Bone mineral disorders in patients on maintenance hemodialysis and after kidney transplantation

Thesis abstract

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Introduction

The prevalence of chronic kidney disease (CKD) is steadily increasing. The estimated prevalence of patients with impaired kidney function in Hungary is around 900 thousand and the number of patients on maintenance hemodialysis reaches 6000.

One of the most common complications of CKD is bone mineral disease, former referred to as renal osteodystrophy. In early stages, it is a silent disease with moderate changes in laboratory results (increased parathyroid hormone secretion, decreased vitamin D levels), but with the progression of kidney insufficiency it can lead to severe complications, such as bone loss, bone fracture, vascular calcification and calciphylaxis; contributing to the high cardiovascular morbidity and mortality in this population.

The incidence of bone fractures and also the mortality following fractures is higher in CKD patients compared to the general population. The association between fractures and postmenopausal osteoporosis is well described in the general population but the relationship between bone loss and fracture risk is not well established in patients with kidney insufficiency.

Bone mass, ultrastructure and the ability to repair micro damage are major determinants of bone fragility. One of the factors that determine those properties is bone turnover, which is mainly regulated by PTH. In CKD, changes in bone turnover will have important effects on bone ultrastructure, repair functions and mineral density as well. In addition, other factors such as vitamin D deficiency, estrogen deficiency, uremic milieu, immobility and chronic inflammation also contribute to the changes of bone metabolism.

In this work, I summarize results of four studies. In the first three studies, I analyzed the associations between parathyroid hormone, vitamin D deficiency, bone mass and fractures among patients on maintenance hemodialysis. In the last study, I report data about the mineral bone disease in patients after renal transplantation.

Aims and hypotheses

Parathyroid function and bone mineral density in patients on maintenance hemodialysis

It seems established that significant hyperparathyroidism, i.e. serum iPTH>300 pg/ml according to the guideline, is usually associated with high bone turnover, and it leads to low bone mineral density (BMD) in patients on hemodialysis. It is much less clear whether low turnover or adynamic bone disease (ABD), usually associated with relatively low serum iPTH (relative hypoparathyroidism: iPTH<100 or 150 pg/ml), is associated with reduced BMD and increased fracture risk.

The aims of the first study were

- to determine whether relative hypoparathyroidism, defined by serum iPTH<100 pg/ml, likely reflecting low bone turnover, is associated with reduced bone mineral density compared to patients with iPTH in the target range (100-300pg/ml)
- to analyze the association between serum iPTH and bone metabolism across the full range of parathyroid function, including relative hypoparathyroidism
- to identify factors associated with low BMD in patients on maintenance hemodialysis.

Vitamin D insufficiency and bone metabolism

Observational studies suggest high prevalence of vitamin D deficiency among patients on hemodialysis. Experimental evidence also suggests that 25-hydroxy vitamin D_3 ($25(OH)D_3$) might have clinically significant effect on bone mineral metabolism in this population.

The aims of this study were

- to describe the prevalence of vitamin D deficiency and its association to parathyroid function
- to analyze the association between vitamin D deficiency and bone mineral density
- to investigate the association between vitamin D deficiency and bone ultrasound parameters, a method that might provide additional information about bone ultrastructure or bone quality.

Factors associated with bone fractures

The incidence of fractures is substantially increased in patients with CKD compared to the general population. The factors associated with increased risk of bone fracture in this population are not well understood. Both hyperparathyroidism and relative hypoparathyroidism have been described to be associated with increased fracture risk. Since previous results suggested that bone density was not decreased in relative hypoparathyroidism, change in bone quality might also be responsible for the increased fracture risk.
In this work, I described the prevalence of symptomatic bone fractures since the initiation of renal replacement therapy. The following hypotheses were tested:

- fracture risk is associated with both hyperparathyroidism and relative hypoparathyroidism
- patients who sustained fractures have decreased bone mineral density compared to those without fractures
- there is an association between bone fracture and bone ultrasound parameters and this relationship is dependent of the parathyroid function

Bone mineral metabolism after kidney transplantation

Impaired graft function is common in kidney transplant recipients and therefore complications of CKD are also prevalent in this population. Increasing evidence supports the association between CKD - mineral and bone disorder (CKD-MBD) and vascular calcification after kidney transplantation as well, likely contributing to the high cardiovascular mortality in this population. Earlier studies described the association between graft function and several cardiovascular risk factors.
The aims of this study were to examine the characteristics of CKD-MBD and its associations with clinical parameters after kidney transplantation. The following hypotheses were tested:

- the presence and severity of disturbances of mineral metabolism depend on the graft function, and so the stratification of kidney insufficiency recommended by the NKF-

KDOQI (National Kidney Foundation – Kidney Disease Outcomes Quality Initiative) guideline can be applied in this population

- hyperphosphatemia is prevalent in patients with severely impaired graft function
- the severity of hyperparathyroidism is negatively correlated with the graft function

I further aimed to investigate the management of disturbances of bone and mineral metabolism and the conformance of those parameters with the recommendations of the guideline.

Patients and Methods

In the studies among patients on hemodialysis

Patients who had been on maintenance hemodialysis for more than 3 months were entered in the studies. Patients who did not agree to participate or had active liver disease with elevated transaminase levels were excluded. Clinical information including demographic data, body weight and diagnosis of diabetes were collected from dialysis charts.

Bone densitometry and quantitative ultrasound

All patients underwent bone densitometry (ODM) that was assessed by dual-energy X-ray absorptiometry (DEXA) using a Norland XR 26 densitometer. Measurements were taken at three standard skeletal sites: lumbar spine (LS), femoral neck (FN) and distal third of radius (DR). Bone density (BMD, g/cm^2), Z-scores and T-scores were tabulated. Quantitative bone ultrasound was performed at the calcaneus by a DTU-one device (Osteometer MediTech, Hawthorne, CA, USA). Broadband ultrasound attenuation (BUA) and speed of sound (SOS) were assessed.

Laboratory data

Blood samples were taken before the mid-week dialysis sessions. Serum calcium was corrected for serum albumin level. Type I collagen crosslinked-C-telopeptide (crosslaps, CTX) (pmol/L) was measured by the Serum Cross-Laps™ One Step ELISA (Osteometer BioTech A/S, Herlev, Denmark). Plasma levels of $25(OH)D_3$ vitamin (nmol/l) were analyzed by a high-performance liquid chromatograph (HPLC) method using Bio-Rad reagents kit (Bio-Rad Laboratories, Inc., Hercules, Ca, USA).

In the first study, serum intact PTH (pg/ml) was determined by second-generation electrochemiluminescence assay (iPTH Elecsys System; Roche, Mannheim, Germany). In the second and third study, second-generation immunoradiometric assay (Bio-Rad) was used.

In the study among patients after renal transplantation

We approached all stable patients at 18 years of age or older (n=1214) who were regularly followed at a single kidney transplant outpatient clinic at the Department of Transplantation and Surgery at Semmelweis University, in Budapest. Exclusion criteria were: current acute rejection (within the last 4 weeks), hospitalization, transplantation in the previous 3 months, acute infection or bleeding. The baseline assessment was conducted between February 2007 and August 2007 (Malnutrition-Inflammation in Transplant - Hungary Study, MINIT-HU Study).

Demographic data, patient's history and most of laboratory data were extracted from the patients' charts. Serum calcium was corrected for serum albumin level. Serum intact PTH (pg/ml) was determined by second-generation electrochemiluminescence assay (iPTH Elecsys System; Roche, Mannheim, Germany).

Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula:

eGFR (ml/min per 1.73 m2) = 186 x $(SCr)^{-1.154}$ x $(Age)^{-0.203}$ (x 0.742 if female).

Patients were stratified based on the estimated GFR into three groups: CKD stage 1+2 (eGFR≥60ml/min/1.73m2), CKD 3 (eGFR: 30-59ml/min/1.73m2), CKD 4-5 (eGFR: <30ml/min/1.73m2). Target levels of calcium (Ca), phosphorous (P) and iPTH were based on the CKD stage according to the recommendations of the NKF-K/DOQI guideline:

	CKD 1-3	CKD 4	CKD 5
iPTH (pg/ml)	35 – 70	70 – 150	150 – 300
Ca (mmol/l)	2.05 – 2.60	2.05 – 2.60	2.10 – 2.54
P (mmol/l)	0.87 – 1.49	0.87 – 1.49	1.13 – 1.78

Results

Parathyroid function and bone mineral density

270 patients on maintenance hemodialysis were included in the analysis. To obtain cohorts which are likely to correspond to low, normal or high bone turnover patients were grouped into three groups based on serum iPTH results: "low PTH" ("relative hypoparathyroidism", likely reflecting low bone turnover): serum iPTH < 100 pg/ml; "target PTH": iPTH 100-300 pg/ml; and "high PTH": iPTH> 300 pg/ml (corresponding to secondary or tertiary hyperparathyroidism and likely high turnover bone disease). The distribution of patients in the three groups was 36%, 40% and 24%, respectively. The groups were comparable in demographic characteristics.

Based on the Z-scores, bone mineral density was moderately reduced in our cohort; this was more pronounced at the femoral neck, while Z scores at the lumbar spine were not reduced:

	Total	**Low PTH**	**Target PTH**	**High PTH**	**p**
n	270	98 (36%)	107 (40%)	65 (24%)	
Radius Z-score	-0.577 ± 1.736	-0.306±1.724	-0.352±1.606	**-1.339±1.755***	<0.001
Femur Z-score	-1.249 ± 1.222	-0.906±0.242	-1.201±1.143	**-1.821±1.124***	<0.001
Lumbar Z-score	-0.037 ± 1.775	0.170±1.855	0.263±1.746	**-0.834±1.463***	<0.001

Patients in the "high PTH" group had significantly lower Z scores at all measurement sites compared to patients in either the "target" or the "low PTH" groups. The average Z score of the "low PTH" group, however, was not different from the average Z score of patients who were in the "target PTH" group, at all measurement site.

Z-scores were negatively correlated with biochemical markers of bone remodeling, namely ALP and CTX, at all measurement sites. Z-scores measured on the femoral neck and lumbar spine also showed significant negative correlation with PTH. In multivariate regression models, higher Z-scores were associated with higher body weight, higher Ca-P product and lower iPTH (DR β=-0.313, p=0.041; FN β=-0.216, p=0.001; LS β=-0.179, p=0.006) at all measurement sites. Longer duration of end-stage renal disease (ESRD vintage) was associated with decreased Z-score only at the radius, whereas higher ALP (reflecting higher bone turnover) was associated with reduced Z-score (independently of serum iPTH) both at the radius and the femoral neck, but not at the lumbar spine.

In the "low PTH" group, serum iPTH and Z-scores were not correlated at any sites, whereas in patients with serum iPTH above 100pg/ml the expected negative correlations were seen between the two variables at all measurement sites. Within the "low PTH" group, the association between Z-scores and CTX (DR: rho=-0.493, p=0.001; FN: rho=-0.294, p=0.077, LS: rho=-0.303, p=0.057), and also between Z-scores and ALP (DR: rho=-0.260, p=0.012, LS: rho=-0.244, p=0.021) were similar to the associations in the total study group. The relationships between iPTH and biochemical markers of bone turnover were highly significant in the whole group (ALP: rho=0.333, $p<0.001$ or CTX: rho=0.388, $p<0.001$), but this correlation was not found in the subgroup of patients with "low PTH".

Vitamin D insufficiency and bone metabolism

Out of the 69 patients included in the analyses, 59% had vitamin D insufficiency ($25(OH)D_3$ < 20nmol/l) and 20% had deficiency ($25(OH)D_3$: 20-30nmol/l). The median serum $25(OH)D_3$ concentration was 17nmol/l (4.1–78.5). $25(OH)D_3$ levels and iPTH were negatively correlated (rho=-0.231, $p<0.05$). None of the patients with $25(OH)D_3$ > 30nmol/l had iPTH > 400pg/ml, whereas 30% of patients with $25(OH)D_3$ < 30nmol/l had iPTH in that range (p=0.073). In multivariate analysis, $25(OH)D_3$ was an independent predictor of iPTH (β=-0.202, $p<0.05$).
BMD was the most reduced at the femoral neck and it was comparable with the general population at the lumbar spine. Negative correlations were found between iPTH and BMD at the femoral neck (rho=-0.257, $p<0.05$) and distal radius (rho=-0.378, $p<0.01$). In the univariate analysis, $25(OH)D_3$ was positively correlated with BMD at the radius (r=0.424, $p<0.01$). In the multivariate analysis, however, this association was no longer significant when iPTH was also entered into the model.
As for the bone ultrasound parameters, the mean BUA was significantly reduced (Z-score: -2.49±0.23), whereas the SOS was not. Only BUA but not SOS was correlated with iPTH (rho=-0.331, $p<0.01$) and $25(OH)D_3$ (r=0.369, $p<0.01$) as well. In multivariate models, $25(OH)D_3$ remained independent predictor of BUA after controlling for other co-variables.

Factors associated with bone fractures

One hundred and thirty patients were included in the analysis. BMD expressed as Z-score was substantially reduced at the femoral neck and distal radius but it was comparable with the age- and gender-matched reference population at the lumbar spine (FZ: -1.38±1.06, RZ: -

1.14±1.87 , LZ: 0.05±1.68). iPTH correlated negatively with Z-score measured at the radius (rho=-0.323, p<0.001) and femur (rho=-0.201, p=0.026). ESRD vintage showed significant negative correlation with the radius Z-score (rho=-0.291, p=0.001). Previous transplantation was associated with lower Z-score at the radius (-2.83±2.21 vs -0.83±1.63, p<0.001) but not at other measurement sites.

Twenty-one (16%) out of 130 patients had at least one low-trauma bone fracture since the start of renal replacement therapy (RRT). No difference was found between patients with versus without fractures in age, body weight and BMI, and the prevalence of diabetes, routine laboratory findings and iPTH were also similar; there were more females in the fractured group (67% vs 40%, p=0.032).

25(OH)D_3 was significantly lower in patients with fractures: 30.0 (28.5) vs. 15.8 (27.0) nmol/l, p=0.029. The prevalence of fractures among patients with 25(OH)D_3 'deficiency', 'insufficiency' and 'normal' 25(OH)D_3 levels were 31%, 17% and 11%, respectively (p=0.075).

Z-scores measured at the radius, but not at the femur nor at the lumbar spine, were lower in the 'fractured' group (-0.89±1.70 vs. -2.40±2.19, p=0.01). Patients with radius Z-scores less than -2.5 SD sustained fractures more likely compared to patients with radius Z-scores above -2.5 (35% vs. 12%, p=0.004). Quantitative bone ultrasound parameters (BUA and SOS) measured at the calcaneus were not different between the fractured and non-fractured groups.

Independent predictors of bone fracture since the initiation of dialysis treatment were assessed in Cox proportional hazard models. The median interval between the start of RRT and the first fracture was 64 months (interquartile range, IQR: 54.5); this was used in the Cox model as time-to-event variable. The final model revealed that previous bone fracture, relative hypoparathyroidism, low 25(OH)D_3 level and low bone density at the distal radius were associated with increased risk of fracture in patients on hemodialysis.

Bone mineral metabolism after kidney transplantation

993 stable patients from the outpatient clinic of the transplantation centre were included in the analyses. The mean estimated GFR (eGFR) was 51±21 ml/min per 1.73m^2, the majority (51%) of patients had CKD stage 3 (eGFR: 30-59ml/min/1.73m2). Graft function was negatively correlated to time elapsed since transplantation (TX vintage): patients with CKD 1-2 had significantly shorter (58 months; IQR: 74) and patients with CKD 4-5 had longer (95 months; IQR: 75) TX vintage compared to the CKD3 (72 months; IQR 73) (p<0.001).

Patients with worse graft function had higher phosphate levels. In patients with eGFR>30ml/min the association was relatively weak ($r=-0.162$, $p<0.001$), in patients with CKD 4-5 we found a strong negative correlation between eGFR and P ($r=-0.633$, $p<0.001$). The percentage of patients who had P levels above the recommended range was 4% in the total population and this was significantly higher (18%) in CKD 4-5 ($p<0.001$).

After adjusting for several co-variables, independent predictors of hyperphosphatemia were the time spent on dialysis before transplantation, intact PTH (iPTH) and eGFR less than 30ml/min (CKD 4-5).

The median iPTH in the study was 67pg/ml. Patients with worse graft function had higher iPTH levels. While no association was found between eGFR and iPTH within the CKD 1-2 group, the correlation was significant ($rho=-0.289$, $p<0.001$) in CKD 3-5. Longer time on dialysis was also associated with higher iPTH levels ($rho=0.114$, $p<0.001$).

The prevalence of hyperparathyroidism was lower in CKD1-2, but it was not different between CKD 3 and CKD 4-5. In the adjusted multivariate model, more severe graft failure was associated with 2-3-fold higher likelihood of hyperparathyroidism. Longer time spent on dialysis was also significant predictor of hyperparathyroidism.

The prevalence of relative hypoparathyroidism was higher in CKD 4-5 (31%) than in the other groups (10% in CKD 3 and 13% CKD 1-2, $p<0.001$). Multivariate analysis revealed that in addition to graft function, the use of vitamin D derivates was also independent predictor of hypoparathyroidism.

The administration of phosphate binding drugs was 6% in the total population. No one in CKD 1-3, and only 20% of patients in CKD 4-5 with phosphate levels above the target range had P-binder prescribed. One third of all patients were prescribed vitamin D. Almost half of the patients who had iPTH below the target range were still on vitamin D therapy. Furthermore, no vitamin D analogs were prescribed for 72% of patients, who had iPTH above the target range.

Summary and novel findings

Parathyroid function and bone mineral density

In the first part of this work, I studied the relationship between parathyroid function and bone mineral density. I demonstrated that

- relative hypoparathyroidism in hemodialysis patients, likely corresponding to adynamic bone, is not associated with reduced bone mineral density compared to patients with serum iPTH in the recommended target range; whereas secondary hyperparathyroidism is associated with significantly reduced bone density
- parathyroid hormone is not associated with bone mineral density and biochemical markers of bone turnover (ALP and CTX) in relative hypoparathyroidism
- serum alkaline phosphatase is an independent predictor of bone density in all ranges of iPTH

Based on these findings I concluded that bone density is not decreased in low bone turnover states, as assessed by biochemical markers. There is a negative correlation between bone turnover and mineral density. Bone biopsies, however, were not performed therefore I could not assess the association between real bone turnover and bone mineral density.

Vitamin D insufficiency and bone metabolism

In the second part, I examined the relationship between vitamin D insufficiency, parathyroid function and bone mineral density. I demonstrated that

- vitamin D insufficiency is common among hemodialysis patients and it is associated with secondary hyperparathyroidism
- there is a relationship between vitamin D levels and bone mineral density measured at the distal radius. This association is likely mediated by the parathyroid hormone.
- vitamin D status is independently associated with broadband ultrasound attenuation measured with calcaneal quantitative ultrasound.

From these data I conclude that vitamin D deficiency may have a negative impact on bone health of patients on maintenance hemodialysis. Furthermore, bone quantitative ultrasound, and specifically BUA, may provide additional information on bone status.

Factors associated with bone fractures

In this study I examined the incidence of symptomatic, low trauma fractures and analyzed the possible risk factors of bone fracture among our patients on maintenance hemodialysis.
The presented data confirmed that

- the fracture incidence in our patients was comparable with that reported in the literature
- vitamin D deficiency and low bone mineral density measured at the distal radius are independent predictors of fractures
- relative hypoparathyroidism is associated with increased fracture risk compared to higher parathyroid hormone levels

These findings provide additional data supporting the role of bone densitometry in assessment of fracture risk in patients on hemodialysis. In addition, vitamin D deficiency was shown to have deleterious effect on bone strength in this population. Further studies are needed to determine if vitamin D supplementation or interventions aiming at increasing serum iPTH would reduce fracture risk in patients on maintenance dialysis.

Bone mineral metabolism after kidney transplantation

In the last study, I examined the characteristics of mineral bone disease after kidney transplantation and its associations with clinical parameters. I demonstrated that

- parameters of bone mineral metabolism are strongly correlated with the graft function in transplanted patients, similarly to non-transplanted CKD populations
- the duration of dialysis prior to transplantation is an important independent predictor of both hyperphosphatemia and hyperparathyroidism
- treatment of bone and mineral disorders are not optimal when compared to the NKF-KDOQI guidelines for non-transplanted CKD patients

The results presented in this work provide additional data suggesting that the NKF-KDOQI guidelines for CKD assessment and risk stratification can be applied after kidney transplantation. The lack of appropriate guidelines is probably the most important factor resulting in suboptimal management of CKD-MBD in this population.

Publications related to the theses

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