)       |

*Correlation is significant at 0.05 (2-tailed)
** Correlation is significant at 0.01 (2-tailed)

https://doi.org/10.1371/journal.pone.0241201.t003
Higher PTH level is an indicator of lower BMD as patients with lower total BMD have higher serum levels of PTH, 792.9 pg/mL among osteoporotic patients compared with 469 pg/mL and 454 pg/mL among osteopenic and normal patient, respectively. See Table 2. This is similar to the findings of a meta-analysis that found serum PTH levels were negatively correlated or, at least, not related with bone density but none found a positive association [26]. Our study data revealed a significantly negative correlation between PTH levels and BMD in Total BMD and Hip BMD which remained significant after controlling for age, gender and duration of dialysis. However, all the PTH values among osteoporotic patient in the three BMD studies were higher than normal and osteopenic patients. The current study found that increased duration of dialysis is associated with lower BMD, p<0.05. These findings correlate with a previous study conducted in Japan that suggested a strong association with the hyperparathyroidism because of long duration on dialysis therapy and generalized bone loss [27]. This is attributed to a combination of factors, including reduction in vitamin D synthesis, hyperphosphatemia, hypocalcemia, and PTH skeletal resistance which will eventually increase the risk of mortality and morbidity as a result of bone disease and fractures [11]. The hyper activated PTH is considered to deteriorate bone mechanical properties, to rescue the state of hypocalcemia among ESRD patients, on the expense of changing bone structure and reducing bone mass [28].

The percentage of patients with osteopenia and osteoporosis were significantly higher among patients ≥60 years of age relative to patients <60 years of age for LS and Hip BMD. This goes against the findings of a study that reported positive correlation between the Spine BMD and age [29] but it correlates with the findings of previous studies [9, 30]. In contrast to other study [9] this research found a significant association between BMD and calcium level (P<0.03) and calcium supplementation (P<0.05 at spine BMD). This might be due to the different patterns of supplemental calcium ingestion among the patients and not due to the pathophysiological problems related to the change in serum PTH given the fact that high serum PTH should be accompanied with low serum calcium as lower ionized calcium levels may influence protein-RNA interactions at the 3-untranslated region of PTH mRNA leading to increased PTH mRNA stability [31].

In this study, eight of the sixteen renal transplant patients had osteoporosis and four had osteopenia. Even though no significant association was found between BMD and history of renal transplantation according to LS or hip (P = 0.059, P = 0.718 respectively), the relationship between bone loss and long term use of immunosuppressive agents in transplant patients requires further study. In a another study, patients who had received glucocorticoids had lower BMD Z-score in both femoral neck and spine compared with patients who had received no such treatment [25]. These patients should thus be considered candidates for a closer continuous monitoring.

The relationship between albumin and BMD has rarely been reported. In a study by Lai et al. showed that there was no association between the serum albumin level and BMD in the hemodialysis patients [32]. Meanwhile, another study revealed that the patients with an albumin level above 4.1 g/dl have a higher BMD [9]. Likewise, this study showed a significant correlation between serum albumin, hip and spine BMD (P<0.05) as osteoporotic patients had a lower serum levels of albumin in the three occasions and this was statistically significant in the LS and Hip, this remained the case even after controlling for Age, gender and duration of dialysis (P = 0.025, P = 0.010 in the LS and hip, respectively)

**Strengths and limitations**

This study included relatively a large number of patients undergoing hemodialysis at NNUH. It is the only center providing peritoneal dialysis therapy and the number of hemodialysis
patients in this unit represents about 20% of all hemodialysis patients in the West Bank, Palestine. So, the demographic, clinical and biochemical characteristics of included hemodialysis patients are likely to be generalizable to hemodialysis population in Palestine. Up to author’s knowledge, it is the first study of its style in Palestine that focuses on this special category of population. The results can be used as framework for further future studies for either follow up or improving patients’ quality of life by closely monitoring and paying more attention for the patients at high risk according to the clinical, demographic and biochemical predictive measures. Our study has some limitations that should be taken into consideration when interpreting the study results. Given the cross-sectional design of the study, we were unable to assess changes in BMD and bone turnover markers over time. BMD sites were limited to the hip and LS and did not include the radius. Other limitation of this study is the small correlation coefficient values observed that might be due to the diverse population in this study; a wide variety of ages, all genders, history of transplantation, etc. Lastly, the small number of PD patients included in this study could have limited its ability to show significant relation between dialysis type and MBD.

Conclusion

This study showed that Palestinian patients with ESRD have low BMD at the hip and spine and the prevalence of osteoporosis and osteopenia is high. This study also adds further evidence that high serum PTH levels is associated with low BMD and makes the patients at increased risk of osteoporosis and bone fractures. Therefore, those patients should be closely monitored especially those with more than one risk factor such as female patients with longer duration on dialysis. They should be advised to stick to their medications to adjust the serum level of PTH and the other minerals to decrease the risk of fractures. Moreover, more attention should be paid for these category of patients to decrease the incidence of falling down and the resulting fractures that might lead to mortality and morbidity.

Supporting information

S1 Data.
(SAV)

Acknowledgments

We are grateful to the Nursing Team at the Dialysis Department at NNUH for supporting the work on this project. A big thank you to all the patients involved in this research as they showed a great deal of cooperation. Special thanks to the team at Al-Rahma Clinic in Nablus for their excellent assistance in obtaining a DEXA scan for patients during the month we were there.

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References

1. Gupta R, Mohammed AM, Alenizi EK, Ben Nekhi A. Bone Mineral Density in Kuwaiti Patients with End-Stage Renal Disease. Medical Principles and Practice. 2011; 20(2):156–8. https://doi.org/10.1159/000319775 PMID: 21252572

2. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney international. 2005; 67(6):2089–100. https://doi.org/10.1111/j.1523-1755.2005.00365.x PMID: 15882252

3. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Annals of internal medicine. 2003; 139(2):137–47. https://doi.org/10.7326/0003-1977-139-2-200307150-00013 PMID: 12859163

4. Levey AS, Coresh J, Bolton K, Cullen B, Harvey KS, Ikizler TA, et al. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American Journal of Kidney Diseases. 2002; 39(2 SUPPL. 1). PMID: 11904577

5. Thomas R, Kanso A, Sedor JR. Chronic kidney disease and its complications. Primary care: Clinics in office practice. 2008; 35(2):329–44. https://doi.org/10.1016/j.pop.2008.01.008 PMID: 18486718

6. Malekmakan L., Tadayon T., Roozbeh J. and Sayadi M., 2018. End-stage renal disease in the Middle East: A systematic review and meta-analysis. Iranian journal of kidney diseases, 12(4), p.195. PMID: 30087213

7. United States Renal Data System. 2018 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2018.

8. Khader MI, Snouber S, Alkhatib A, Nazzal Z, Dudin A. Prevalence of patients with end-stage renal disease on dialysis in the West Bank, Palestine. Saudi Journal of Kidney Diseases and Transplantation. 2013; 24(4):832. https://doi.org/10.4103/1319-2442.113913 PMID: 23817415

9. Huang G-S, Chu T-S, Lou M-F, Hwang S-L, Yang R-S. Factors associated with low bone mass in the hemodialysis patients–a cross-sectional correlation study. BMC Musculoskeletal Disorders. 2009; 10(1):60. https://doi.org/10.1186/1471-2474-10-60 PMID: 19497099

10. Gupta R, Mohammed AM, Alenizi EK, Ben Nekhi A. Bone Mineral Density in Kuwaiti Patients with End-Stage Renal Disease. Medical Principles and Practice. 2011; 20(2):156–8. https://doi.org/10.1159/000319775 PMID: 21252572

11. Sawalmeh O., Moala S., Hamdan Z., Masri H., Ayoub K., Khazneh E., et al. 2018. Pulse versus daily oral Alfacalcidol treatment of secondary hyperparathyroidism in hemodialysis patients: a randomized controlled trial. International journal of nephrology and renovascular disease, 11, p.25. https://doi.org/10.2147/IJNRD.S149877 PMID: 29391823

12. Yuen NK, Ananthakrishnan S, Campbell MJ. Hyperparathyroidism of renal disease. The Permanente Journal. 2016; 20(3):78. https://doi.org/10.7812/TPP/15-127 PMID: 27479950

13. Ketteler Markus, Block Geoffrey A., Evenepoel Pieter, Fukagawa Masafumi, Herzog Charles A., Linda McCann. Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) Guideline Update: what’s changed and why it matters. 2017. https://doi.org/10.1016/j.kint.2017.04.006 PMID: 28646895

14. Omidvar B, Ghorbani A, Tamadon MR, Broujeni ZS, Bahadoram M, Dargahi M. Relationship of bone density with serum parathyroid hormone in hemodialysis patients; a single center study. Journal of Parathyroid Disease. 2018; 6(2):58.

15. Orlc L, Crncevic Z, Pavlovic D, Zaputovic L. Bone mineral densitometry in patients on hemodialysis: difference between genders and what to measure. Renal Failure. 2010; 32(3):300–8. https://doi.org/10.3109/08860221003611661 PMID: 20970444
16. 015 ISCD Official Positions–Adult [Internet]. 2015. Available from: http://www.iscd.org/official-positions/2015-iscd-official-positions-adult/.

17. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Brmj. 1996; 312(7041):1254–9. https://doi.org/10.1136/bmj.312.7041.1254 PMID: 8634613

18. Genant H.K., Cooper C., Poor G., Reid I., Ehrlich G., Kanis J., et al. 1999. Interim report and recommendations of the World Health Organization task-force for osteoporosis. Osteoporosis international, 10(4), p.259. https://doi.org/10.1007/s001980050224 PMID: 10692972

19. Raisz L.G., 2005. Screening for osteoporosis. New England Journal of Medicine, 353(2), pp.164–171. https://doi.org/10.1056/NEJMc042092 PMID: 16014886

20. Mirfakhraee S, Saikhaee K, Zerwekh J, Adams-Huet B, Gruntermans U. Risk factors for diminished bone mineral density among male hemodialysis patients—a cross-sectional study. Archives of Osteoporosis. 2012; 7(1):283–90. https://doi.org/10.1007/s11657-012-0110-3 PMID: 23152064

21. Zayour D, Daouk M, Medawar W, Salamon M, El-Hajj Fuleihan G. Predictors of bone mineral density in patients on hemodialysis. Transplantation proceedings. 2004; 36(5):1297–301. https://doi.org/10.1016/j.transproceed.2004.05.069 PMID: 15251316

22. Binici DN, Gunes N. Risk factors leading to reduced bone mineral density in hemodialysis patients with metabolic syndrome. Renal Failure. 2010; 32(4):469–74. https://doi.org/10.3109/08860221003675260 PMID: 20446786

23. Yucel AE, Kart-Koseoglu H, Isiklar I, Kuruncu E, Ozdemir FN, Arslan H. Bone mineral density in patients on maintenance hemodialysis and effect of chronic hepatitis C virus infection. Ren Fail. 2004; 26 (2):159–64. https://doi.org/10.1081/rd-120038501 PMID: 15287200

24. Ambrus C., Almasi C., Berta K., Deak G., Marton A., Molnar M.Z., et al. 2011. Bone mineral density and parathyroid function in patients on maintenance hemodialysis. International urology and nephrology, 43(1), pp.191–201. https://doi.org/10.1007/s11255-009-9702-2 PMID: 20091221

25. Nybo M. Determinants of bone mineral density in patients on haemodialysis or peritoneal dialysis—a cross-sectional, longitudinal study. 2013; 23(3):342–50. https://doi.org/10.11613/bm.2013.042 PMID: 24266305

26. Ott SM. Bone density in patients with chronic kidney disease stages 4-5. Nephrology. 2009; 14(4):395–403. https://doi.org/10.1111/j.1440-1797.2009.01159.x PMID: 19563381

27. Atsumi K., Kushida K., Yamazaki K., Shimizu S., Ohmura A. and Inoue T., 1999. Risk factors for vertebral fractures in renal osteodystrophy. American journal of kidney diseases, 33(2), pp.287–293. https://doi.org/10.1016/s0272-6386(99)70302-1 PMID: 10023640

28. Kazama JJ, Wakisugi M. Parathyroid Hormone and Bone in Dialysis Patients. Therapeutic Apheresis and Dialysis. 2018; 22(3):229–35. https://doi.org/10.1111/1744-9987.12678 PMID: 29883066

29. Malluche H.H., Davenport D.L., Cantor T. and Monier-Faugere M.C., 2014. Bone mineral density and serum biochemical predictors of bone loss in patients with CKD on dialysis. Clinical Journal of the American Society of Nephrology, 9(7), pp.1254–1262. https://doi.org/10.2215/CJN.09470913 PMID: 24948144

30. Slouma M., Sahli H., Bahlous A., Laadhar L., Smaoui W., Rekik S., et al. 2020. Mineral bone disorder and osteoporosis in hemodialysis patients. Advances in Rheumatology, 60. https://doi.org/10.1186/s42358-020-0118-0 PMID: 32102689

31. Elder G., 2002. Pathophysiology and recent advances in the management of renal osteodystrophy. Journal of Bone and Mineral Research, 17(12), pp.2094–2105. https://doi.org/10.1359/jbmr.2002.17.12.2094 PMID: 12469904

32. 賴銘南, 許逸生, 陳雅吟, 紀美智, 高銘聰. Osteoporosis and Associated Risk Factors for Chronic Hemodialysis Patients. Acta Nephrologica. 2002; 16(1):25–30.