Quality of care and monitoring in paediatric end stage renal disease

van Huis, Maike

Citation for published version (APA):
van Huis, M. (2016). Quality of care and monitoring in paediatric end stage renal disease
Low bone mineral density measured with DXA does not predict bone disease in adulthood after childhood renal failure

M. van Huis, J.H van der Lee, A.M. Boot, J.L. Vogelzang and J.W. Groothoff

Submitted BMC Nephrology.
ABSTRACT

Background
In 2000, we conducted a late outcome study in all Dutch adult patients, born before 1979 with childhood onset of end-stage renal disease (ESRD). We found a very low bone mineral density (BMD) measured by DXA in these patients. In the present study we aim to investigate the predictive value of BMD measured in 2000 by DXA for clinical bone disease (CBD) and fractures in the subsequent 10 years.

Methods
Data on CBD and fractures were gathered by reviewing medical charts and by questionnaires. Logistic regression analysis was used to calculate the association between BMD in 2000 and CBD and fractures in the period 2000-2010. Volumetric BMD of the lumbar spine was calculated to correct for small height.

Results
Between 2000 and 2010 sixty-three (47%) and nineteen (14%) of all 133 patients suffered from CBD or fractures, respectively. Logistic regression showed no association between (volumetric) BMD and the presence of CBD or fractures. The area under the curve [95%CI] of the diagnostic ROC curve for the ability of DXA (volumetric BMD of the lumbar spine) to distinguish patients who would develop fractures was 54% [41%-68%].

Conclusion
CBD was highly prevalent among middle aged patients with paediatric ESRD, but not predicted by DXA 10 years earlier. Other modes of imaging are indicated for clinical surveillance of these patients.
BACKGROUND

Chronic kidney disease induced mineral and bone disorder (CKD-MBD) is a common complication of end-stage renal disease (ERSD), which often leads to severely disabling motor disabilities. Inadequately treated CKD-MBD and corticosteroid induced osteoporosis can cause chronic bone pain, fractures and motor impairment. Patients on dialysis are at risk for fractures, as shown in a study by Alem et al [1], in which dialyzed patients in their 40s had a 80-fold increased risk for hip fracture. In a long-term follow up study in 2000 of patients with childhood onset ESRD, we found that 37% of these patients, who were aged 20-40 years and had spent on average 75% of their renal replacement therapy (RRT) time with a functioning graft, daily suffered from symptoms of bone disease[2]. At the same time, we found on average extremely low values of bone mineral density (BMD) of femur neck and lumbar spine as measured by Dual Energy X-ray Absorptiometry (DXA), i.e. mean [SD] Z-score BMD of the lumbar spine was -2.1 [1,4]. In the general population, BMD measured by DXA is a good predictor for fractures in both adults and children [3-5]. The validity of DXA in the group of patients with CKD is disputable as data on the predictive value of DXA BMD scores in CKD are conflicting [6-8]. Despite these uncertainties, DXA is still regarded as a useful tool in the diagnosis and monitoring of ROD and routinely used for this purpose in many centres. In this study we investigated the impact of childhood ESRD on clinical manifestations of bone disease after more than 27 years of RRT, and in particular we wanted to know to what extent the low BMD values that we found in 2000 predicted clinical manifestations of bone disease and fractures in the subsequent 10 years of follow-up. In addition to unadjusted BMD values, we calculated volumetric BMD of the lumbar spine in order to see if adjustment of BMD to the small height of the patients would improve the predictive value of DXA for clinical bone disease and fractures.

SUBJECTS AND METHODS

Study population
This study is part of a comprehensive study on the Late Effects of Renal Insufficiency in Children (LERIC) which comprised all Dutch patients born before 1979 who started renal replacement therapy at age 0-15 years between 1972 and 1992. The cohort consisted of 249 patients, of whom 63 were deceased at time of first analysis in 1999-2000. Of all 249 patients data were retrieved from medical charts. All living 186 patients were asked to participate in the cross-sectional part of the LERIC study by visiting the Academic Medical Centre (AMC) in Amsterdam in 1999 and 2000, and 140 of these patients, aged 20-40 years, were willing to participate in the cross-sectional part of the study. DXA scan of the lumbar spine and femoral neck was performed in all these individuals. Disease characteristics of participants and non-participants were comparable [2]. In 2010, all surviving patients of the LERIC cohort were again invited to participate in a 10 years extension of the LERIC study.
We gathered data on clinical manifestations of bone disease by reviewing medical charts and by sending questionnaires to the patients. If necessary, people were contacted directly by telephone. For this study we were able to use data of 133 patients (see figure 1). Written informed consent from all participants and approval from the ethical board of the Academic Medical Center were obtained.

Definition of variables

BMD was measured with the Hologic Dual Energy X-ray Absorptiometry (QDR 4500A Hologic Inc., Waltham, Mass., USA). BMD was assessed at the lumbar spine (LS) (L1-L4) and femur neck (FN). To correct for bone size – and consequently height- we calculated volumetric bone mineral density (vBMD) of the lumbar spine as described by Ward et al.[9]:

\[ \text{LS vBMD} \ (\text{g/cm}^3) = \frac{(\text{BMC}_1 + \text{BMC}_2 + \text{BMC}_3 + \text{BMC}_4)}{(V_1+V_2+V_3+V_4)} \]

where \(V_1\) (volume of vertebral 1) is calculated as area of \(L1^3/2\), similarly for L2-L4 and BC1 – BC4 are Bone Mineral Content values of the individual vertebral bodies as provided by the device. Since reference values for adult vBMD are lacking, vBMD reference values for 17 year olds as provided by Ward et al. [9] were used. Z-scores were calculated with the LMS-method by Cole and Green[10]. Reference values of the 17 year olds were used, since this is nearly the age of peak lumbar spine vBMD as shown by Boot et al. [4].

Clinical bone disease (CBD) was defined as the presence of one or more of the following conditions: bone deformations, chronic bone-related pain, motor disabilities, aseptic bone necrosis, (non-traumatic) fractures and hospital admission or surgery due to bone related problems.

Reference values of weight and height per gender were derived from the National Dutch Health Statistics[11].

Statistical analysis

Values are presented as mean [SD] unless stated otherwise. Characteristics of living and deceased patients were compared to investigate mortality as a potential source of selection bias.

We performed logistic regression analysis to estimate the association between (v)BMD Z-scores in 2000 and the presence of clinical bone disease and (pathologic) fractures in the 10 years follow-up. We investigated potential confounding and effect modification of this association by mortality by adding this variable and its interaction term with BMD as additional determinants in the logistic regression model. The area under the curve of the diagnostic ROC curve was calculated to evaluate the ability of DXA to distinguish patients who would develop CBD and/or (pathological) fractures. All analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

In 2010, we could include data from 133 patients, of whom 20 patients had died between 2000 and 2010. A flowchart of the cohort is presented in Figure 1. 73 of the patients (55%) were male (table 1). Median [range] age at time of DXA was 28.8 [20.9-42.0] years, at the
end of the observational period 39.9 [32.0-52.4] years (Table 2). Mean [SD] height at time of DXA was 165.1 [9.4] and 156.7 [8.7] cm for males and females, respectively. Mean [SD] height Z-score at time of DXA was -2.3 [1.2]. Median [range] time on RRT was 18.0 [0.6 – 29.9] years, patients spent the greater part of their RRT time with a renal transplant. Sixty-three (47%) of all 133 patients had signs of CBD between 2000 to 2010. Nineteen (14%) patients suffered from one or more fractures. Fifty percent (10/20) of all patients who died between 2000 and 2010 and 47% (63/133) of patients alive in 2010 suffered from CBD (95% CI of the difference -21% –27%). Sixteen (14%) of all patients alive in 2010 and 3 (15%) of all patients who died between 2000 and 2010 suffered from one or more fractures. An overview of general characteristics and outcomes is given in tables 1-3.

Bone Mineral Density and volumetric Bone Mineral Density
Mean [SD] Z-score of all patients of the LS and FN was -2.1 [1.4] and -1.7 [1.3], respectively. Mean BMD Z-score of the LS and FN was significantly lower in patients who died between 2000 and 2010 than in those still alive in 2010 (p=0.01 and p=0.03 for FN and LS, respectively). Mean [SD] of the vBMD of the LS was -1.0 [1.5] and did not differ significantly between patients alive and deceased in 2010 (p=0.09). The results of the logistic regression analyses are presented in table 4. No significant association was found between either BMD of the FN or LS and the presence of CBD or fractures. The vBMD of the LS was not associated with the presences of CBD or fractures in the subsequent 10 years (table 4). Adjustment for mortality did not lead to a change in these associations; effect modification was not statistically significant.

The area under the curve (AUC) [95%CI] of the diagnostic ROC curve for the ability of DXA (vBMDLS) to distinguish patients who would develop CBD or fractures was 47% [37%-57%] and 54% [41%-68%], respectively (Figure 2a-b).

DISCUSSION
As far as we know, this study provides the longest follow up of childhood onset of ESRD. We found that 47% of survivors aged 30-50 years old of paediatric ESRD suffer daily from clinical bone disease. Despite the fact that 10 years ago, these patients had a very low BMD as assessed by DXA, nor the BMD values nor the vBMD values were predictive for the manifestations of CBD or fractures in the consecutive years. This implies that DXA is not a valid tool for predicting clinical bone disease and fracture risk in patients with paediatric ESRD.

CKD-MBD is an important disabling comorbidity of renal failure. Our study shows that patients with paediatric ESRD are particularly at risk to suffer from CKD-MBD at a relatively young age, despite the fact that over 80% of the total RRT time was spent with a functioning graft. It is always believed that close monitoring of biomarkers of CKD-MBD and imaging of bone is essential in order to optimize bone protective therapy and hence to
Low bone mineral density measured with DXA in renal failure

prevent the development of CBD or fractures in ESRD patients. Several studies advocate DXA as an important and reliable tool for predicting fracture risk in patients with ESRD and chronic kidney disease [12-14], especially after transplantation. Jamal et al. [13] found an increased fracture risk (OR 1.56) for BMD at the radius measured by DXA in a cohort of 221 CKD stage 3-5 patients with a mean age of 63.3 years. A study in 2012 on the diagnostic usefulness of BMD in 485 CKD stage 5D patients on haemodialysis by Iimori et al. [14] concluded that total hip BMD measured by DXA can be used to predict fracture risk in females with low PTH. Iimori et al. also examined 13 studies that were reviewed by the KDIGO CKD-MBD guideline development group and found highly variable results between the studies assessing the association between fractures and BMD in CKD [14]. In a meta-analysis of Jamal et al. [15] of studies in adult long term on haemodialysis, subjects with fractures had significantly lower BMD of the spine or radius than subjects without fractures. All these studies addressed patients with a mean age over 60 years. At this age, females may also have postmenopausal osteoporosis and also in males over 60 years of age BMD will decrease with age with a higher risk of fractures. This makes these studies hard to compare with the present study in which the mean age at the time of DXA was is 29 years. Studies in children with a functioning renal graft are scarce. In a 5-year follow-up study in 106 paediatric renal transplant patients, mean BMD Z-score did not differ between patients with and without a vertebral fracture. In 2011, Wesseling et al. stated that DXA is inappropriate to use in children with CKD and this is in accordance with the current guidelines of the International Society of Clinical Densitometry (ICSD) [16]. Currently as far as we know, no studies have assessed the predictive value of DXA in young to middle-aged adult ESRD patients.

The fact that we found no association between BMD in 2000 and CBD and fractures in 2010 nevertheless contrasted with our expectations in 2000 [2]. We speculated that the BMD values in our population were partly determined by the small stature of our patients. We therefore calculated volumetric BMD for the lumbar spine. We found that the vBMD LS z-scores were indeed higher than the BMD z-scores in our cohort, but still significantly lower than in healthy subjects. This implies that the low BMD that we found in these patients was not merely a reflection of short stature and smaller bones.

The pathophysiology of CKD-MBD may explain the problems of DXA in detecting the disease. CKD-BMD can be due to either high or low turnover bone disease and can affect both cortical or trabecular bone. High turnover bone disease initially results in irregularly thickening of the trabecular bone and an increase of the bone volume. With progression of the disease, trabecular bone degrades and bone volume decreases. As the disease further progresses, high turnover bone disease will eventually lead to degradation and loss of volume of trabecular bone and to a decrease of cortical bone thickness. In contrast, low turnover bone disease is characterized by a decreased bone volume at all stages and may lead to all kinds of alterations in trabecular bone [17, 18]. DXA cannot discriminate between cortical and trabecular bone and does not give information on bone microarchitecture. Hence it
cannot discriminate between high and low turnover bone disease. As high turnover bone disease could partly lead to an increased BMD, albeit with an abnormal bone structure, it could go undetected by DXA. This hypothesis is supported by several studies in which no correlation was found between BMD measured with DXA and histopathological findings in bone biopsies [19-22]. This may explain why the predictive value of DXA for fracture risk in patients suffering from end-stage renal disease is so unclear [14, 23-26] and warrants more extensive and prospective studies [27-29].

When patients suffer from ESRD since childhood, CKD-BMD can already occur at a young age. As in young adults with ESRD, DXA in paediatric ESRD is hampered by even more challenges. First of all, DXA provides an underestimation of the BMD in people with a short stature, as DXA represents a two dimensional image of a three dimensional object in which it does not account for bone size [26, 30]. Secondly, reference data for paediatric DXA should ideally be matched for gender, height, weight and age, as well as for ethnicity and pubertal development [9]. Therefore, with the current software, misinterpretation of BMD in children can easily occur due to incorrect reference data [31]. The use of DXA is not recommended by KDIGO for the measurement of BMD in children with CKD [20].

Apart from CKD-BMD and short stature, a low BMD could also be the reflection of low lean body mass. Our patients had a normal BMI, but a short stature, which complicates the interpretation of the DXA results. Furthermore, due to vascular calcifications, the BMD at the lumbar spine may be overestimated [32].

More recent studies [33-36] have shown that new imaging methods, such as pQCT, have good reproducibility and are able to discriminate between trabecular and cortical bone. Christoforidis et al [37] showed that quantitative ultrasound correlated more with biochemical indices of CKD-BMD than with DXA. These new imaging methods might be able to detect bone loss at an earlier stage and hence enable better management of bone disease and prevention of future fracture risk [8].

LIMITATIONS

Our study has several limitations. First, we did not have the ability to analyse serial DXA measurements, as we only had one DXA scan per patient. Possibly, with serial DXA measurement a more accurate prediction of fracture risk is possible. Secondly, we were not able to calculate vBMD of the femur neck, which is considered to be a more reliable predictor of fracture risk. Finally, we were not accurately informed on the use of drugs enhancing bone mineral density, such as bisphosphonates. Therefore, we were not able to assess the effect of these drugs on BMD measurements and outcome. Finally, due to the low numbers of fractures in our study population, we might not have been able to find any association with BMD. However, to our knowledge, this paper demonstrated the longest follow up of adults with childhood onset ESRD so far.
CONCLUSIONS

Clinical bone disease occurs in about half of all survivors of paediatric ESRD aged 30-50 years. BMD measured by DXA is not useful in predicting clinical bone disease or fractures in patients with childhood onset ESRD. Given the high prevalence, other imaging methods are needed in order to monitor and prevent fracture risk and motor disabilities from CKD-BMD in these patients.
FIGURES

Figure 1.
Flowchart of study population
Low bone mineral density measured with DXA in renal failure

Figure 2a.
The area under the curve (AUC) [95% CI] of the diagnostic ROC curve for the ability of DXA (vBM-DLS) to distinguish patients who would develop CBD was 47% [37%-57%].

Figure 2b.
The area under the curve (AUC) [95% CI] of the diagnostic ROC curve for the ability of DXA (vBM-DLS) to distinguish patients who would develop fractures was 54% [41%-68%].
TABLES

**Table 1 General characteristics 2010**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>% of total (133)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>55</td>
</tr>
<tr>
<td>Deceased in 2010</td>
<td>20</td>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start of RRT(^1)</td>
<td>133</td>
<td>11.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Age at assessment (years)</td>
<td>113</td>
<td>28.8</td>
<td>20.9</td>
</tr>
<tr>
<td>Time on RRT(^1) (years)</td>
<td>113</td>
<td>27.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

# Number of patients
\(^1\) Renal replacement therapy

**Table 2 Characteristics at time of Dual Energy X-ray Absorptiometry (1999-2000)**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>mean</th>
<th>SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD(^a) FN(^b) (g/cm(^2))</td>
<td>131</td>
<td>0.33</td>
<td>0.07</td>
</tr>
<tr>
<td>BMD(^a) LS(^c) (g/cm(^2))</td>
<td>133</td>
<td>0.83</td>
<td>0.15</td>
</tr>
<tr>
<td>BMD(^a) FN(^b) Z-score</td>
<td>131</td>
<td>-1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>BMD(^a) LS(^c) Z-score</td>
<td>133</td>
<td>-2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>vBMD(^d) LS (g/cm(^3))</td>
<td>133</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>vBMD(^d) LS Z-score</td>
<td>133</td>
<td>-1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Height Z-score</td>
<td>133</td>
<td>-2.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Total duration of RRT(^1) (years)</td>
<td>133</td>
<td>18.3</td>
<td>5.4</td>
</tr>
<tr>
<td>Total duration with renal transplant (years)</td>
<td>133</td>
<td>13.7</td>
<td>6.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at assessment (years)</td>
<td>133</td>
<td>39.9</td>
<td>32.0</td>
</tr>
<tr>
<td>Time on RRT(^1) (years)</td>
<td>133</td>
<td>18.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Time on transplantation (years)</td>
<td>128</td>
<td>13.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Time on haemodialysis (years)</td>
<td>121</td>
<td>2.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Time on peritoneal dialysis (years)</td>
<td>51</td>
<td>1.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

# Number of patients
* Standard Deviation
\(^a\) Bone Mineral Density
\(^b\) Femur Neck
\(^c\) Lumbar Spine
\(^d\) Volumetric Bone Mineral Density
\(^e\) Renal Replacement Therapy
REFERENCES

