Trabecular bone score and phalangeal quantitative ultrasound are associated with muscle strength and fracture risk in hemodialysis patients

Antonino Catalano†, Agostino Gaudio‡, Federica Bellone†, Mattia Miriam La Fauci†, Anastasia Xourafa‡, Guido Gembillo†, Giorgio Basile†, Giuseppe Natale‡, Giovanni Squadrito†, Francesco Corica‡, Nunziata Morabito§, and Domenico Santoro‡

1Department of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy, 2Department of Clinical and Experimental Medicine, University Hospital of Catania, Catania, Italy, 3Mineral Metabolism and Nephrology Clinic of Vibo Valentia Hospital, Vibo Valentia, Italy

There is growing interest in the relationship between chronic kidney disease (CKD) and fragility fracture risk. Bone mineral density (BMD) is a major determinant of bone strength, although its role as a predictor of fracture in advanced CKD and hemodialysis is still under debate. We aimed to further investigate surrogates of bone quality and their associations with muscle strength and fracture risk in hemodialysis. Multiple clinical risk factors for fracture and an estimated 10-year probability of fracture, BMD at lumbar spine and femur, trabecular bone score (TBS), X-ray vertebral morphometry, phalangeal bone quantitative ultrasonography (QUS), tibial pulse-echo ultrasonography (PEUS), and handgrip strength were evaluated in a setting of hemodialysis patients in treatment with acetate-free biorefiltration (AFB) or bicarbonate hemodialysis. The bone ultrasound measurements, both at phalangeal and tibial sites, were significantly associated with lumbar and femoral DXA values. Handgrip strength was significantly associated with the 10-year probability of fracture ($r = -0.57$, $p < 0.001$ for major fractures and $r = -0.53$, $p < 0.001$ for hip fracture, respectively), with femur neck, total femur, and L1–L4 BMD values ($r = 0.47$, $p = 0.04$; $r = 0.48$, $p = 0.02$; $r = 0.58$, $p = 0.007$, respectively), with TBS at the lumbar spine ($r = 0.71$, $p < 0.001$) and with the phalangeal QUS measure of AD-SoS ($r = 0.369$, $p = 0.023$). In the hemodialysis group, 10 participants (24.3%) reported at least one morphometric vertebral fracture (Vfx); conversely, only six participants (15%) showed Vfx in the control group. In the hemodialysis group, participants with Vfx compared with participants without Vfx reported significantly different TBS, bone transmission time (BTT), cortical thickness, and handgrip strength ($p < 0.05$). At multiple regression analysis, by identifying as dependent variable the 10-year fracture risk for major fracture, after correcting for age, BMI, time since dialysis,
**Introduction**

Fragility fractures are common in patients with chronic kidney disease (CKD), particularly in the end-stage, and are often associated with excess morbidity and mortality (1).

Disorders of mineral metabolism and bone microarchitecture arise early in the CKD course and gradually worsen along with the deterioration of kidney function; as a result, half of the CKD patients initiating dialysis treatment have already had a fracture (2). Particularly, the risk of fracture at the femur site is approximately fourfold greater in patients with end-stage disease than in the general population fracture rate (1, 3). Incident femur fractures increase the mortality rate by two times in end-stage CKD patients compared with matched end-stage CKD patients without fractures (3). Vertebral fractures (Vfx) are also a common occurrence in CKD. In fact, Vfx was revealed in approximately one out of five patients with 3–5 stage CKD; the prevalence of Vfx was correlated with poor survival and raised as an independent predictor of all-cause mortality (4).

Patients with CKD who fracture because of low-grade trauma, in accordance with the Kidney Disease Improving Global Outcomes (KDIGO) classification, present a CKD-Mineral and Bone Disorder (CKD-MBD); this latter is a systemic disorder of mineral and bone metabolism manifested by either one or a combination of the following: vascular or other soft tissue calcification; abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism; or abnormalities in bone turnover, mineralization, volume, linear growth, or strength (5).

Low bone mineral density (BMD), as measured by dual-energy X-ray absorptiometry (DXA), is a recognized major predictor of fracture in the general population. However, studies have reported conflicting results on the association between DXA and fracture in end-stage CKD (2). Moreover, by considering a large population (n = 13,848) from the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994), it has been observed that while BMD decreased along with decreasing kidney function (based on estimated creatinine clearance (eCcr) calculated using the Cockcroft–Gault (CG) formula), after controlling for only sex, age, and weight, any negative association between BMD and kidney function was extinguished (6). Because of the possibility of falsely elevated BMD values due to vascular or paraspinal tissue calcifications or age-related changes in the lumbar spine, the prevalence of osteoporosis in patients with advanced CKD may be undervalued based on a T-score value of ≤ −2.5 standard deviations (SD) if BMD is measured at the lumbar spine (6–9). These findings demonstrate that BMD testing to estimate fracture risk might not always be advantageous in advanced stages of CKD. However, the 2017 KDIGO guidelines recommend that in patients with evidence of CKD-MBD and/or risk factors for osteoporosis, BMD measurement of bone density is expected to impact treatment decisions (10). The Fracture Risk Assessment Tool (FRAX) index is a validated resource for the 10-year prediction of major osteoporotic fractures, assessing clinical risk factors together with BMD, particularly in CKD stages 2–5 (11, 12). FRAX was able to discriminate fracture status among men and women with CKD but performed no better than femoral BMD alone (12). In particular, in a cohort of 718 hemodialysis patients who were...
followed up for 2 years, Przedlacki et al. identified the FRAX value of 5% as the prognostic threshold for an increased risk of major osteoporotic fracture (13).

Besides the bone density impairment, CKD patients are more likely to fracture because of the deterioration of bone quality. Bone strength, in fact, also depends on bone microarchitecture and materials’ properties that cannot be measured by DXA (5, 14).

The trabecular bone score (TBS) represents a novel texture parameter reflecting bone microarchitecture. It results from the computed analysis of gray-level changes in pixels of lumbar spine DXA images and may contribute to fracture risk assessment (15–17). Moreover, bone quantitative ultrasonography (QUS) has been proposed to explore fracture risk, taking into account that QUS measurements are related to some physical properties of bone tissue (e.g., structure and elasticity) that contribute to bone strength. Previous studies correlated QUS with DXA measurements, prevalent Vfx, and risk of future fractures (11, 14, 18–20). Additionally, studies using pulse-echo ultrasonography (PEUS), a novel ultrasound method that measures the thickness of cortical bone, have shown a significant correlation between density index (DI), a PEUS-derived parameter, and BMD at the hip in postmenopausal women (21, 22).

High fracture risk in hemodialysis patients is also likely to be related to a propensity to falls due to poor muscle strength and impaired balance secondary to poor nutrition, inactivity, myopathy, and peripheral neuropathy (23). Previous studies have studied the positive effects of muscle function on bone health, and the relationship between muscle strength and BMD has been highlighted (24–26). However, very little evidence exists on this association in dialysis patients (27, 28), and no data are available on the association between muscle strength and BMD or QUS/PEUS measurements intended as surrogates of bone quality or bone strength.

The primary aim of this study was to investigate bone health in hemodialysis patients with both DXA and bone ultrasonometry tools, and the secondary purpose was to measure muscle strength and investigate the possible associations between muscle and surrogates of bone strength.

Materials and methods

Participants

This cross-sectional study included adult (>18 years) Caucasian subjects with CKD 5D, referred to the Nephrology Unit of the Department of Medical Sciences, University Hospital of Messina (Messina, Italy). The enrolled patients were selected from the entire hemodialysis cohort followed up at our University Center. The research protocol was approved by the Local Ethics Committee for Medical Research, Messina University Hospital “G. Martino” and carried out in accordance with the 1964 Declaration of Helsinki and its later amendments.

Exclusion criteria were dementia or cognitive impairment; history of cancer; hypo- or hyperthyroidism; malabsorption diseases; and previous use of active bone agents, including denosumab, selective estrogen receptor modulators, and strontium ranelate. Controls were consecutively enrolled from outpatients referred to the metabolic bone disease service of the Geriatric Unit of the Department of Medical Sciences, University Hospital of Messina (Messina, Italy).

All the participants signed an informed consent before entering the study.

Clinical evaluation

Height and weight were measured at baseline according to standard procedures, and BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m²).

Fracture risk assessment was estimated by the Fracture Risk Assessment Tool (FRAX®), which is a computer-based algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of a major fracture (hip, clinical spine, humerus, or wrist fracture) and the 10-year probability of hip fracture. According to FRAX, calibrated for Italian subjects, fracture risk was derived from age, BMI, and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, and exposure to oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol consumption. FRAX score was calculated without considering BMD (11).

A trainer examiner assessed muscle strength by measuring handgrip strength using a Jamar dynamometer, following a standardized protocol consisting of three consecutive grip strength measurements with the second handle position of the device for each hand, with a rest period of 30 s between successive attempts. Maximal handgrip strength was recorded.

Bone status evaluation

BMD was assessed by a DXA densitometer (Hologic Discovery Wi) at the lumbar spine (L1–L4) and femoral sites (neck and total femur). The DXA densitometer was calibrated daily according to the manufacturer’s instructions, and its coefficient of variation (CV) was 0.5% at the lumbar spine and femoral site. In addition, we investigated TBS through further evaluation of DXA images by iNsight software (version 3.0, Medimaps Group, Geneva, Switzerland). TBS was evaluated considering the variogram of the trabecular bone–projected image, calculated as the sum of the squared gray-level differences between pixels at a specific distance and angle. TBS
was then calculated as the slope of the log–log transform of this variogram (29).

To assess bone status, we also performed QUS measurements at the proximal phalangeal metaphysis of the last four fingers of the nondominant hand using a DBM Sonic Bone Profiler (Igea, Carpi, Italy) as previously described (30). Briefly, amplitude-dependent speed of sound (AD-SoS), bone transmission time (BTT), fast-wave amplitude (FWA), signal dynamic (SDy), and the derived ultrasound bone profile index (UBPI) (UBPI = −(0.0018 × SDy − 0.0560 × FWA 0.0560 − 1.1467 × BTT + 3.0300)) were the considered QUS variables.

Moreover, ultrasound measurements were conducted at the tibial site by using a PEUS device (Bindex® (g/cm²) was automatically calculated (27). To indicate the measurement at exactly one-third of the proximal tibia, meaning a third of the distance from the knee joint space to the medial malleolus, by multiplying the time of flight between the ultrasound echoes from the periosteal and endosteal surfaces by the speed of sound (SOS). An appropriate ruler was used to indicate the measurement at exactly one-third of the tibia length. From CTh, age, weight, and height, a DI (g/cm²) was automatically calculated (27).

Vertebral fracture assessment

All the participants underwent a lateral thoracic and lumbar spine X-ray scan to evaluate morphometric Vfx. As previously described, Vfx was diagnosed if a vertebral body had at least a 20% height reduction in the anterior, middle, or posterior height compared with the same or adjacent vertebra (31).

Hemodialysis treatment characteristics

Patients on hemodialysis were regularly treated with the Artis Physio system (Baxter Healthcare Corporation, One Baxter Parkway, Deerfield, IL 60015 USA). The scheduled hemodialysis group are shown in Table 2. Hemodialysis patients and controls did not differ for age and BMI but significantly differed for FRAX-derived 10-year hip fracture risk, BMD values at the lumbar spine, TBS, QUS parameters, PTH, phosphorus, and hemoglobin levels, as shown in Table 1. Handgrip strength was also significantly different between hemodialysis patients and controls (Table 1).

The associations between DXA, QUS, and PEUS variables in the hemodialysis group are shown in Table 2. Ultrasonic measurements, both at phalangeal (i.e., AD-SoS, UBPI, BTT) and tibial sites (i.e., Cth, DI), were all significantly associated with lumbar and femoral BMD values (p < 0.05). Moreover, phalangeal AD-SoS was significantly related to tibial cortical thickness and DI (r = 0.36, p = 0.02 and r = 0.49, p = 0.004, respectively). The same association was observed between phalangeal BTT with Cth and DI at the tibial site (r = 0.41, p = 0.04 and r = 0.4, p = 0.04, respectively).

The 10-year probability of major fracture and hip fracture was significantly associated with femur neck BMD (r = −0.59, p = 0.003 and r = −0.581, p = 0.005, respectively), DXA-derived TBS at the lumbar spine (r = −0.45, p = 0.03), and QUS measurements; in particular, AD-SoS and BTT were significantly associated with femur neck BMD (r = −0.37, p = 0.01 and r = −0.43, p = 0.03), whereas DI was associated with the 10-year probability of hip fracture (r = −0.36, p = 0.02). Handgrip strength measurements were significantly associated with the 10-year probability of fracture (r = −0.57, p < 0.001 for major fractures and r = −0.53, p < 0.001 for hip fracture, respectively), with femur neck, total femur, and L1–L4 BMD values (r = 0.47, p = 0.04; r = 0.48, p = 0.02; r = 0.58, p = 0.007, respectively).

Statistical analysis

Statistical analyses were performed using MedCalc software (version 20.113). Data were reported as means ± SD or median (IQR) for continuous variables and percentages for categorical variables. The Kolmogorov–Smirnov test confirmed the normal distribution of values. Student’s t-tests for unpaired observations and the Mann–Whitney test were used as appropriate. Fisher’s exact test was used to calculate differences in categorical variables. Spearman’s coefficient verified the degree of association between two variables. Multiple regression analysis was performed to analyze the relationship between a dependent variable and one or more independent variables. All reported p-values were two-sided, and values of p < 0.05 were considered to indicate statistical significance.

Results

The main clinical features of participants are shown in Table 1. Hemodialysis patients and controls did not differ for age and BMI but significantly differed for FRAX-derived 10-year hip fracture risk, BMD values at the lumbar spine, TBS, QUS parameters, PTH, phosphorus, and hemoglobin levels, as shown in Table 1. Handgrip strength was also significantly different between hemodialysis patients and controls (Table 1).
with DXA-derived TBS at the lumbar spine \((r = 0.71, p < 0.001)\) and with AD-SoS values \((r = 0.369, p = 0.023)\). No significant associations were observed between handgrip strength and metabolic parameters \((p > 0.05)\) in patients and controls.

### TABLE 1 Main clinical features of hemodialysis patients and controls.

|                     | Patients (n = 41) | Controls (n = 44) | p-value |
|---------------------|------------------|-------------------|---------|
| Age (years)         | 74.23 ± 11.7     | 71.82 ± 8.1       | 0.28    |
| BMI (kg/m²)         | 26.21 ± 6.19     | 26.45 ± 4.16      | 0.83    |
| Males (%)           | 56               | 57                |         |
| Time since hemodialysis (years) | 4.5 ± 4 | -- |         |
| Acetate-free biofiltration (%) | 83 | -- |         |
| Bicarbonate dialysis (%) | 17 | -- |         |
| Ki/V                | 1.2 (1.1 to 1.2) | --                |         |
| Calcium (g/dl)      | 8.9 ± 1          | 9.1 ± 1.2         | 0.40    |
| Phosphorus (g/dl)   | 4.8 ± 1.3        | 3.2 ± 0.5         | <0.001  |
| Parathyroid hormone (pg/ml) | 224.2 ± 163.9 | 45.2 ± 12.3      | <0.001  |
| Hemoglobin (g/dl)   | 11 ± 4.5         | 13.5 ± 1.3        | <0.001  |
| Albumin (g/dl)      | 3.8 ± 0.4        | 3.7 ± 0.3         | 0.19    |

#### Dual-energy X-ray absorptiometry

|                     | L1-L4 BMD (g/cm²) | L1-L4 T-score (SD) | Femur neck BMD (g/cm²) | Femur neck T-score (SD) | Total femur BMD (g/cm²) | Total femur T-score (SD) | Trabecular bone score |
|---------------------|-------------------|--------------------|------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Patients            | 0.9 ± 0.14        | −1.45 ± 1.12       | 0.58 ± 0.06            | −2.5 ± 0.5              | 0.74 ± 0.09             | −1.78 ± 0.62            | 1.21 ± 0.12           |
| Controls            | 0.79 ± 0.18       | −2.51 ± 0.32       | 0.59 ± 0.08            | −2.4 ± 0.13             | 0.73 ± 0.1              | −1.98 ± 0.22            | 1.30 ± 0.07           |
| p-value             | 0.002             | <0.001             | 0.52                   | 0.22                    | 0.6                     | 0.06                    | 0.0001               |

#### Phalangeal QUS

|                     | AD-SoS (m/s)      | UBPI (U)           | BTT (m/s)              |
|---------------------|-------------------|--------------------|------------------------|
| Patients            | 1.636 ± 0.04      | 0.15 ± 0.08        | 1.05 ± 0.41            |
| Controls            | 1.874 ± 0.22      | 0.32 ± 0.18        | 1.19 ± 0.15            |
| p-value             | <0.0001           | <0.0001            | 0.04                   |

#### Tibial PEUS

|                     | Cortical thickness (mm) | Density index (g/cm²) | Handgrip strength (kg) | 10-year probability of fracture |
|---------------------|-------------------------|-----------------------|------------------------|---------------------------------|
| Patients            | 2.8 ± 1.2               | 0.79 ± 0.1            | 18 ± 9.6               | Major fracture (%)               |
| Controls            | 2.7 ± 1                 | 0.81 ± 0.1            | 22.5 ± 8.2             | 12.7 ± 9.4                      |
| p-value             | 0.6                     | 0.37                  | 0.02                   | 0.13                             |

#### Muscle strength

|                     | Hip fracture (%)       | 10-year probability of fracture |
|---------------------|------------------------|---------------------------------|
| Patients            | 6.6 ± 7.3              | Major fracture (%)               |
| Controls            | 3.4 ± 2                | 12.7 ± 9.4                      |
| p-value             | 0.001                  | 0.13                             |

In the hemodialysis group, 10 participants (24.3%) reported at least one morphometric Vfx; conversely, only six participants (15%) showed Vfx in the control group. In the dialysis group, participants with Vfx compared with participants without Vfx reported

### TABLE 2 Coefficients of association (r) between DXA and ultrasound measurements in hemodialysis patients.

| DXA measurements | Ultrasound measurements |
|------------------|-------------------------|
|                  | AD-SoS | UBPI | BTT | DI | Cth |
| Femur neck BMD   | 0.46*  | 0.49 | 0.81* | 0.508* | 0.387 |
| Total femur BMD  | 0.88*  | 0.62* | 0.82* | 0.376 | 0.201 |
| Lumbar spine BMD | 0.72*  | 0.67* | 0.61* | 0.644* | 0.334* |
| Trabecular bone score | 0.42* | 0.62* | 0.07 | 0.07 | 0.08 |

*p < 0.05, statistical significance. BMD, bone mineral density; AD-SoS, amplitude-dependent speed of sound; BTT, bone transmission time; UBPI, ultrasound bone profile index; DI, density index; Cth, cortical thickness.
significantly different values of TBS, BTT, cortical thickness, and handgrip strength ($p < 0.05$, Figure 1).

Finally, we performed a multiple regression analysis, identifying as a dependent variable the 10-year fracture risk for major fracture, whereas age, BMI, time since dialysis, AD-SoS, BTT, cortical bone thickness, TBS, and handgrip strength were included as independent variables. In this analysis, only BTT ($\beta = -15.21$, $SE = 5.91$, $p = 0.02$) and TBS ($\beta = -54.69$, $SE = 21.88$, $p = 0.02$) turned out to be independently associated with fracture risk. Analysis showed a variance inflation factor for BTT and TBS of 1.624, excluding multicollinearity problems in this model.

**Discussion**

This study investigated surrogates of bone strength in hemodialysis patients by the gold-standard DXA and by ultrasonography. Simultaneously, it explored the association between muscle strength and the instrumental surrogates of bone strength, including the DXA-derived TBS. Hemodialysis patients presented poorer bone quality as suggested by reduced TBS and low QUS values compared to controls. Handgrip strength was also lower in hemodialysis patients and was significantly associated with quantitative and qualitative indices of bone strength.

Considering the aging of the CKD population, the relevance of osteoporosis is considerably increasing in this group (21). As a result, adequate screening for bone fragility to prevent the burden of osteoporotic fracture in terms of economic costs, morbidity, and mortality is urgently needed (11). Consequently, the identification of dialysis patients at high fracture risk should be encouraged and included in the diagnostic work-up of CKD patients (31, 32).

Bone fragility encompasses all the characteristics that promote fractures, mainly bone structure, bone turnover, and mineralization deficits that are all observed in CKD (21). However, the association between BMD obtained by DXA, which is the most recognized determinant of bone strength,
and fragility fracture observed in CKD patients is not as strong as in the general population (31). Accordingly, Jamal et al. found no association between fractures, hip, and spine BMD; however, tests of neuromuscular function, namely the time up and go, functional reach, and the 6-min walk test, were able to discriminate among patients with and without fractures (25).

These observations are consistent with our findings, particularly regarding the association between the handgrip strength and all of the QUS/PEUS surrogates of bone strength. In hemodialysis patients, we observed that participants with reduced handgrip strength were those not only with lower BMD at the lumbar spine and femur but also with lower TBS and AD-SoS, which are accepted markers of bone quality. In particular, TBS and QUS variables have been shown to correlate significantly with bone structural parameters measured by histomorphometry (33).

The reduction in muscle strength could accordingly capture both quantitative and qualitative alterations in bone. The associations shown in Table 2 between BMD, intended as a quantitative measure of bone strength, and the qualitative indices such as TBS, and also QUS and PEUS, support this hypothesis. These findings also suggest an overall (qualitative/quantitative) bone impairment in hemodialysis patients (34).

Moreover, poorer handgrip strength was noted in the participants with a higher prevalence of morphometric Vfx in the hemodialysis group; conversely, BMD alone was not able to discriminate between hemodialysis patients with Vfx. Consistently, hemodialysis patients, in comparison with the controls, presented BMD values not significantly different at the femoral level and even significantly higher at the lumbar spine. This result highlights that BMD has a low predictive value for fracture in end-stage kidney disease (9).

Since lower muscle performance is also correlated with a higher propensity to fall, it could also explain the higher rate of fractures (35).

Also, due to its simple, inexpensive, rapid, and noninvasive measurement, the handgrip strength evaluation may be considered in the clinical evaluation of CKD to identify patients suitable for further instrumental assessment of bone fragility. For the reason that DXA remains the gold-standard method to check for bone fragility, it appears valuable to also comprise the TBS calculation, at least in dialysis patients (36–40).

In this study, we explored cortical bone by PEUS. Even if no significant differences between dialysis patients and controls were found, consistent with previous data (28, 41), we observed an association between Cth and DI with BMD; D1 was also significantly associated with the 10-year probability of femur fracture. The assessment of cortical bone structure in CKD could be critical since it is predominantly affected by the bone loss that is correlated with high PTH and with peripheral fractures (42). BMD measurement by DXA cannot discriminate between cortical and trabecular bone, and PEUS measurement of Cth may contribute, at least in part, to bone status evaluation, even though it is not able to capture microporosity (27).

The 10-year probability of major osteoporotic fractures was independently associated with BTT, suggesting that QUS can help distinguish patients at high risk of fracture. QUS measurements have previously been proven to be related to mineral metabolism alterations in hemodialysis (43). Furthermore, the 10-year probability of major osteoporotic fractures was independently inversely associated with TBS, which in turn was strictly related to QUS measurements, probably all of these assessments being dependent on bone quality characteristics such as microarchitecture. Recently, in patients with CKD, Rampersad et al. observed that lower TBS scores were associated with lower eGFR and increased fracture risk in patients with eGFR ≥ 60 ml/min/1.73 m² (44). Nevertheless, the role of TBS in predicting clinical fractures in prospective studies focused on dialysis patients has not yet been demonstrated (45). However, an association with higher bone turnover and prevalent fractures has recently been evidenced in end-stage CKD and dialysis (40, 46, 47).

This research has some limitations represented by the small sample size and the cross-sectional design. On the other hand, it represents the first study to investigate fracture risk by DXA and QUS/PEUS together and to explore the association of muscle strength with indices of bone quality in hemodialysis patients.

In conclusion, we observed a higher fracture risk in hemodialysis patients in comparison with controls. Hemodialysis patients showed lower indices of bone quality, including TBS and phalangeal QUS measurements; moreover, they showed lower handgrip strength. Handgrip strength was associated not only with fracture risk per se but also with TBS and phalangeal QUS measurements, which were markers of bone strength and strictly related to the probability of fracture.

Further longitudinal studies looking at the predictive values of surrogates of bone quality on fracture are needed to improve fracture risk management in hemodialysis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Research Committee Policlinico G. Martino of Messina. The patients/participants provided their written informed consent to participate in this study.
Author contributions

AC and NM designed the study. AC, AG, and DS analyzed data and wrote the manuscript. AC, FB, and MF collected data. AX, GG, GB, and GN evaluated the literature included in the study. GS, FC, and AG acquired funding. All the authors had full access to all the data in the study and take responsibility for the integrity and the accuracy of the data analysis. All authors reviewed the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was partially funded by the 2020/2022 Research Plan “Piaceri” of the University of Catania, Open Access line.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, et al. Increased risk of hip fracture among patients with end-stage renal disease. Kidney Int (2000) 58(1):396–9. doi: 10.1046/j.1523-1755.2000.01178.x
2. Jamal SA, Hayden JA, Beyene J. Low bone mineral density and fractures in long-term hemodialysis patients: A meta-analysis. Am J Kidney Dis (2007) 49(5):674–81. doi: 10.1053/j.ajkd.2007.02.264
3. Mittelknichel A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. Am J Kidney Dis (2004) 44(4):672–9. doi: 10.1016/S0272-6386(04)00958-8
4. Castro-Alonso C, D’Marco L, Pomes J, Del Amo Conill M, Garcia-Diez AI, Molina P, et al. Prevalence of vertebral fractures and their prognostic significance in the survival in patients with chronic kidney disease stages 3–5 not on dialysis. J Clin Med (2020) 9(5):1604. doi: 10.3390/jcm9051604
5. Khairallah P, Nickolas TL. Updates in CKD-associated osteoporosis. Curr Osteoporos Rep (2018) 16(6):712–23. doi: 10.1007/s11914-018-0491-3
6. Hsu CY, Cummings SR, McCulloch CE, Chen T, GM. Bone mineral density is not diminished by mild to moderate chronic renal insufficiency. Kidney Int (2002) 61(5):1814–20. doi: 10.1046/j.1523-1755.2002.00306.x
7. Jamal SA, West SL, Miller PD. Fracture risk assessment in patients with chronic kidney disease. Osteoporosis Int (2012) 23(4):1191–8. doi: 10.1007/s00198-011-1781-0
8. Mirza F, Canalis E. Management of endocrine disease: Secondary osteoporosis. Pathophysiology and management. Eur J Endocrinol (2015) 173(3):R131–51. doi: 10.1530/EJE-15-0119
9. Kim K, Song SH, Kim JJ, Jeon YK. Is dual-energy absorptionmetry accurate in the assessment of bone status of patients with chronic kidney disease? Osteoporosis Int (2021) 32(9):1859–68. doi: 10.1007/s00198-020-05670-z
10. Ketteler M, Block GA, Enevendop P, Fukuagawa M, Herzog CA, McCann L, et al. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder guideline update: What’s changed and why it matters. Kidney Int (2017) 92(1):26–36. doi: 10.1016/j.kint.2017.04.006
11. Catalano A, Morabito N, Basile G, Fusco S, Castagna G, Retano F, et al. Fracture risk assessment in postmenopausal women referred to an Italian center for osteoporosis: A single day experience in Messina. Clin aus. Miner Bone Metab (2013) 10(3):191–4
12. Jamal SA, West SL, Nickolas TL. The clinical utility of FRAX to discriminate fracture status in men and women with chronic kidney disease. Osteoporosis Int (2014) 25(1):171–6. doi: 10.1007/s00198-013-2524-1
13. Przedlacki J, Buczyńska Chyl J, Kozięmiska P, Niemczyk E, Wójcieszak E, Gigiel E, et al. FRAX prognostic and intervention thresholds in the management of major bone fractures in hemodialysis patients: A two-year prospective multicenter cohort study. Bone (2020) 131:15188. doi: 10.1016/j.bone.2019.15188

Catalano A, Morabito N, Agostoni RM, Basile G, Gaudioso A, Atteriano M, et al. Bone health assessment by quantitative ultrasound and dual-energy x-ray absorptiometry in postmenopausal women with breast cancer receiving aromatase inhibitors. Menopause (2017) 24(1):85–91. doi: 10.1097/GME.0000000000001222
15. Harvey NC, Gliser CC, Binkley N, McCloskey EV, Brandi ML, Cooper C, et al. Trabecular bone score (TBS) as a new complementary approach for osteoporosis evaluation in clinical practice. Bone (2015) 78:216–24. doi: 10.1016/j.bone.2015.05.016
16. Leib E, Winzenrieth R, Lamy O, Hans D. Comparing bone microarchitectural by trabecular bone score (TBS) in Caucasian American women with and without osteoporotic fractures. Calcif Tissue Int (2014) 95(3):201–8. doi: 10.1007/s00223-014-9882-3
17. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. Adjusting fracture probability by trabecular bone score. Calcif Tissue Int (2015) 96(6):506–9. doi: 10.1007/s00223-015-9980-x
18. Giguhlmi G, Njeh CF, DEterlizi F, De Serio DA, Scillitani A, Cammisa M, et al. Phalangeal quantitative ultrasound, phalangeal morphometric variables, and vertebral fracture discrimination. Calcif Tissue Int (2003) 72(4):469–77. doi: 10.1007/s00223-001-1092-0
19. Gliser CC, Eastell R, Reid DM, Felsenburg D, Roux C, Barkmann R, et al. Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in a population-based sample: the OPUS study. J Bone Miner Res (2004) 19(5):782–93. doi: 10.1159/00008-04.03084
20. Kanis JA, Johnell O, Oden A, DElaet C, DEterlizi F. Ten-year probabilities of clinical vertebral fractures according to phalangeal quantitative ultrasonography. Osteoporos Int (2005) 16(9):1065–70. doi: 10.1007/s00198-004-1805-0
21. Miller PD. Bone disease in CKD: a focus on osteoporosis diagnosis and management. Am J Kidney Dis (2014) 64(2):290–304. doi: 10.1053/j.jkd.2013.12.018
22. Gerdhem P, Ringberg KA, Axesson K, Obrant KJ. Influence of muscle strength, physical activity and weight on bone mass in a population-based sample of 1004 elderly women. Osteoporosis Int (2003) 14(9):768–72. doi: 10.1007/s00198-003-1444-x
23. Sirola J, Rikkonen T, Tuppurainen M, Juvonen JS, Alhava E, Kröger H. Grip strength may facilitate fracture prediction in postmenopausal women with normal BMD: A 15-year population-based study. Calcif Tissue Int (2008) 83(2):93–100. doi: 10.1007/s00223-008-9155-0
24. Rikkonen T, Sirola J, Salovaara K, Tuppurainen M, Juvonen JS, Honkanen R, et al. Muscle strength and body composition are clinical indicators of osteoporosis. Calcif Tissue Int (2012) 91(2):131–8. doi: 10.1007/s00223-012-9618-1
25. Jamal SA, Leiter RE, Jassal V, Hamilton CJ, Bauer DC. Impaired muscle strength is associated with fractures in hemodialysis patients. Osteoporos Int (2006) 17(9):1390–7. doi: 10.1007/s00198-006-0133-y

26. Chen SC, Chung WS, Wu PY, Huang JC, Chiu YY, Chang JM, et al. Associations among geriatric nutrition risk index, bone mineral density, body composition and handgrip strength in patients receiving hemodialysis. Nutrition (2019) 65:6–12. doi: 10.1016/j.nut.2019.02.013

27. Schoubye JT, Riekkinen O, Kajalainen J. Prediction of hip osteoporosis by DXA using a novel pulse-echo ultrasound device. Osteoporos Int (2017) 28(1):85–93. doi: 10.1007/s00198-016-3722-4

28. Kajalainen JP, Riekkinen O, Krüger H. Pulse-echo ultrasound method for detection of post-menopausal women with osteoporotic BMD. Osteoporos Int (2018) 29(5):1193–99. doi: 10.1007/s00198-018-4408-x

29. Catalano A, Gaudio A, Agostino RM, Morabito N, Bellone F, Lasco A. Trabecular bone score and quantitative ultrasound measurements in the assessment of bone health in breast cancer survivors assuming aromatase inhibitors. J Endocrinol Invest (2019) 42(11):1337–43. doi: 10.1007/s40618-019-01063-0

30. Catalano A, Morabito N, Di Vesta G, Pintaudi B, Cucinotta D, Lasco A, et al. Phalangeal quantitative ultrasound and metabolic control in pre-menopausal women with type 1 diabetes mellitus. J Endocrinol Invest (2013) 36(3):347–51. doi: 10.3257/8646

31. Hansen D, Olsen JB, Gislason GH, Abrahamsen B, Hommel K. Risk of fracture in adults on renal replacement therapy; a Danish national cohort study. Nephrol Dial Transplant (2016) 31(10):1654–62. doi: 10.1093/ndt/gfw073

32. Tentori F, McCullough K, Kilpatrick RD, Bradbury BD, Robinson BM, Kerr PG, et al. High rates of death and hospitalization follow bone fracture among end stage kidney disease patients. Kidney Int (2014) 85(1):166–73. doi: 10.1038/ki.2013.279

33. Ramalho J, Marques IDB, Hans D, Dempster D, Zhou H, Patel P, et al. The trabecular bone score: Relationships with trabecular and cortical microarchitecture measured by HR-pQCT and histomorphometry in patients with chronic kidney disease. Bone (2018) 116:215–20. doi: 10.1016/j.bone.2018.08.006

34. Abdalbary M, Sobh M, Elbagir S, Elhady AM, Elshabrawy N, Abdelalam M, et al. Management of osteoporosis in patients with chronic kidney disease. Osteoporos Int (2022). doi: 10.1007/s00198-022-06462-3

35. Greco EA, Pietschmann P, Migliaccio S. Osteoporosis and sarcopenia increase frailty syndrome in the elderly. Front Endocrinol (Lausanne) (2019) 10:255. doi: 10.3389/fendo.2019.00255

36. Shevroja E, Lamy O, Hans D. Review on the utility of trabecular bone score, a surrogate of bone micro-architecture, in the chronic kidney disease spectrum and in kidney transplant recipients. Front Endocrinol (Lausanne) (2018) 9:561. doi: 10.3389/fendo.2018.00561

37. Dusceac R, Nicolae DA, Dobre R, Dragne MC, Taceu C, Peride I, et al. Chronic hemodialysis is associated with lower trabecular bone score, independent of bone mineral density: A case–control study. Arch Osteoporos (2018) 13(1):125. doi: 10.1007/s11657-018-0541-6

38. Yun HJ, Ryoo SR, Kim JB, Choi YJ, Park I, Shin GT, et al. Trabecular bone score may indicate chronic kidney disease-mineral and bone disorder (CKD-MBD) phenotypes in hemodialysis patients: A prospective observational study. BMC Nephrol (2020) 21(1):299. doi: 10.1186/s12882-020-02194-0

39. Brunovska L, Kasalický P, Verešová J, Potocková J, Rychlik I. Loss of bone mineral density and trabecular bone score in elderly hemodialysis patients: A 2-year follow-up, prospective, single-centre study. Int Urol Nephrol (2020) 52(2):379–85. doi: 10.1007/s11255-020-02378-1

40. Alekssova J, Kurniawan S, Elder GJ. The trabecular bone score is associated with bone mineral density, markers of bone turnover and prevalent fracture in patients with end stage kidney disease. Osteoporos Int (2018) 29(6):1447–55. doi: 10.1007/s00198-018-4468-y

41. Chiba K, Suetsobi R, Creatin D, Arai T, Kawajiri T, Okayama A, et al. Development of a QUS device to evaluate deterioration of cortical bone: Verification by HR-pQCT and measurements in healthy individuals and dialysis patients. J Clin Densitom (2021) 24(1):94–105. doi: 10.1016/j.jocd.2020.02.002

42. Nickolas TL, Jamal SA. Bone kidney interactions. Rev Endocr Metab Disord (2015) 16(2):157–63. doi: 10.1007/s11154-015-9314-3

43. Zywicz J, Pluwicki W, Adamszcz P, Skobala A, Guemprecht J. Phalangeal quantitative ultrasound measurements in chronic hemodialysis patients: A 4-year follow-up. Ultrasound Med Biol (2012) 38(6):962–71. doi: 10.1016/j.ultrasmedbio.2012.02.035

44. Rampersad C, Whitlock RH, Leslie WD, Rigatto C, Komenda P, Bohm C, et al. Trabecular bone score in patients with chronic kidney disease. Osteoporos Int (2020) 31(10):1905–12. doi: 10.1007/s00198-020-05438-1

45. Poiana C, Duscear C, Niculescu DA. Utility of trabecular bone score (TBS) in bone quality and fracture risk assessment in patients on maintenance dialysis. Front Med (Lausanne) (2022) 8:782837. doi: 10.3389/fmed.2021.782837

46. Fusaro M, Aggi A, Mereu MC, Giusti A. Fratture da fragilità nella malattia renale cronica (MRC) [Fragility fracture in the chronic kidney disease (CKD)]. G Ital Nefrol (2017) 34:2017–vol6.

47. Malle O, Bergbächer M, Krüper P, Amrein K, Dumai HP, Kirsch AH, et al. usefulness of the trabecular bone score in maintenance dialysis patients: A single center observational study. Wien Klin Wochenschr (2022) 134(11-12):442–8. doi: 10.1007/s00508-022-02011-4