Proyecto Prometeo

Metabolismo Ca/P

30 de Septiembre y 1 de Octubre 2011
Alcalá de Henares

Dossier Bibliográfico

Grupo II

Manifestaciones Clínicas y Métodos Diagnósticos Metabolismo Ca/P

Portavoz

Dra. Marta Crespo
Hospital del Mar, Barcelona

Con el patrocinio de:

Sociedad Española de Nefrología

Cátedra de Trasplante UAM-ROCHE

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PROMETEO V: Metabolismo Ca/P

GRUPO 2- Manifestaciones Clínicas y Métodos Diagnósticos Metabolismo Ca/P

Portavoz: Marta Crespo

	Apellidos	Nombre	Hospital	Ciudad	Artículos asignados	Nº Bibl.
1	Alonso Melgar	Ángel	Hospital Universitario La Paz (TX Pediatricos)	Madrid	**1. Failure of successful renal transplant to produce appropriate levels of 1,25-dihydroxyvitamin D.** Fleseriu M, Licata AA. Osteoporos Int. 2007 Mar;18(3):363-8. Epub 2006 Oct 24. **2. Calcium metabolism and skeletal problems after transplantation.** Torres A, Lorenzo V, Salido E. J Am Soc Nephrol. 2002 Feb;13(2):551-8.	36 56
2	Cofan Pujol	Frederic	Hospital Clínic	Barcelona	**1. Calcium and phosphate changes after renal transplantation.** Messa P, Cafforio C, Alfieri C. J Nephrol. 2010 Nov-Dec;23 Suppl 16:S175-81. **2. Fibroblast growth factor-23 and parathyroid hormone are associated with post-transplant bone mineral density loss.** Kanaan N, Claes K, Devogelaer JP, Vanderschueren D, Depresseux G, Goffin E, Evenepoel P. Clin J Am Soc Nephrol. 2010 Oct;5(10):1887-92.	2 3
3	Díaz Gómez	Joan Manuel	Fundación Puigvert	Barcelona	**1. Serum phosphate and calcium concentrations are associated with reduced patient survival following kidney transplantation.** Moore J, Tomson CR, Tessa Savage M, Borrows R, Ferro CJ. Clin Transplant. 2010 Jun 28. [Epub ahead of print] **2. Calcium, phosphate and parathyroid metabolism in kidney transplanted patients.** Ambrus C, Molnar MZ, Czira ME, Rosivall L, Kiss I, Remport A, Szathmari M, Mucsi I. Int Urol Nephrol. 2009 Dec;41(4):1029-38. Epub 2009 Aug 22.	5 14
4	Errasti	Pedro	Clínica Universitaria de Navarra	Pamplona	**1. Bone disease after renal transplantation.** Malluche HH, Monier-Faugere MC, Herberth J.Nat Rev Nephrol. 2010 Jan;6(1):32-40. Epub 2009 Nov 17. **2. Hyperparathyroidism and vitamin D deficiency predispose to bone loss in renal transplant recipients.** Lim WH, Coates PS, Russ GR, Coates PT. Transplantation. 2009 Sep 15;88(5):678-83.	13 17
5	Fijo López-Viota	Julia	Hospital Virgen del Rocío (TX Pediátrico)	Sevilla	**1. Assessment of bone mass following renal transplantation in children.** Leonard MB. Pediatr Nephrol. 2005 Mar;20(3):360-7. Epub 2005 Feb 4. **2. Posttransplant acidosis and associated disorders of mineral metabolism in patients with a renal graft.** Yakupoglu HY, Corsenca A, Wahl P, Wüthrich RP, Ambühl PM. Transplantation. 2007 Nov 15;84(9):1151-7.	45 30
6	Gutiérrez Dalmau	Alex	Hospital Miguel Servet	Zaragoza	**1. KDOQI US commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD).** Uhlig K, Berns JS, Kestenbaum B, Kumar R, Leonard MB, Martin KJ, Sprague SM, Goldfarb S.Am J Kidney Dis. 2010 May;55(5):773-99. Epub 2010 Apr 3. **2. Changes in bone and mineral metabolism in kidney transplant patients with chronic kidney disease.** [Article in Spanish]. López Oliva MO, Del Castillo Caba D, Sánchez Plumed J. Nefrologia. 2009;29 Suppl 1:31-7.	6 11
7	Hernández	Ana	Hospital Universitario 12 de Octubre	Madrid	**1. Abnormal bone and mineral metabolism in kidney transplant patients--a review.** Sprague SM, Belozeroff V, Danese MD, Martin LP, Olgaard K. Am J Nephrol. 2008;28(2):246-53. Epub 2007 Nov 7. **2. Bone mineral density and fracture prevalence in long-term kidney graft recipients.** Durieux S, Mercadal L, Orcel P, Dao H, Rioux C, Bernard M, Rozenberg S, Barrou B, Bourgeois P, Deray G, Bagnis CI.Transplantation. 2002 Aug 27;74(4):496-500.	26 55
8	Jimeno	Luisa	Hospital Virgen de la Arrixaca	Murcia	**1. Renal osteodystrophy after successful renal transplantation: a histomorphometric analysis in 57 patients.** Lehmann G, Ott U, Stein G, Steiner T, Wolf G. Transplant Proc. 2007 Dec;39(10):3153-8. **2. Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation.** Borchhardt K, Sulzbacher I, Benesch T, Födinger M, Sunder-Plassmann G, Haas M.Am J Transplant. 2007 Nov;7(11):2515-21.	28 29

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9	López Oliva	María	Hospital Universitario La Paz	Madrid	**1. Histologic evolution of bone disease 6 months after successful kidney transplantation.** Cruz EA, Lugon JR, Jorgetti V, Draibe SA, Carvalho AB. Am J Kidney Dis. 2004 Oct;44(4):747-56. **2. The pathogenesis of osteodystrophy after renal transplantation as detected by early alterations in bone remodeling.** Rojas E, Carlini RG, Clesca P, Arminio A, Suniaga O, De Elguezabal K, Weisinger JR, Hruska KA, Bellorin-Font E. Kidney Int. 2003 May;63(5):1915-23.	47 52
10	**Crespo**	**Marta**	**Hospital del Mar**	**Barcelona**		
11	Romero Burgos	Rafael	Hospital Clínico Universitario de Santiago	Santiago de Compostela (A Coruña)	**1. Posttransplant bone disease: evidence for a high bone resorption state.** Cayco AV, Wysolmerski J, Simpson C, Mitnick MA, Gundberg C, Kliger A, Lorber M, Silver D, Basadonna G, Friedman A, Insogna K, Cruz D, Bia M.Transplantation. 2000 Dec 27;70(12):1722-8. **2. Bone loss after renal transplantation: role of hyperparathyroidism, acidosis, cyclosporine and systemic disease.** Heaf J, Tvedegaard E, Kanstrup IL, Fogh-Andersen N.Clin Transplant. 2000 Oct;14(5):457-63. **3.Hyperparathyroidism and long-term bone loss after renal transplantation.** Heaf J, Tvedegaard E, Kanstrup IL, Fogh-Andersen N.Clin Transplant. 2003 Jun;17(3):268-74.	59 61 50
12	Sanahuja Ibáñez	Mª José	Hospital Universitario La Fe	Valencia	**1. Bone loss in long-term renal transplantation: histopathology and densitometry analysis.** Cueto-Manzano AM, Konel S, Hutchison AJ, Crowley V, France MW, Freemont AJ, Adams JE, Mawer B, Gokal R.Kidney Int. 1999 May;55(5):2021-9. **2. Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients.** Grotz WH, Mundinger FA, Rasenack J, Speidel L, Olschewski M, Exner VM, Schollmeyer PJ. Nephrol Dial Transplant. 1995 Nov;10(11):2096-100.	66 72
13	Sánchez Hemández	Rosa	Hospital General de Segovia	Segovia	**1. Bone metabolism according to chronic kidney disease stages in patients undergoing kidney transplantation: a 5-year database analysis.** Fernández-Fresnedo G, Rodrigo E, Ruiz JC, Martín de Francisco AL, Arias M.Transplant Proc. 2009 Jul-Aug;41(6):2403-5. **2. Musculoskeletal complications after renal transplantation: pathogenesis and treatment.** Julian BA, Quarles LD, Niemann KM.Am J Kidney Dis. 1992 Feb;19(2):99-120.	19 77

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Manifestaciones Clínicas y Métodos Diagnósticos Metabolismo Ca/P

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2. J Nephrol. 2010 Nov-Dec;23 Suppl 16:S175-81.

Calcium and phosphate changes after renal transplantation.

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Hypercalcemia and hypophosphatemia are frequently observed in recipients of a kidney transplant (KTx). Hypercalcemia has been reported in up to 66% of KTx patients. Many factors have been suggested as the putative causal factors; however, the persistence of moderate-severe secondary hyperparathyroidism, associated with a change in the set-point of the Ca-controlled parathyroid hormone (PTH) secretion, is considered to play a prominent role. Hypercalcemia can negatively impact on both the graft and patient outcome, increasing the incidence of nephrocalcinosis, which can induce a worse graft outcome, inducing vascular calcifications, and increasing the incidence of pancreatitis. In addition, severe hypercalcemia after KTx often requires parathyroidectomy, which is not universally considered a safe medical solution in this clinical setting. After KTx, phosphate levels often fall below the normal range, with hypophosphatemia being observed in up to 40% of patients. The putative causal factors for this metabolic alteration are persistent hyperparathyroidism, increased levels of FGF-23, tubular damage secondary to the immunological effects, and toxic and vascular effectors. Hypophosphatemia can negatively impact on either skeletal or muscular systems, contributing to the increased incidence of bone fractures in KTx patients. The current therapeutic options should take into account an accurate pretransplant treatment and screening of the waiting-list patient and should also evaluate the efficacy and safety profile of the new pharmacological tools (calcimimetics) in comparison with the classical surgical approach (parathyroidectomy).

PMID: 21170877 [PubMed - in process]

3. Clin J Am Soc Nephrol. 2010 Oct;5(10):1887-92.

Fibroblast growth factor-23 and parathyroid hormone are associated with post-transplant bone mineral density loss.

Kanaan N, Claes K, Devogelaer JP, Vanderschueren D, Depresseux G, Goffin E, Evenepoel P.

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BACKGROUND AND OBJECTIVES: Among the multiple factors contributing to bone mineral density (BMD) loss after renal transplantation, hypophosphatemia is increasingly recognized to play an important role. Hypophosphatemia occurs in up to 90% of the renal transplant recipients in the early post-transplant period and is caused by renal phosphate wasting. We hypothesized that a high pretransplant level of the recently described phosphaturic hormone fibroblast growth factor 23 (FGF-23) is a risk factor for accelerated BMD loss occurring within the first post-transplant year.
DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: We performed a two-center observational retrospective cohort study in 127 incident renal transplant recipients. Serum full-length FGF-23, parathyroid hormone (PTH), and parameters of mineral metabolism were determined at the time of transplantation. BMD was assessed by osteodensitometry at the time of transplantation and 1 year later.
RESULTS: A moderate decrease of BMD was observed during the first post-transplant year. High FGF-23 levels were associated with BMD loss at the lumbar spine and total hip region, whereas low PTH levels were associated with BMD loss at all three regions. Cumulative doses of prednisone and post-transplant serum phosphate level were not correlated with BMD changes.
CONCLUSION: Our data indicate that patients with a high serum FGF-23 level and/or a low PTH level at the time of transplantation are at risk for increased BMD loss during the first post-transplant year.

PMCID: PMC2974391 [Available on 2011/10/1]
PMID: 20634326 [PubMed - indexed for MEDLINE]

5. Clin Transplant. 2010 Jun 28. [Epub ahead of print]

Serum phosphate and calcium concentrations are associated with reduced patient survival following kidney transplantation.

Moore J, Tomson CR, Tessa Savage M, Borrows R, Ferro CJ.

Department of Renal Medicine, University Hospital Birmingham and University of Birmingham, Birmingham, UK.

The impact of disordered mineral and bone metabolism following kidney transplantation is not well defined. We studied the association of serum phosphate and calcium concentrations, and surrogate measures of arterial stiffness (augmentation index: AIx and Timing of the reflected wave: Tr), with long-term kidney transplant recipient and allograft survival. Prevalent adult renal transplant patients (n = 270) were prospectively studied over a median 88-month follow-up. Detailed demographic, clinical and laboratory data, in addition to both peripheral and central non-invasive blood pressure measurements, were recorded. Higher serum phosphate and calcium levels were associated with increased all-cause mortality (HR: 1.21; 95% CI 1.09,1.35, $p < 0.001$ and HR: 1.22; 95% CI 1.01,1.48; $p < 0.04$, respectively; adjusted Cox model) and death-uncensored graft loss ($p < 0.001$ and $p = 0.03$, respectively). In addition, serum calcium and phosphate were associated with death-censored graft loss on univariable analysis ($p < 0.001$ and $p = 0.02$, respectively), but did not retain significance on multivariable analysis. AIx and Tr were not associated with mortality or graft loss on multivariable analysis. This is the first report to demonstrate that both higher serum phosphate and calcium levels are associated with increased mortality in kidney transplant recipients. It highlights the need for randomized trials assessing current interventions available for improving disordered mineral-bone metabolism post transplantation.
PMID: 20608946 [PubMed - as supplied by publisher]

6. Am J Kidney Dis. 2010 May;55(5):773-99. Epub 2010 Apr 3.

KDOQI US commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD).

Uhlig K, Berns JS, Kestenbaum B, Kumar R, Leonard MB, Martin KJ, Sprague SM, Goldfarb S.

Tufts Medical Center, Tufts University School of Medicine, Boston MA, USA.

This commentary provides a US perspective on the 2009 KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). KDIGO is an independent international organization with the primary mission of the promotion, coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines for the care of patients with kidney disease. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), recognizing that international guidelines need to be adapted for each country, convened a group of experts to comment on the application and implementation of the KDIGO guideline for patients with CKD in the United States. This commentary puts the KDIGO guideline into the context of the supporting evidence and the setting of care delivered in the United States and summarizes important differences between prior KDOQI guidelines and the newer KDIGO guideline. It also considers the potential impact of a new bundled payment system for dialysis clinics. The KDIGO guideline addresses the evaluation and treatment of abnormalities of CKD-MBD in adults and children with CKD stages 3-5 on long-term dialysis therapy or with a kidney transplant. Tests considered are those that relate to laboratory, bone, and cardiovascular abnormality detection and monitoring. Treatments considered are interventions to treat hyperphosphatemia, hyperparathyroidism, and bone disease in patients with CKD stages 3-5D and 1-5T. Limitations of the evidence are discussed. The lack of definitive clinical outcome trials explains why most recommendations are not of level 1 but of level 2 strength, which means weak or discretionary recommendations. Suggestions for future research highlight priority areas.

PMID: 20363541 [PubMed - indexed for MEDLINE]

11. Nefrologia. 2009;29 Suppl 1:31-7.

[Changes in bone and mineral metabolism in kidney transplant patients with chronic kidney disease].

[Article in Spanish]

López Oliva MO, Del Castillo Caba D, Sánchez Plumed J.

Servicio de Nefrología, Hospital La Paz, Madrid.

DESCRIPTION: Recently, the Foundation has proposed new definitions KDIGO to refer to the alterations of bone - mineral metabolism in patients with chronic renal disease (CRD), relegating the traditional term of renal osteodystrophy (ODR). RECOMMEND: The term ODR exclusively to define alterations in bone morphology and architecture characteristic of the ERC. - And the term of bone-mineral alteration associated with the CRD to describe biochemical changes, and skeletal calcifications that occur as a result of alterations in mineral metabolism in the CRD. PATHOPHYSIOLOGY: The different metabolic abnormalities are secondary to the progressive loss of renal mass and renal function that leads to retention of phosphorus and a decrease in the levels of calcitriol which are responsible for the skeletal resistance to the action of PTH. CLINICAL FEATURES: The main clinical manifestations of abnormal bone mineral metabolism are posttransplantation osteoporosis and osteopenia producing an increase in fractures, osteonecrosis, and bone pain. DIAGNOSTIC METHODS: Biochemical parameters (calcium, phosphorus, PTH, 25 hydroxyvitamin D), X-ray bone densitometry and bone biopsy. (Evidence B). THERAPEUTIC ALTERNATIVES: It is recommended for the treatment and prevention of osteopenia - osteoporosis in transplant patients based on data from clinical evidence available from other study populations, such as in patients with chronic kidney disease. In addition to specific treatment, we must take into account the preventive measures to reduce the risk of fractures. Treatment includes specific measures for the prevention of bone loss (active metabolite of vitamin D analogues and bisphosphonates) and the treatment of persistent hyperparathyroidism (calcimiméticos). (Evidence B).

PMID: 19675659 [PubMed - indexed for MEDLINE]

13. Nat Rev Nephrol. 2010 Jan;6(1):32-40. Epub 2009 Nov 17.

Bone disease after renal transplantation.

Malluche HH, Monier-Faugere MC, Herberth J.

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In light of greatly improved long-term patient and graft survival after renal transplantation, improving other clinical outcomes such as risk of fracture and cardiovascular disease is of paramount importance. After renal transplantation, a large percentage of patients lose bone. This loss of bone results from a combination of factors that include pre-existing renal osteodystrophy, immunosuppressive therapy, and the effects of chronically reduced renal function after transplantation. In addition to low bone volume, histological abnormalities include decreased bone turnover and defective mineralization. Low bone volume and low bone turnover were recently shown to be associated with cardiovascular calcifications, highlighting specific challenges for medical therapy and the need to prevent low bone turnover in the pretransplant patient. This Review discusses changes in bone histology and mineral metabolism that are associated with renal transplantation and the effects of these changes on clinical outcomes such as fractures and cardiovascular calcifications. Therapeutic modalities are evaluated based on our understanding of bone histology.

PMID: 19918255 [PubMed - indexed for MEDLINE]

14. Int Urol Nephrol. 2009 Dec;41(4):1029-38. Epub 2009 Aug 22.

Calcium, phosphate and parathyroid metabolism in kidney transplanted patients.

Ambrus C, Molnar MZ, Czira ME, Rosivall L, Kiss I, Remport A, Szathmari M, Mucsi I.

Department of Nephrology, University Health Network, University of Toronto, Toronto, Canada.

INTRODUCTION: Impaired kidney function is common in kidney-transplanted patients and complications of chronic kidney disease (CKD), such as mineral and bone disorders (MBD) are also prevalent in this population. Similarly to other stages of CKD, increasing evidence supports the association between MBD and cardiovascular risk after kidney transplantation as well. Still, little is known about the prevalence, clinical correlates of MBD and its management in transplanted patients. In this study, we aimed to examine the characteristics of MBD and its associations with clinical parameters in a large prevalent cohort of patients after kidney transplantation.
METHODS: Nine hundred and ninety stable patients followed at a single kidney transplant outpatient clinic were included in the study. Detailed medical history, demographic data and routine laboratory results, including Ca, P and intact PTH were collected. Estimated GFR was calculated using the abbreviated MDRD formula, patients were stratified into three groups based on eGFR. Target levels for Ca, P and iPTH were based on CKD stages according to the NKF-K/DOQI guidelines. Standard statistical procedures, binomial and multinomial regressions were used in the analysis.
RESULTS: The mean age was 51 years, 57% were males and 21% were diabetic, with 72 months (median) post-transplantation. Most of the patients were in CKD stage 3. Serum phosphorus showed strong negative correlation with graft function in CKD stages 4-5 ($r = -0.633$, $P < 0.001$). Hyperphosphatemia was independently associated with the time spent on dialysis before transplantation, serum iPTH and CKD stages 4-5. iPTH showed negative correlation with eGFR in CKD stages 3-5 ($rho = -0.289$, $P < 0.001$) and weak positive correlation with time spent on dialysis prior to transplant ($rho = 0.114$, $P < 0.001$). Both hyperparathyroidism (42%) and relative hypoparathyroidism (15%) were frequent. The prescription of P-binders (6%) and vitamin D analogs (33%) was sporadic.
CONCLUSION: Disturbances of bone and mineral metabolism after transplantation are prevalent and are strongly correlated with the kidney function, similarly to non-transplanted CKD patients. MBD in this population is not adequately managed.

PMID: 19701690 [PubMed - indexed for MEDLINE]

17. Transplantation. 2009 Sep 15;88(5):678-83.

Hyperparathyroidism and vitamin D deficiency predispose to bone loss in renal transplant recipients.

Lim WH, Coates PS, Russ GR, Coates PT.

Department of Renal Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia.
BACKGROUND: Bone disease is common postrenal transplantation resulting in increased fracture rates and morbidity. The cause is multifactorial including hyperparathyroidism, corticosteroids, and possibly calcium and vitamin D deficiencies. The aim of this study was to identify modifiable factors contributing to bone disease in long-term renal transplant (RT) recipients. METHODS: Ninety-seven RT recipients were prospectively recruited over a 6-month period from a single center. Bone-related parameters were collected including bone mineral density at lumbar spine and total hip sites, serum and urinary markers of bone-turnover and calcium metabolism, and intact parathyroid hormone levels. RESULTS: The mean time posttransplant of RT recipients was 9.5 years and mean estimated glomerular filtration rate was 70.3 mL/min. Up to 50% of recipients had biochemical evidence of calcium and vitamin D deficiencies. In the multiple regression models, elevated intact parathyroid hormone levels and calcium deficiency, which are affected by estimated glomerular filtration rate and vitamin D levels, are significantly associated with reduction in bone mineral density measurements. CONCLUSIONS: Hyperparathyroidism and vitamin D deficiency are common and are likely to contribute to bone loss postrenal transplantation. Measures aim to correct these problems pre- and posttransplant may improve bone health in RT recipients.

PMID: 19741465 [PubMed - indexed for MEDLINE]

19. Transplant Proc. 2009 Jul-Aug;41(6):2403-5.

Bone metabolism according to chronic kidney disease stages in patients undergoing kidney transplantation: a 5-year database analysis.

Fernández-Fresnedo G, Rodrigo E, Ruiz JC, Martín de Francisco AL, Arias M.

Nephrology Service, University Hospital Marqués de Valdecilla. Santander, Cantabria, Spain. nefffg@humv.es

INTRODUCTION: While kidney transplantation successfully reverses many complications of uremia that are not corrected with dialysis therapy, elevated parathyroid hormone (PTH) levels and other alterations of mineral metabolism persist in transplant recipients.
PATIENTS AND METHODS: A single-center cohort retrospective database analysis was performed of 497 consecutive adult patients who underwent first kidney transplantation between 1994 and 2004. At 1- and 5-year follow-up, a descriptive analysis was performed of mineral metabolism parameters of chronic kidney disease stage according to NKF KDOQI (National Kidney Foundation Kidney Disease Outcomes Quality Initiative) in patients with a functional graft at 1 year. Glomerular filtration rate was estimated using the abbreviated MDRD (Modification of Diet in Renal Disease) equation.
RESULTS: Most of the transplants (99.2%) were from cadaveric donors. Mean (SD) patient age was 47.7 (13.3) years, and 69% of patients were men. The causes of chronic kidney disease were glomerular (35.4%), congenital (15.4%), systemic (14.1%), vascular (11.3%), interstitial (10.1%), and other (<1%). The percentage of patients in each stage of chronic kidney disease with calcium levels less than 8.5 mg/dL, phosphorus greater than 4.5 mg/dL, and PTHi greater than 150 pg/mL increased as graft function declined. Six posttransplantation parathyroidectomies were performed. Only 130 patients received secondary hyperparathyroidism treatment within 5 years after transplantation: calcium carbonate, 36.9%; calcium acetate, 1.5%; calcium carbonate plus cholecalciferol, 21%; calcitriol, 71%; and calcifediol, 0.8%.
CONCLUSIONS: The prevalence of hypocalcemia, hyperphosphatemia, and elevated PTH level increased with chronic kidney disease stage. Classification of renal transplant recipients by KDOQI stage may enable clinicians to identify patients at increased risk and to target appropriate therapy to improve outcome. There is an opportunity for enhanced management of secondary hyperparathyroidism in these patients.

PMID: 19715933 [PubMed - indexed for MEDLINE]

26. Am J Nephrol. 2008;28(2):246-53. Epub 2007 Nov 7.

Abnormal bone and mineral metabolism in kidney transplant patients--a review.

Sprague SM, Belozeroff V, Danese MD, Martin LP, Olgaard K.

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BACKGROUND/AIMS: Abnormal bone and mineral metabolism is common in patients with kidney failure and often persists after successful kidney transplant.
METHODS: To better understand the natural history of this disease in transplant patients, we reviewed the literature by searching MEDLINE for English language articles published between January 1990 and October 2006 that contained Medical Subject Headings and key words related to secondary or persistent hyperparathyroidism and kidney transplant.
RESULTS: Parathyroid hormone levels decreased significantly during the first 3 months after transplant but typically stabilized at elevated values after 1 year. Calcium tended to increase after transplant and then stabilize at the higher end of the normal range within 2 months. Phosphorus decreased rapidly to within or below normal levels after surgery and hypophosphatemia, if present, resolved within 2 months. Low levels of 1,25(OH)2 vitamin D typically did not reach normal values until almost 18 months after transplant.
CONCLUSION: This review provides evidence demonstrating that abnormal bone and mineral metabolism exists in patients after kidney transplant and suggests the need for treatment of this condition. However, better observational and interventional research is needed before advocating such a treatment guideline.

PMID: 17989497 [PubMed - indexed for MEDLINE]

28. Transplant Proc. 2007 Dec;39(10):3153-8.

Renal osteodystrophy after successful renal transplantation: a histomorphometric analysis in 57 patients.

Lehmann G, Ott U, Stein G, Steiner T, Wolf G.

Department of Rheumatology/Osteology, Clinic of Internal Medicine III, Jena, Germany.

Renal transplantation is the treatment of choice for patients with end-stage renal disease. It corrects most of the metabolic abnormalities that cause renal osteodystrophy. Nevertheless, renal osteodystrophy persists in many transplant recipients. The aim of this study was to investigate frequency and histomorphometric pattern of bone disease after renal transplantation. Bone biopsy specimens were taken from the iliac crest of 57 patients, including 28 women (26-70 years old) and 29 men (27-67 years old). Indications for biopsy were hypercalcemia, elevation of parathyroid hormone, and, in 19 cases, without suspected bone abnormalities based on laboratory parameters. The mean time of dialysis prior to renal transplantation was 43 months (range, 6-91 months in women and 10-111 months in men) and the mean interval between transplantation and bone biopsy was 53.5 months (range, 4-191 months in women and 5-90 months in men). Fourteen patients were treated with either 25-hydroxyvitamin D3 and/or 1-alpha hydroxyvitamin D3 or 1,25 dihydroxyvitamin D3, 3 with phosphate-binding agents. The immunosuppression consisted of cyclosporine, azathioprine, and prednisolone. The cumulative dosage of corticosteroids was 5569+/-5305 mg. For static and dynamic histomorphometry, we used American Society of Bone and Mineral Research nomenclature. Mild osteitis fibrosa and osteitis fibrosa, the most frequent forms of renal osteodystrophy, were observed in 13. (22.8%) and 14 patients (24.6%), respectively. Mixed uremic osteodystrophy was found in 7 patients (12.3%), adynamic renal bone disease in 3 patients (5.3%), and osteomalacia in 2 patients (3.5%). In 13 patients (22.8%), reduced bone mass and structural damage without typical signs of renal osteodystrophy, such as endosteal fibrosis or osteoclasia, were detected, and 5 patients (8.7%) showed normal histomorphometric parameters. We concluded that renal osteodystrophy, especially forms with high bone turnover, persisted in many patients after successful renal transplantation. This finding may be due to preexisting conditions, such as duration of dialysis and degree of hyperparathyroidism. Bone disease is increased by corticosteroid and immunosuppressive therapy after renal transplantation and requires close monitoring.

PMID: 18089342 [PubMed - indexed for MEDLINE]

29. Am J Transplant. 2007 Nov;7(11):2515-21.

Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation.

Borchhardt K, Sulzbacher I, Benesch T, Födinger M, Sunder-Plassmann G, Haas M.

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Hypercalcemia in persistent secondary hyperparathyroidism after kidney transplantation is considered to result from increased bone resorption. Bone biopsies' studies, however, have never been performed in these patients. Bone biopsies after double tetracycline labeling were obtained from 17 patients with hypercalcemic hyperparathyroidism and an estimated glomerular filtration rate > 30 mL/min/1.73 m2. Serologic bone markers, calcitriol, intact fibroblast growth factor-23 (iFGF-23), and serum and 24h urine concentration of calcium and phosphate were measured in all patients. Tubular maximum for phosphate corrected for GFR (TmP/GFR), and the fractional excretion of calcium (FeCa) were calculated. High-turnover renal osteodystrophy (ROD) was present in nine and low-turnover ROD in eight patients. The bone formation rate was significantly associated with bone alkaline phosphatase, c-telopeptide and osteocalcin. In patients with high turnover ROD, osteocalcin was also significantly higher than in patients with decreased bone formation. The FeCa was normal or below normal in 14/17 patients. TmP/GFR was below normal in all patients. Neither intact PTH nor iFGF-23 was associated with TmP/GFR, FeCa or any histomorphometric bone parameter. We conclude that hypercalcemia of posttransplant hyperparathyroidism can be associated with high or low turnover bone disease. Decreased calcium excretion suggests an additive tubular effect on hypercalcemia.

PMID: 17725680 [PubMed - indexed for MEDLINE]

30. Transplantation. 2007 Nov 15;84(9):1151-7.

Posttransplant acidosis and associated disorders of mineral metabolism in patients with a renal graft.

Yakupoglu HY, Corsenca A, Wahl P, Wüthrich RP, Ambühl PM.

Department of Nephrology, University Hospital, Zurich, Switzerland.

Comment in:
Transplantation. 2007 Nov 15;84(9):1075-6.

BACKGROUND: Persisting disturbances in acid/base homeostasis may have an impact on several metabolic aspects of individuals with a kidney graft, specifically with regard to mineral metabolism and bone.
METHODS: We undertook a cross-sectional analysis among 823 unselected patients being transplanted with a functioning renal allograft who had at least one measurement of venous serum bicarbonate available within a 4-year period before May 1, 2005. As a determinate of metabolic acidosis bicarbonate was measured along with serum calcium, phosphate, parathyroid hormone, and other routine serological and epidemiological parameters. Data were assessed according to quartiles of serum bicarbonate and by univariate analysis. A multivariate regression model examined the effects of potential predictors of acidosis.
RESULTS: Mean serum bicarbonate was 22.5+/-4 mmol/L, with 58.1% of the examined renal transplant patients having metabolic acidosis as defined by a venous bicarbonate of <24 mmol/L. Bicarbonatemia was highly associated with serum parathyroid hormone, phosphate, and calcium but also with renal graft function (determined as calculated glomerular filtration rate). Multiple stepwise regression analysis revealed age, glomerular filtration rate, parathyroid hormone, and albumin to be the strongest predictors of serum bicarbonate concentration. Therapy with any calcineurin inhibitor was not associated with an increased likelihood of acidosis (odds ratio 1.04), but a significant difference was found between cyclosporine A and tacrolimus, which had an attributed odds ratio for acidosis of 0.6 and 1.8, respectively.
CONCLUSIONS: Metabolic acidosis is highly prevalent among an unselected cohort of renal transplant patients. A clear association exists between the severity of acidosis and disturbances of mineral metabolism. Thus, persisting acid/base disorders may accentuate bone disease in a setting with other factors predisposing for posttransplant osteopathy.

PMID: 17998871 [PubMed - indexed for MEDLINE]

36. Osteoporos Int. 2007 Mar;18(3):363-8. Epub 2006 Oct 24.

Failure of successful renal transplant to produce appropriate levels of 1,25-dihydroxyvitamin D.

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INTRODUCTION: Bone metabolism disturbances following renal transplantation (RT) are complex and multifactorial in origin. Abnormalities in 1,25-dihydroxyvitamin D levels in RT patients under treatment at our Bone Center prompted this retrospective study.
METHODS: Parameters of vitamin D metabolism were compared in RT patients and a cohort of patients with primary hyperparathyroidism (PHTP) who mimicked the hyperparathyroid state of the RT patients. Thirty-one RT recipients (from 300 reviewed) matched our inclusion criteria with a stable graft function for more than 1 year and a glomerular filtration rate (GFR) >50 mL/min per 1.73 m(2) (Group A); these were compared with 42 consecutive patients with PHTP who had been referred to the same Bone Center for treatment for over 1 month (Group B). Statistical analysis included the chi-square or Fisher's exact tests for categorical data and the Wilcoxon rank sum test for quantitative measures.
RESULTS: The mean (+/-SD) 1,25-dihydroxyvitamin D level was significantly lower ($p < 0.001$) in Group A patients (29.8 +/- 16.2) than in Group B patients (70.2 +/- 25.9) despite non-significant differences in the levels of parathyroid hormone (PTH) (mean: 184.0 vs.101.1;$p < 0.29$), phosphorus (mean: 3.2 vs. 3.1; $p < 0.3$) and 1,25-vitamin D (mean: 19.5 vs. 25.2; $p < 0.06$). Group A patients had lower levels ($p < 0.05$) of mean serum calcium and calculated GFR (9.3 mg/dL, 65.7 mL/min) than Group B patients (10.6 mg/dL, 97.6 mL/min). 1,25-Dihydroxyvitamin D significantly correlated with calcium ($p < 0.001$), 25-vitamin D ($p < 0.005$) and GFR ($p < 0.001$) in both groups, but there was a notable lack of association between 1,25-dihydroxyvitamin D and PTH ($p < 0.64$) or phosphorus ($p < 0.26$) in Group A patients. In this group, 1,25-dihydroxyvitamin D was not influenced by the type of immunosuppresion regimen ($p < 0.06$), use of biphosphonates ($p < 0.73$), presence of diabetes ($p < 0.59$), menopause in women ($p < 0.08$), season ($p < 0.43$) or race ($p < 0.31$). Our data indicate that 1,25-dihydroxyvitamin D metabolism remains disturbed for a considerable time after successful RT, with the result that the level of 1,25-dihydroxyvitamin D in RT patients is lower despite physiological signals that should stimulate its production. Our analysis of many clinical variables was unable to elucidate the underlying mechanism(s) for this disturbance.
CONCLUSION: Successful RT may not produce appropriate levels of 1,25-dihydroxyvitamin D commensurate to the elevated levels of PTH. This abnormality along with sustained hyperparathyroidism may contribute to bone loss following transplantation.

PMID: 17061149 [PubMed - indexed for MEDLINE]

45. Pediatr Nephrol. 2005 Mar;20(3):360-7. Epub 2005 Feb 4.

Assessment of bone mass following renal transplantation in children.

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Throughout childhood and adolescence, skeletal growth results in site-specific increases in trabecular and cortical dimensions and density. Childhood osteoporosis can be defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Pediatric renal transplant recipients have multiple risk factors for impaired bone density and bone strength, including pre-existing renal osteodystrophy, delayed growth and development, malnutrition, decreased weight-bearing activity, inflammation, and immunosuppressive therapies. Dual energy X-ray absorptiometry (DXA) is the most-common method for the assessment of skeletal status in children and adults. However, DXA has many important limitations that are unique to the assessment of bone health in children. Furthermore, DXA is limited in its ability to distinguish between the distinct, and sometimes opposing, effects of renal disease on cortical and trabecular bone. This review summarizes these limitations and the difficulties in assessing and interpreting bone measures in pediatric transplantation are highlighted in a review of select studies. Alternative strategies are presented for clinical and research applications.

PMID: 15692834 [PubMed - indexed for MEDLINE]

47. Am J Kidney Dis. 2004 Oct;44(4):747-56.

Histologic evolution of bone disease 6 months after successful kidney transplantation.

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BACKGROUND: The histologic patterns of bone disease, as well as the evolution of renal osteodystrophy after kidney transplantation (Tx), are not well defined. Information in this regard is scarce and contradictory.
METHODS: Before and 6 months after Tx, analysis of biochemical, hormonal, and bone histomorphometric parameters were performed. Twenty patients (14 men and 6 women) entered the study. Median age was 36.5 (range, 20 to 55) years, and median time on dialysis was 22 (9 to 88) months.
RESULTS: Bone histomorphometric diagnoses at pre-Tx were adynamic bone disease, 12; mixed bone disease, 3; mild disease, 3; and osteitis fibrosa, 2. After Tx, 11 had adynamic bone disease; 8, mild disease; and 1, osteomalacia. As a whole, dynamic parameters improved significantly in patients who had adynamic bone. Five of the 12 with this diagnosis completely recovered their bone turnover. Pre-Tx hyperparathyroidism bone features improved or resolved, but 5 of the 8 patients had low-turnover bone disease (adynamic disease, 4; osteomalacia, 1). Three of them had persistence of aluminum and/or iron deposits on bone surface, and the other 2 had hypophosphatemia and high intact parathyroid hormone levels. Overall, biochemical parameters tended toward normalization. Serum intact parathyroid hormone before Tx was correlated negatively with post-Tx trabecular thickness.
CONCLUSION: Six months after Tx, bone histology remained abnormal. The high turnover bone disease improved in all cases, but in most of them low turnover bone disease emerged. Nearly half of the cases with pre-Tx adynamic bone disease recovered their bone turnover completely with some improvement observed in the majority of the remaining cases.

PMID: 15384027 [PubMed - indexed for MEDLINE]

50. Clin Transplant. 2003 Jun;17(3):268-74.

Hyperparathyroidism and long-term bone loss after renal transplantation.

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BACKGROUND: While early bone loss after renal transplantation (RT) is well described, factors affecting the long-term fate of bone have received less attention.
METHODS: Whole body (WB), lumbar spine (LS) and femoral neck (FN) bone mineral density (BMD) was measured using dual energy X-ray absorptionometry in 126 stable RT patients and repeated in 114 survivors after 3 yr. Percentage change per year (%/yr) was correlated to clinical and biochemical markers of bone metabolism.
RESULTS: Low bone mass was a marker of increased mortality (FN < 80% normal 6.3%/yr; >80% 2.2%/yr). Percent change was WB -0.7 +/- 1.5 ($p < 0.01$); LS -0.3 +/- 2.6; FN -1.0 +/- 3.0 ($p < 0.01$) and, corrected for expected loss for age and sex: WB -0.5 ($p < 0.01$); LS 0.0; FN -0.8 ($p < 0.05$). Factors associated with increased loss rates were (LS%): short RT duration [<2 yr: -3.1 ($p < 0.01$)], high prednisone dose [>9 mg/d: -1.9 ($p < 0.01$)], high cyclosporine trough concentration [>175 ng/L: -1.9 ($p < 0.05$)], high hyperparathyroidism (PTH) [>150 ng/L: -1.5 ($p < 0.05$)], high alkaline phosphatase [>275 U/L: -1.6 ($p < 0.05$)], high osteocalcin [>75 microg/L: -1.6 ($p < 0.05$)]. Marginal detrimental effects of uremia, hypoalbuminemia and hyperphosphatemia were noted. Thiazide treatment seemed to protect against, and furosemide to exacerbate, bone loss, but this may have been related to associated uremia. Patients treated with vitamin D gained bone, while untreated patients with low initial 1,25-dihydroxyvitamin D lost bone [FN%-2.1 ($p < 0.05$)]. The prevalence of PTH (52%) and hypercalcemia (22%) remained unchanged. There was no effect of sex hormone levels, calcium and phosphate excretion, or serum calcium.
CONCLUSION: While LS BMD stabilizes after RT, there is a continuing loss of WB and FN BMD. The major causes of bone loss are steroid therapy and continuing PTH, with no tendency towards spontaneous resolution. Increased vitamin D and calcium therapy should be considered for this patient group, and more aggressive therapy, e.g. parathyroidectomy given for patients with resistant PTH of >150 ng/L.

PMID: 12780679 [PubMed - indexed for MEDLINE]

52. Kidney Int. 2003 May;63(5):1915-23.

The pathogenesis of osteodystrophy after renal transplantation as detected by early alterations in bone remodeling.

Rojas E, Carlini RG, Clesca P, Arminio A, Suniaga O, De Elguezabal K, Weisinger JR, Hruska KA, Bellorin-Font E.

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BACKGROUND: Loss of bone mass after transplantation begins in the early periods after transplantations and may persist for several years, even in patients with normal renal function. While the pathogenesis of these abnormalities is still unclear, several studies suggest that preexisting bone disease, glucocorticoid therapy, and alterations in phosphate metabolism may play important roles. Recent studies indicate that osteoblast apoptosis and impaired osteoblastogenesis play important roles in the pathogenesis of glucocorticoid-induced osteoporosis.
OBJECTIVES: To examine the early alterations in osteoblast number and surfaces during the period following renal transplantation.
METHODS: Twenty patients with a mean age of 36.5 +/- 12 years were subjected to bone biopsy 22 to 160 days after renal transplantation. In 12 patients, a control biopsy was performed on the day of transplantation. Bone sections were evaluated by histomorphometric analysis and cell DNA fragmentation by the methods of terminal deoxynucleotidyl transferase-mediated uridine triphosphate nick end labeling (TUNEL), using immunoperoxidase and direct immunofluorescence techniques.
RESULTS: The main alterations in posttransplant biopsies were a decrease in osteoid and osteoblast surfaces, adjusted bone formation rate, and prolonged mineralization lag time. Peritrabecular fibrosis was markedly decreased. None of the pretransplant biopsies revealed osteoblast apoptosis. In contrast, TUNEL-positive cells in the proximity of osteoid seams or in the medullary space were observed in nine posttransplant biopsies of which four had mixed bone disease, two had adynamic bone disease, one had osteomalacia, one had osteitis fibrosa, and one had mild hyperparathyroid bone disease. Osteoblast number in posttransplant biopsies with apoptosis was lower as compared with posttransplant biopsies without apoptosis. In addition, most of them showed a marked shift toward quiescence from the cuboidal morphology of active osteoblasts. Serum phosphorus levels were lower in patients showing osteoblast apoptosis and correlated positively with osteoblast number and negatively with the number of apoptotic osteoblasts. In addition, posttransplant osteoblast surface correlated positively with parathyroid hormone (PTH) levels and negatively with glucocorticoid cumulative dose.
CONCLUSION: The data suggest that impaired osteoblastogenesis and early osteoblast apoptosis may play important roles in the pathogenesis of posttransplant osteoporosis. The possible mechanisms involved in the pathogenesis of theses alterations include posttransplant hypophosphatemia, the use of glucocorticoids, and the preexisting bone disease. PTH seems to have a protective effect by preserving osteoblast survival.

PMID: 12675872 [PubMed - indexed for MEDLINE]

55. Transplantation. 2002 Aug 27;74(4):496-500.

Bone mineral density and fracture prevalence in long-term kidney graft recipients.

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Comment in:
Transplantation. 2002 Aug 27;74(4):438-9.

BACKGROUND: Renal transplantation triggers an early bone loss that increases the subsequent risk of osteoporosis and fractures. Little is known about the long-term outcome of bone status and fracture prevalence several years after transplantation. Therefore, we conducted a cross-sectional evaluation of bone status to find out the frequency and predictors of osteoporotic fractures in late kidney graft patients.
METHODS: Changes in spinal, hip, and total body bone mineral density were assessed using a DEXA Hologic QRD 1000 scanner, and fractures were quantified in all kidney graft patients presenting for routine evaluation with a minimal follow-up of 5 years after transplantation (with a mean follow-up 8.5+/-3.1 years). We measured biochemical markers of bone metabolism and collected clinical and dietary intake data.
RESULTS: Fifty-nine renal graft recipients were enrolled in the study within 9 months. Osteoporosis, according to the World Health Organization definition, was observed in 31 patients (53% of the total population) and fractures occurred in 26 patients (44% of the total population and 51.6% of patients with osteoporosis). Femoral neck bone mineral density was positively correlated with patient's weight and cyclosporin current dosage. Steroid cumulative dosage correlated only to lumbar spine Z score. Dietary calcium, serum 25 hydroxyvitamin D, parathyroid hormone, and urinary N-telopeptides excretion were normal.
CONCLUSIONS: These data emphasize the substantial prevalence of osteoporosis and fractures among very long-term kidney graft recipients. Therapeutic intervention in these patients is urgently needed.

PMID: 12352908 [PubMed - indexed for MEDLINE]

56. J Am Soc Nephrol. 2002 Feb;13(2):551-8.

Calcium metabolism and skeletal problems after transplantation.

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PMID: 11805187 [PubMed - indexed for MEDLINE]

59. Transplantation. 2000 Dec 27;70(12):1722-8.

Posttransplant bone disease: evidence for a high bone resorption state.

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Loss of bone is a significant problem after renal transplant. Although bone loss in the first post transplant year has been well documented, conflicting data exist concerning bone loss after this time. It is equally unclear whether bone loss in long-term renal transplant recipients correlates with bone turnover as it does in postmenapausal osteoporosis. To examine these issues, we conducted a cross-sectional study to define the prevalence of osteoporosis in long-term (> 1 year) renal transplant recipients with preserved renal function (mean creatinine clearance 73 +/- 23 ml/min). Bone mineral density (BMD) was measured at the hip, spine and wrist by DEXA in 69 patients. Markers for bone formation (serum osteocalcin) and bone resorption [urinary levels of pyridinoline (PYD) and deoxypyridinoline (DPD)] were also measured as well as parameters of calcium metabolism. Correlations were made between these parameters and BMD at the various sites. The mean age of the patients was 45 +/- 11 years. Eighty eight percent of patients were on cyclosporine (12% on tacrolimus) and all but 2 were on prednisone [mean dose 9 +/- 2 mg/day)]. Osteoporosis (BMD more than 2.5 SD below peak adult BMD) at the spine or hip was diagnosed in 44% of patients and osteopenia was present in an additional 44%. Elevated levels of intact parathyroid hormone (i PTH) were observed in 81% of patients. Elevated urinary levels of PYD or DPD were present in 73% of patients and 38% had elevated serum levels of osteocalcin. Levels of calcium, and of 25(OH) and 1,25(OH)2 vitamin D were normal. In a stepwise multiple regression model that included osteocalcin, PYD, DPD, intact PTH, age, years posttransplant, duration of dialysis, cumulative prednisone dose, smoking, and diabetes: urinary PYD was the strongest predictor of bone mass. These results demonstrate that osteoporosis is common in long-term renal transplant recipients. The data also suggest that elevated rates of bone resorption contribute importantly to this process.

PMID: 11152104 [PubMed - indexed for MEDLINE]

61. Clin Transplant. 2000 Oct;14(5):457-63.

Bone loss after renal transplantation: role of hyperparathyroidism, acidosis, cyclosporine and systemic disease.

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In order to determine risk factors for bone loss after renal transplantation, dual energy X-ray absorptiometry was performed in 125 renal transplant patients. The bone mineral density (BMD) was expressed as a percentage of the normal population (BMD%) and Z-score (SD from normal). The whole body, lumbar spine and femoral neck BMD% (Z-score) values were 93.9 +/- 8.9 (-0.90 SD), 91.6 +/- 14.9 (-0.98 SD) and 87 +/- 15.3 (-1.0 SD)%, respectively. Low BMD% was associated with low creatinine clearance (< 40 mL/min: 91.6 +/- 7.9, > 40 mL/min: 95.6 +/- 8.0, p < 0.01), repeated graft loss (0: 94.4 +/- 9.1, > 1: 87.4 +/- 9.3, p < 0.05), long dialysis duration (< 1 yr: 95.2 +/- 7.9, > 5: 90.1 +/- 10.6, p < 0.05), acidosis (bicarbonate < 21 mmol/L: 89.6 +/- 8.0, > 27: 96.7 +/- 7.2, p < 0.01), secondary and tertiary hyperparathyroidism (< 50 ng/L: 95.9 +/- 7.1, > 200: 87.7 +/- 5.0, p < 0.01), raised alkaline phosphatase (< 200 units/L: 95.7 +/- 7.2, > 300: 85.6 +/- 13.2, p < 0.001), osteocalcin (< 50 microg/L: 95.2 +/- 6.7, > 100:89.3 +/- 7.6, p < 0.01) and urinary deoxypyridinoline (< 5 nM/mM creatinine: femoral neck 89.6 +/- 10.7, > 10: 82.1 +/- 20.1, p < 0.05), low 25-OH-vitamin D (< 10 microg/L: 91.3 +/- 9.8, > 20: 96.9 +/- 7.4, p < 0.001) and high cyclosporine concentration (0 ng/L: 98.3 +/- 7.0, > 150: 92.1 +/- 9.3, p < 0.05). Patients with clinical atherosclerosis (91.7 +/- 8.6 vs. 95.4 +/- 8.8, p < 0.01), hypoalbuminemia (< 550 micromol/L: 87.6 +/- 13.2, > 550: 94.2 +/- 7.8, p < 0.01), renovascular disease (89.7 +/- 5.7 vs. 95.0 +/- 5.7, p < 0.05) and diabetic nephropathy (femoral neck 76.6 +/- 8.8 vs. 89.3 +/- 15.1, p < 0.01) had lower bone masses. High bone mass was associated with previous dialysis alphacalcidol therapy (0: 92.2 +/- 7.5, > 3 microg/wk: 97.3 +/- 6.9, p < 0.05). No relationships with transplantation duration, 1,25-OH-vitamin D, aluminium, calcium or steroid dose were found. No involutional changes in tertiary hyperparathyroidism could be discerned. CONCLUSION: The major threats to bone mass after renal transplantation appear to be ongoing hyperparathyroid bone disease, low renal function, acidosis, systemic disease and hypo-vitaminosis D.

PMID: 11048990 [PubMed - indexed for MEDLINE]

66. Kidney Int. 1999 May;55(5):2021-9.

Bone loss in long-term renal transplantation: histopathology and densitometry analysis.

Cueto-Manzano AM, Konel S, Hutchison AJ, Crowley V, France MW, Freemont AJ, Adams JE, Mawer B, Gokal R.

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BACKGROUND: There is little information of the spectrum and factors implicated in the bone loss in long-term renal transplantation, and virtually no data using both histomorphometric and densitometric analysis.
METHODS: Twenty-three males and 22 females (13 postmenopausal) were studied with a bone biopsy and densitometry. Sixteen patients were on cyclosporine A monotherapy, 20 on azathioprine + prednisolone, and 9 on cyclosporine A + prednisolone or triple therapy. The mean time after transplantation was 127 +/- 70 months.
RESULTS: No group had a significant decrease in bone mineral density (BMD) of the axial skeleton compared with an age- and sex-matched normal population. Compared with sex-matched young controls, osteopenia was observed in all groups at the femoral neck (except premenopausal women and triple therapy) and in the triple-therapy group at the L1-L4 spine region. At the distal radius, osteopenia was found in all the groups. Histopathological diagnosis was mixed uremic osteodystrophy in 46.5%, adynamic bone in 23.2%, hyperparathyroid disease in 13.9%, and normal bone in 16.3%. The diagnosis was not different according to immunosuppressive therapy, but men tended to show more mixed uremic bone disease. There was no significant difference in BMD between histopathological subtypes. In general, patients showed slight osteoclast function increase, osteoblast function decrease, and marked retardation of dynamic parameters. The cyclosporine A monotherapy group had a significantly lower appositional rate than azathioprine + prednisolone. Men had a significantly lower bone volume than women, and premenopausal women had a significantly lower mineralizing surface than postmenopausal women and men. In the multivariate analysis, male gender, time after transplantation, old age, and time on dialysis prior to transplantation were significant predictive factors for a negative effect on bone mass.
CONCLUSIONS: Long-term renal transplant-patients showed reduced BMD in both trabecular and cortical bone. This reduction in BMD was not as severe as in short-term reports and was associated with osteoclast stimulation, osteoblast suppression, and retardation of mineral apposition and bone formation rates. Bone mass loss was not different between the immunosuppression therapy groups. Male gender and age were the strongest predictive factors for low bone mass.

PMID: 10231467 [PubMed - indexed for MEDLINE]

72. Nephrol Dial Transplant. 1995 Nov;10(11):2096-100.

Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients.

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BACKGROUND: Bone loss is an important problem in renal transplant recipients immediately after surgery. No data are available about the bone loss beyond the first post-transplantation year.
METHODS: In a longitudinal, uncontrolled observational study bone mineral density (BMD) was measured by dual X-ray absorptiometry in 115 renal graft recipients starting at different times after transplantation (0-20 years after transplantation) with a follow-up time of 12 months.
RESULTS: A total of 56 patients showed a reduction of BMD during the observation period. Bone loss depended on the time after transplantation. Mean reduction of BMD at lumbar spine was 7 +/- 10%, 1 +/- 9% during the first and second postoperative year. Beyond the third year bone mineral density did not change or even increased slightly (0 +/- 4% during 3-5th year, 1 +/- 6% during 6-10th year and 2 +/- 4% during 11-20th year after transplantation). Decrease of BMD correlated with a higher mean daily prednisone dosage ($P < 0.001$), a higher cumulative prednisone dose ($P < 0.01$), a more frequent and more steroid-resistant rejection ($P < 0.001$) and a higher initial parathyroid hormone level ($P < 0.001$). Patients with 25-OH-cholecalciferol therapy ($P < 0.05$) or more physical activity ($P < 0.05$) had a smaller bone loss.
CONCLUSIONS: Reduction of BMD after transplantation is highest within the first post-transplant year. The effects of acute graft rejection, prednisone dosage and initial parathyroid hormone level are predominant among the multiple factors associated with pronounced bone loss.

PMID: 8643174 [PubMed - indexed for MEDLINE]

77. Am J Kidney Dis. 1992 Feb;19(2):99-120.

Musculoskeletal complications after renal transplantation: pathogenesis and treatment.

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Department of Medicine, University of Alabama, Birmingham 35294.

Comment in:
Am J Kidney Dis. 1992 Nov;20(5):531.

Renal transplantation is associated with several abnormalities of function and structure of the musculoskeletal system. Some of these skeletal problems result from incomplete resolution of abnormalities of bone and mineral metabolism present at the time of transplantation. In this regard, persistent hyperparathyroidism, diabetes mellitus type 1, and accumulation of beta 2-microglobulin may lead to residual skeletal effects despite excellent function of the allograft. Persistent hyperparathyroidism may accelerate bone loss and increase the risk for osteonecrosis, as well as cause hypercalcemia and hypophosphatemia; some patients with severe hyperparathyroidism require parathyroid surgery. Osteonecrosis is the most debilitating skeletal complication after transplantation and frequently requires surgical therapy. Although osteomalacia associated with aluminum overload generally resolves after transplantation, bone complications due to dialysis amyloidosis and diabetes mellitus type 1 often fail to improve. Alternatively, skeletal abnormalities can be acquired after transplantation. Most of the new derangements of bone and mineral metabolism are due to the immunosuppressive medications. Toxic effects of glucocorticoids on bone contribute to the pathogenesis of osteonecrosis, increase the risk for fractures by decreasing cancellous bone mass and synthesis of bone matrix, and dampen the linear growth response in pediatric recipients. Whether cyclosporine independently causes appreciable toxic effects on bone metabolism is not yet clear, but use of this drug increases the prevalence of gout and dental problems. Osteonecrosis, osteopenia, and short stature remain important skeletal complications in recipients of renal allografts. Therapeutic efforts should be directed toward alleviating pretransplant bone disease and attenuating bone loss after transplantation.

PMID: 1739106 [PubMed - indexed for MEDLINE]

Proyecto Prometeo

Referencias Bibliográficas

Grupo I

Etiopatogenia Metabolismo Ca/P en Trasplante Renal

Con el patrocinio de:

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Roche

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1. Transplant Proc. 2010 May;42(4):1148-55.

Immunosuppressive agents and bone disease in renal transplant patients with hypercalcemia.

Sessa A, Esposito A, Iavicoli GD, Lettieri E, Dente G, Costa C, Bergallo M, Rossano R, Capuano M.

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Renal transplantation is the definitive treatment for many metabolic abnormalities of uremic patients, although it is only partially effective for renal osteodystrophy, which may interact with posttransplant renal osteopathy. Osteopenic-osteoporotic syndrome represents, together with fractures secondary to osteoporosis and osteonecrosis, the bone complication most related to renal transplantation. Several factors contribute to the pathogenesis of posttransplantation osteoporosis, particularly immunosuppressive treatment. In this study, we evaluated the prevalence of factors related to posttransplant renal osteopathy and the clinical impact of immunosuppressive protocols. We studied 24 renal transplant recipients with hypercalcemia. Glomerular filtration rate was >50 mL/min. Mean age, time on dialysis, and time from transplantation were 49.6, 5.4, and 6.9 years, respectively. We evaluated serum and urine calcium and phosphorus, calcitonin, parathormone, bone-specific alkaline phosphatase, osteocalcin, urine deoxypyridinoline, telopeptide of type 1 procollagen, 1,25-(OH)(2) and 25-OH vitamin D, parathyroid ultrasound, and computerized bone mineralometry. The combination of sirolimus and steroids resulted in the most disadvantageous outcomes regarding alkaline phosphatase and mineralometry. Calcineurin inhibitors did not significantly influence bone metabolism markers; mycophenolate mofetil evidenced no effect on bone. According to the literature, steroids account for the abnormalities found in our patients and in severe osteopenia. Several factors may contribute to the development of osteoporosis and fractures in transplantation patients, although they are overcome by the prominent effect of steroids. In patients at high risk of osteoporosis, steroid-free therapy should be considered. Everolimus is indicated for diseases with bone loss. Combined therapy with everolimus and mycophenolic acid without cyclosporine and steroids, seemed to be particularly indicated. Prophylactic treatments should be commenced early. No single marker was useful to diagnose posttransplant renal osteopathy. The definitive diagnosis should be made by bone biopsy during transplantation, and noninvasive procedures, such as densitometry and evaluation of biologic markers, may be useful during follow-up.

PMID: 20534247 [PubMed - indexed for MEDLINE]

2. Int Urol Nephrol. 2009 Dec;41(4):1029-38. Epub 2009 Aug 22.

Calcium, phosphate and parathyroid metabolism in kidney transplanted patients.

Ambrus C, Molnar MZ, Czira ME, Rosivall L, Kiss I, Remport A, Szathmari M, Mucsi I.
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INTRODUCTION: Impaired kidney function is common in kidney-transplanted patients and complications of chronic kidney disease (CKD), such as mineral and bone disorders (MBD) are also prevalent in this population. Similarly to other stages of CKD, increasing evidence supports the association between MBD and cardiovascular risk after kidney transplantation as well. Still, little is known about the prevalence, clinical correlates of MBD and its management in transplanted patients. In this study, we aimed to examine the characteristics of MBD and its associations with clinical parameters in a large prevalent cohort of patients after kidney transplantation. METHODS: Nine hundred and ninety stable patients followed at a single kidney transplant outpatient clinic were included in the study. Detailed medical history, demographic data and routine laboratory results, including Ca, P and intact PTH were collected. Estimated GFR was calculated using the abbreviated MDRD formula, patients were stratified into three groups based on eGFR. Target levels for Ca, P and iPTH were based on CKD stages according to the NKF-K/DOQI guidelines. Standard statistical procedures, binomial and multinomial regressions were used in the analysis. RESULTS: The mean age was 51 years, 57% were males and 21% were diabetic, with 72 months (median) post-transplantation. Most of the patients were in CKD stage 3. Serum phosphorus showed strong negative correlation with graft function in CKD stages 4-5 ($r = -0.633$, $P < 0.001$). Hyperphosphatemia was independently associated with the time spent on dialysis before transplantation, serum iPTH and CKD stages 4-5. iPTH showed negative correlation with eGFR in CKD stages 3-5 (rho = -0.289, $P < 0.001$) and weak positive correlation with time spent on dialysis prior to transplant (rho = 0.114, $P < 0.001$). Both hyperparathyroidism (42%) and relative hypoparathyroidism (15%) were frequent. The prescription of P-binders (6%) and vitamin D analogs (33%) was sporadic. CONCLUSION: Disturbances of bone and mineral metabolism after transplantation are prevalent and are strongly correlated with the kidney function, similarly to non-transplanted CKD patients. MBD in this population is not adequately managed.

PMID: 19701690 [PubMed - indexed for MEDLINE]

3. Am J Transplant. 2009 Nov;9(11):2470-8. Epub 2009 Aug 14.

Localization, etiology and impact of calcium phosphate deposits in renal allografts.

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Hypercalcemia, hypophosphatemia and renal phosphate wasting are common after kidney transplantation. Animal data suggest that these alterations in mineral metabolism may contribute to calcium phosphate (CaPhos) deposition in the kidney and renal dysfunction. We tested the hypothesis that CaPhos deposition is highly prevalent in the early posttransplant period and is related to a disturbed mineral metabolism. For this purpose, biomarkers of mineral metabolism and renal calcium and phosphorus handling were prospectively assessed in 201 renal transplant recipients. CaPhos deposits were observed in 4.6, 30.4 and 24.7% of protocol biopsies obtained at the time of engraftment, and 3 and 12 months thereafter, respectively. In multivariate logistic regression analysis, high calcium and low serum phosphorus levels were independently associated with renal CaPhos deposition at month 3. The extent of CaPhos deposition correlated significantly with the severity of mineral metabolism disturbances. Renal function after a mean follow-up of 33 months was similar in patients with and without CaPhos deposition at month 3. In conclusion, our data demonstrate that CaPhos deposition is highly prevalent in the early posttransplant period and suggest that a disordered mineral metabolism is implicated in its pathogenesis. The clinical relevance of CaPhos deposition remains to be established.

PMID: 19681815 [PubMed - indexed for MEDLINE]

4. Nephrol Dial Transplant. 2009 Aug;24(8):2439-45.

The correlation between dental calculus and disturbed mineral metabolism in paediatric patients with chronic kidney disease.

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BACKGROUND: Vascular calcifications have been documented in children with end-stage renal disease. However, only a few reports have described abundant dental calculus formation in children suffering from chronic kidney disease (CKD). Moreover, dental calculus scores (DCS) and their correlation with renal disease severity have not been studied. METHODS: DCS in 74 young CKD patients were evaluated: 25 pre-dialytic (PrD), 18 on dialysis (D) and 31 with transplants (T) compared to 32 healthy participants (C). Saliva and serum analysis included creatinine (Cr), urea (U), calcium (Ca), phosphorous (P), magnesium (Mg) as well as intraoral pH levels. RESULTS: All patient groups presented high DCS. DCS and pH levels were higher in the D group with a positive correlation between pH and lower incisor DCS ($r = 0.56$, $P = 0.017$). The highest salivary Ca was found in the PrD group. Salivary P in the PrD group was found to be higher than in the T and C groups. The lowest salivary Mg was found in the D group while the highest salivary Ca x P product was found in the PrD group. In all patient groups, salivary U was higher than in the C group with a 2.5-fold increase in the D group. Salivary Cr resembled the U salivary concentrations. CONCLUSIONS: Alterations in salivary Ca, P, Mg, U, Cr and intraoral pH levels were observed in the patient groups. DCS correlated with renal disease severity and therefore may be a reflection of other tissue calcification pathologies found in these patients.

PMID: 19297359 [PubMed - indexed for MEDLINE]

5. Transplant Proc. 2009 Jul-Aug;41(6):2403-5.

Bone metabolism according to chronic kidney disease stages in patients undergoing kidney transplantation: a 5-year database analysis.

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INTRODUCTION: While kidney transplantation successfully reverses many complications of uremia that are not corrected with dialysis therapy, elevated parathyroid hormone (PTH) levels and other alterations of mineral metabolism persist in transplant recipients.
PATIENTS AND METHODS: A single-center cohort retrospective database analysis was performed of 497 consecutive adult patients who underwent first kidney transplantation between 1994 and 2004. At 1- and 5-year follow-up, a descriptive analysis was performed of mineral metabolism parameters of chronic kidney disease stage according to NKF KDOQI (National Kidney Foundation Kidney Disease Outcomes Quality Initiative) in patients with a functional graft at 1 year. Glomerular filtration rate was estimated using the abbreviated MDRD (Modification of Diet in Renal Disease) equation.
RESULTS: Most of the transplants (99.2%) were from cadaveric donors. Mean (SD) patient age was 47.7 (13.3) years, and 69% of patients were men. The causes of chronic kidney disease were glomerular (35.4%), congenital (15.4%), systemic (14.1%), vascular (11.3%), interstitial (10.1%), and other (<1%). The percentage of patients in each stage of chronic kidney disease with calcium levels less than 8.5 mg/dL, phosphorus greater than 4.5 mg/dL, and PTHi greater than 150 pg/mL increased as graft function declined. Six posttransplantation parathyroidectomies were performed. Only 130 patients received secondary hyperparathyroidism treatment within 5 years after transplantation: calcium carbonate, 36.9%; calcium acetate, 1.5%; calcium carbonate plus cholecalciferol, 21%; calcitriol, 71%; and calcifediol, 0.8%.
CONCLUSIONS: The prevalence of hypocalcemia, hyperphosphatemia, and elevated PTH level increased with chronic kidney disease stage. Classification of renal transplant recipients by KDOQI stage may enable clinicians to identify patients at increased risk and to target appropriate therapy to improve outcome. There is an opportunity for enhanced management of secondary hyperparathyroidism in these patients.

PMID: 19715933 [PubMed - indexed for MEDLINE]

6. Clin J Am Soc Nephrol. 2009 Mar;4(3):665-72. Epub 2009 Mar 4.

Calcium metabolism in the early posttransplantation period.

Evenepoel P, Van Den Bergh B, Naesens M, De Jonge H, Bammens B, Claes K, Kuypers D, Vanrenterghem Y.

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BACKGROUND AND OBJECTIVES: Information on the time course of serum calcium levels after renal transplantation is scanty, especially in the early posttransplantation period. Both the abrupt cessation of calcium-containing phosphorus binders and vitamin D (analogs) at the time of surgery and the recovery of renal function may be hypothesized to affect serum calcium levels in this period.
DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS: In this prospective observational study, biointact parathyroid hormone, calcidiol, calcitriol, calcium, and phosphorus levels were monitored in 201 renal transplant recipients at the time of transplantation and 3 mo thereafter. In addition, the serum calcium nadir and peak in each individual patient within this time frame were identified and the urinary fractional calcium excretion was determined at month 3.
RESULTS: Serum calcium levels followed a biphasic pattern with a significant decline during the first postoperative week, followed by a significant increase. High pretransplantation parathyroid hormone levels protect against hypocalcemia within the first postoperative week but put patients at risk for hypercalcemia later. These complications, occurring in 41 and 14% of the patients, respectively, most probably reflect inappropriate calcium release from the skeleton, rather than inappropriate renal calcium handling.
CONCLUSIONS: Our data indicate that both hypo- and hypercalcemia are prevalent in the early posttransplantation period. Pretransplantation parathyroid function is an important predictor of posttransplantation calcium levels.

PMID: 19261823 [PubMed - indexed for MEDLINE]

7. Nefrologia. 2009;29 Suppl 1:31-7.

[Changes in bone and mineral metabolism in kidney transplant patients with chronic kidney disease].

[Article in Spanish]

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DESCRIPTION: Recently, the Foundation has proposed new definitions KDIGO to refer to the alterations of bone - mineral metabolism in patients with chronic renal disease (CRD), relegating the traditional term of renal osteodystrophy (ODR). RECOMMEND: The term ODR exclusively to define alterations in bone morphology and architecture characteristic of the ERC. - And the term of bone-mineral alteration associated with the CRD to describe biochemical changes, and skeletal calcifications that occur as a result of alterations in mineral metabolism in the CRD. PATHOPHYSIOLOGY: The different metabolic abnormalities are secondary to the progressive loss of renal mass and renal function that leads to retention of phosphorus and a decrease in the levels of calcitriol which are responsible for the skeletal resistance to the action of PTH. CLINICAL FEATURES: The main clinical manifestations of abnormal bone mineral metabolism are posttransplantation osteoporosis and osteopenia producing an increase in fractures, osteonecrosis, and bone pain. DIAGNOSTIC METHODS: Biochemical parameters (calcium, phosphorus, PTH, 25 hydroxyvitamin D), X-ray bone densitometry and bone biopsy. (Evidence B). THERAPEUTIC ALTERNATIVES: It is recommended for the treatment and prevention of osteopenia - osteoporosis in transplant patients based on data from clinical evidence available from other study populations, such as in patients with chronic kidney disease. In addition to specific treatment, we must take into account the preventive measures to reduce the risk of fractures. Treatment includes specific measures for the prevention of bone loss (active metabolite of vitamin D analogues and bisphosphonates) and the treatment of persistent hyperparathyroidism (calcimiméticos). (Evidence B).

PMID: 19675659 [PubMed - indexed for MEDLINE]

8. Nefrologia. 2009;29(2):143-9. doi: 10.3265/Nefrologia.2009.29.2.5006.en.full.

[Changes in the pre-transplant bone-mineral metabolism do not affect the initial progress of the renal graft].
[Article in Spanish]

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BACKGROUND: Abnormalities in serum calcium, phosphate, and Parathyroid Hormone (PTH) concentrations are common in patients with chronic kidney disease and have been associated with increased morbidity and mortality. One of the most common problems in the first weeks after renal transplantation is Delayed Graft Function (DGF). There are several well-known risk factors for DGF development, but the role of calcium phosphate-PTH homeostasis as a risk factor for early graft dysfunction is controversial. This issue was addressed in the current study.
METHODS: Pretransplant PTH, calcium and phosphate values were gathered in 449 patients that received a renal transplant in our center between 1994 and 2007. Other variables expected to influence the risk for delayed graft function were included from the clinical charts.
RESULTS: The incidence of DGF was 27.3%. DGF development was significantly associated with recipient age, type and need of renal replacement therapy, peak panel reactive antibodies, transfusion number and donor age. There were no significant differences in the mean pretransplant values of calcium (9.4 +/- 1.0 vs. 9.5 +/- 0.9 mg/dl, p = 0.667), phosphate (5.7 +/- 1.8 vs. 5.5 +/- 1.5 mg/dl, p = 0.457), calcium-phosphate product (53.5 +/- 17.2 vs. 51.8 +/- 14.6 mg(2)/dl(2), p = 0.413) and PTH (315 +/- 312 vs. 340 +/- 350 pg/ml, p = 0.530) between patients with and without DGF.
CONCLUSIONS: In our study population pretransplant serum PTH, calcium and phosphorus levels have no influence on the risk for DGF.

PMID: 19396320 [PubMed - indexed for MEDLINE]

9. Am J Nephrol. 2008;28(2):246-53. Epub 2007 Nov 7.

Abnormal bone and mineral metabolism in kidney transplant patients--a review.

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BACKGROUND/AIMS: Abnormal bone and mineral metabolism is common in patients with kidney failure and often persists after successful kidney transplant. METHODS: To better understand the natural history of this disease in transplant patients, we reviewed the literature by searching MEDLINE for English language articles published between January 1990 and October 2006 that contained Medical Subject Headings and key words related to secondary or persistent hyperparathyroidism and kidney transplant. RESULTS: Parathyroid hormone levels decreased significantly during the first 3 months after transplant but typically stabilized at elevated values after 1 year. Calcium tended to increase after transplant and then stabilize at the higher end of the normal range within 2 months. Phosphorus decreased rapidly to within or below normal levels after surgery and hypophosphatemia, if present, resolved within 2 months. Low levels of 1,25(OH)2 vitamin D typically did not reach normal values until almost 18 months after transplant. CONCLUSION: This review provides evidence demonstrating that abnormal bone and mineral metabolism exists in patients after kidney transplant and suggests the need for treatment of this condition. However, better observational and interventional research is needed before advocating such a treatment guideline.

PMID: 17989497 [PubMed - indexed for MEDLINE]

10. Endocrinol Metab Clin North Am. 2007 Dec;36(4):923-35; viii.

Calcium and bone metabolism pre- and post-kidney transplantation.

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Chronic kidney disease (CKD) is associated with significant disturbances in bone and mineral metabolism, the manifestations of which are heterogeneous in their expression and clinical impact. Over the last 2 decades, advances in the management of CKD and improved outcomes of kidney transplantation have led to the emergence of post-transplantation bone disease as a serious cause of morbidity in long-term survivors. The management of post-kidney transplantation bone disease represents a difficult challenge because of its complex pathophysiology and the paucity of clinical data on effective therapies. The optimal management of disturbances of bone and mineral metabolism before kidney transplantation forms the cornerstone of their successful management after transplantation. Therapeutic strategies to effectively and safely decrease skeletal morbidity after kidney transplantation are not yet clearly established.

PMID: 17983929 [PubMed - indexed for MEDLINE]

11. Exp Clin Transplant. 2007 Dec;5(2):670-2.

Calcium and phosphorus metabolism in stable renal transplant recipients.

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Erratum in:
Exp Clin Transplant. 2008 Mar;6(1):following 94.

OBJECTIVES: This study sought to elucidate the status of calcium, phosphorus, and parathyroid hormone in patients following kidney transplant. MATERIALS AND METHODS: In this cross-sectional study, 20 renal transplant recipients were evaluated. For each patient, age, sex, time since transplant, and body weight were recorded. Inclusion criteria were age > 14 years and good allograft function defined as a serum creatinine level < 132.6 micromol/L for at least 6 months after transplant. Exclusion criteria were immunosuppressive therapy other than the standard triple regimen (cyclosporine, prednisolone, and mycophenolate mofetil or azathioprine) and use of any drug known to alter calcium hemostasis. Levels of 24-hour urine calcium, phosphorus, creatinine, and uric acid, as well as concentrations of hemoglobin, serum creatinine, calcium, and phosphorus were measured. To obtain a mean value of serum intact parathyroid hormone in transplant recipients at our center, serum intact parathyroid hormone levels were additionally quantitated in another group of 30 renal transplant recipients. RESULTS: The mean hemoglobin level was 135.6 +/- 17.7 g/L, the mean serum creatinine level was 105.0 +/- 15.3 micromol/L, and the mean serum calcium and phosphorus levels were 2.25 +/- 0.17 mmol/L (normal range, 2.02-2.60 mmol/L) and 1.28 +/- 0.24 mmol/L (normal range, 0.81-1.61 mmol/L), respectively. The mean serum intact parathyroid hormone level was 33.17 +/- 14.67 ng/L (normal range, 10-60 ng/L). Mean 24-hour urine calcium and phosphorus values were 2.32 +/- 1.68 mmol/day (normal, 2.49-6.24 mmol/day) and 19.77 +/- 8.31 mmol/day (normal, 12.91-41.98 mmol/day), respectively. A positive correlation was found between serum calcium and alkaline phosphatase levels (r = +0.71, P = .006). Hemoglobin level was negatively correlated with serum phosphorus level (r = -0.65, P = .003) and sex (r = -0.57, P = .003) and positively correlated with urine creatinine levels (r = +0.69, P = .001). CONCLUSIONS: Renal transplant recipients with stable allograft function may have normal serum calcium, phosphorus, and intact parathyroid hormone levels. However, presence of hypocalciuria and elevated serum alkaline phosphatase levels might imply impaired calcium metabolism in these patients.

PMID: 18194119 [PubMed - indexed for MEDLINE]

12. Transplant Proc. 2007 May;39(4):1033-5.

Calcium and phosphorus metabolism disturbances after renal transplantation.

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INTRODUCTION: Several studies have noted that, despite beneficial correction of abnormalities of mineral metabolism after successful renal transplantation, renal functional recovery is incomplete. Also, persistence of hyperparathyroidism and metabolic acidosis among patients with chronic impairment of graft function together with the use of loop diuretics and immunosuppressive drugs with adverse effects may alter mineral metabolism. We determined calcium and phosphorus levels in recipients.
METHODS: This cross-sectional study enrolled 398 recipients in 2 medical centers in Iran from 1988 to 2004 to evaluate serum calcium and phosphorus levels after 1 month in relation to graft and patient survivals. Cyclosporine was the constant part of the immunosuppressive treatment in all study subjects.
RESULTS: The median follow-up time was 8 months (range, 1-180 months). One and 10-year survival rates of patients were 97.9% and 91.1%. Mean (SD) serum calcium levels before and after transplantation were 8.79 (1.26) and 8.50 (1.39) mg/dL, respectively (P=.020). The mean (SD) phosphate levels before and after transplantation were 6.43 (2.42) and 3.64 (1.71) mg/dL, respectively (P=.000). There was no significant difference in survival considering changes in serum calcium and phosphorus levels. There was no correlation between serum calcium and phosphorus level changes among study patients.
CONCLUSIONS: Despite reports suggesting hypercalcemia as a posttransplantation finding, we did not observe this condition, but, consistent with other reports in this field, we observed a significant decrease in serum phosphorus levels showing correction of this mineral level.
PMID: 17524884 [PubMed - indexed for MEDLINE]

13. Am J Transplant. 2007 Mar;7(3):718-21. Epub 2007 Jan 11.

Familial hypocalciuric hypercalcemia in the donor and recipient of a living related donor kidney transplant.

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Familial hypocalciuric hypercalcemia (FHH) is caused by heterozygous inactivation of the calcium-sensing receptor, which is notably expressed in parathyroid and kidney. FHH is characterized by asymptomatic hypercalcemia and hypophosphatemia and confers minimal, if any, morbidity. Renal transplantation in patients with FHH has not been described previously. This report describes a patient with FHH who developed end-stage renal disease from another cause and subsequently received a living related donor kidney transplant from her FHH-affected daughter. The excellent posttransplant clinical course of both recipient and donor is emphasized.

PMID: 17217434 [PubMed - indexed for MEDLINE]

14. Transplant Proc. 2005 Jun;37(5):2151-3.

Correlations between leptin, body composition, bone mineral density, and bone metabolism in kidney transplant recipients.

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INTRODUCTION: In kidney transplant recipients leptin levels are often elevated and bone mineral density (BMD) decreased. However, to date there are no about correlations between leptin and BMD in this population. It has been suggested that leptin is a predictor of BMD in postmenopausal women. Moreover, leptin acts as a marker of fat stores. We examined the relationships between leptinemia, some markers of nutritional status, BMD, and bone metabolism in kidney transplant recipients. We also assessed whether leptin was a significant and independent predictor of BMD in this population.
METHODS: BMD and fat content (global, percentage, trunk) were measured using dual-energy X-ray absorptiometry in 27 kidney allograft recipients. Markers of bone turnover and leptin were studied using commercially available kits.
RESULTS: Leptin correlated with the percentage of body fat, trunk fat, lean body mass, serum creatinine, and urea. Insulin growth factor binding protein 1 was negatively related to waist-hip ratio and global and trunk fat, whereas BMD of the lumbar spine was correlated with the daily dose of prednisone, azathioprine, cyclosporine trough levels, serum calcium, as well as osteoprotegerin level.
CONCLUSIONS: Leptin levels are associated with graft function and body fat in kidney allograft recipients. Leptin is not related to nutritional status, BMD, or bone metabolism in kidney allograft recipients, but is associated with the current dosage of immunosuppressants and the serum calcium.

PMID: 15964364 [PubMed - indexed for MEDLINE]

15. Transplant Proc. 2005 Mar;37(2):1014-9.

Changes in bone mineral density and selected metabolic parameters over 24 months following renal transplantation.

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Our aim was to evaluate changes in serum levels of selected bone metabolism indicators and bone density over 24 months following renal transplant. A partial objective was assessment of the effectiveness of prophylactic administration of vitamin D and calcium preparations to prevent progression of osteopathy after kidney transplantation. Forty patients after kidney transplantation were prophylactically given vitamins A and D (800 IU) and calcium (1000 mg) a day. During monitoring, the serum creatinine in all recipients was <200 micromol/L (subgroup A with creatinine concentration < 120 micromol/L versus subgroup B with creatinine 120 to 200 micromol/L). The concentration of serum parathormone, serum level of bone fraction of alkaline phosphatase, serum concentrations of phosphorus and calcium urinary 24-hour excretion of phosphorus and calcium were examined at 2 weeks and 2 years after transplantation. In the same time period, radiographs of thoracic, lumbar spine, and hip joints were obtained. Bone density (BMD) of the lumbar (L) spine and the hip was determined by dual-energy X ray (Lunar Prodigy). Two years after transplantation in subgroup A, the BMD showed decrease in 80% of recipients in the L spine area but hip showed a 15% BMD increase. In subgroup B, the BMD decreased in 95% recipients in L and hip and only 25% showed a BMD increase. No clinical or radiographic sign of fracture was detected in this group. We conclude that prophylactic administration of vitamin D and calcium is not sufficient to prevent the progression of osteopathy after renal transplantation. Changes in bone density evaluated after the kidney transplantation are affected by graft function.

PMID: 15848609 [PubMed - indexed for MEDLINE]

16. Nephrol Dial Transplant. 2004 May;19(5):1281-7. Epub 2004 Feb 19.

Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study.

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BACKGROUND: The natural history of parathyroid function after successful renal transplantation (RT) and the factors predisposing to persistent hyperparathyroidism (HPT) are not well established. A better knowledge of these data may be helpful in the development of algorithms for optimal surveillance and treatment of HPT after successful RT. Our aim was to evaluate the post-transplant natural history of parathyroid function and calcium metabolism in patients with a functional renal graft and to identify risk factors for persistent HPT.
METHODS: Charts of 1165 allograft kidney recipients transplanted between 1989 and 2000 were reviewed. Patients with an intact parathyroid hormone (iPTH) level available at the time of transplantation were identified. The charts of the latter patients were checked for a variety of demographic and clinical data, and all determinations of the iPTH concentration available since transplantation were recorded. Serum levels of calcium, phosphorus, alkaline phosphatases and creatinine, concurrently determined, were also registered.
RESULTS: After an initial fall, iPTH levels showed a slow but steady decline towards the upper normal limit. The prevalence of persistent HPT, defined as an iPTH level > or =2.5 times the upper normal limit or the need for parathyroidectomy following transplantation, remained stable at approximately 17% up to 4 years after transplantation. Patients with persistent HPT had significantly elevated serum levels of iPTH, calcium and phosphorus at the time of RT, and had spent a longer time on dialysis. Post-transplant iPTH levels correlated significantly with transplant kidney function.
CONCLUSION: Kidney transplant recipients with a high iPTH and calcium x phosphate product at the time of transplantation are at risk for persistent HPT especially when renal function is suboptimal. Therapy for persistent HPT, if considered, should be initiated 3 months post-transplantation since further spontaneous improvement of parathyroid function thereafter is limited.

PMID: 14993493 [PubMed - indexed for MEDLINE]

17. Transplantation. 2004 Mar 27;77(6):868-73.

Calcium levels as a risk factor for delayed graft function.

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BACKGROUND: Delayed graft function (DGF) occurs in up to 50% of renal transplants. Hypercalcemia and hyperparathyroidism are associated with impaired renal function. Little is known on the effects of serum calcium levels on DGF. This issue was addressed in the current study.
METHODS: Patients receiving a cadaveric renal transplant between 1986 and 1996 were studied. Data on calcium metabolism and histologic characteristics of nephrocalcinosis, acute tubular necrosis (ATN), and acute rejection in biopsies taken within the first week were related to the occurrence of DGF.
RESULTS: The incidence of DGF in a cohort of 585 cadaveric transplants was 31%. DGF correlated independently with serum calcium levels (odds ratio [OR] 1.14 [95% confidence interval (CI) 1.04-1.26] per 0.1 mmol/L). The use of calcium channel blockers before transplantation protected against DGF (OR 0.5 [95% CI 0.29-0.87]). In this selected group, we found an association with histologic signs of ATN and DGF. However, most of the biopsies also had features of acute rejection or nephrocalcinosis. Nephrocalcinosis was found in 12 of 71 biopsies and was not associated with serum calcium levels or the occurrence of DGF.
CONCLUSIONS: In this study, serum calcium levels were independently associated with DGF. This could not be explained by the presence of microscopic nephrocalcinosis. Therefore, DGF is attributed to high intracellular calcium levels. Because calcium supplementation and vitamin D analogues are commonly used in dialysis practice, hypercalcemia influences long-term graft outcome by its effect on DGF. The pretransplant use of calcium channel blockers has a protective effect on the occurrence of DGF.

PMID: 15077029 [PubMed - indexed for MEDLINE]

18. Transplant Proc. 2003 Nov;35(7):2724.

Bone loss in the early period after renal transplantation.

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PMID: 14612092 [PubMed - indexed for MEDLINE]

19. Int J Gynaecol Obstet. 2003 Feb;80(2):111-6.

Calcium-phosphorus-magnesium homeostasis in pregnant women after renal transplantation.

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OBJECTIVE: The aim of the study was the assessment of calcium-phosphorus-magnesium homeostasis in pregnant women after renal transplantation.
METHODS: The study covered 64 pregnant women in the third trimester of gestation including: 33 women after renal transplantation (the study group) and 31 healthy pregnant women (the control group). Women from both groups were at the similar age: 30.8+/-4.7 vs. 31.3+/-5.0 years (NS) and at the same gestational age 34.8+/-2.4 vs. 35.3+/-2.6 weeks (NS). The mean body mass index (BMI) in the women from the study group before pregnancy was 21.49+/-2.81 vs. 22.1+/-3.02 in the control group (NS), BMI before delivery was 25.43+/-3.05 vs. 26.0+/-3.35 (NS), the percentage of the BMI increase during pregnancy was 18.7+/-7.68 vs. 17.65+/-7.13 (NS) and BMI increase during gestation was 3.93+/-1.56 vs. 3.90+/-1.54, respectively (NS). Arterial blood pressure at the time of blood samples collection for biochemical tests was 151.4+/-26.8/92.5+/-16.9 in women from the study group comparing to 115.0+/-6.0/68.0+/-7.0 mmHg (P<0.001) in the patients from the control group. The maximal blood pressure during pregnancy was 169.2+/-20.7/102.7+/-14.0 vs. 118.0+/-7.0/70.0+/-8.0 mmHg (P<0.001), respectively. We estimated serum levels of: total Ca, ionized Ca(2+), inorganic phosphorus (P(i)), Mg, total protein, albumin and blood morphology. Moreover, urine levels of Ca, P(i), Mg and protein were assessed.
RESULTS: The pregnant women after renal transplantation presented increases in serum concentrations of total Ca (2.54+/-0.20 vs. 2.16+/-0.10 mmol/l; P<0.001) and ionized Ca(2+) (1.322+/-0.104 vs. 1.12+/-0.07 mmol/l; P<0.001) and the decrease in P(i) level (1.013+/-0.211 vs. 1.10+/-0.16 mmol/l; P<0.05), total protein (59.3+/-7.0 vs. 65+/-5 g/l; P<0.001) and albumin (461.6+/-65.65 vs. 493.2+/-59 micromol/l; P<0.05). Moreover, in the study group drop in red blood cells count to 3.71+/-0.56 vs. 4.01+/-0.35 x 10(12)/l (P<0.02) in the control group was detected. Despite increased volume of 24-h urine collection in the kidney recipients we observed significantly decreased urine 24-h calcium excretion 2.47+/-0.92 vs. 6.72+/-3.49 mmol (P<0.001) and simultaneous increase in urine Mg excretion 3.422+/-1.025 vs. 2.18+/-0.52 mmol/24 h (P<0.001). There was no difference in urine 24-h P(i) excretion between the study and the control group. The pregnant renal transplant recipients presented proteinuria of 1.19+/-1.9 g/24 h.
CONCLUSIONS: Women after kidney grafting present vital aberrations in calcium-phosphorus-magnesium homeostasis during pregnancy. The most significant changes are associated with calcium metabolism (high increase in serum Ca levels and impairment of renal elimination of calcium). The observed changes may be influenced by the doses of immunosuppressive agents and disturbed renal function.

PMID: 12566182 [PubMed - indexed for MEDLINE]

20. Nefrologia. 2003;23 Suppl 2:127-30.

Osteoporosis after renal transplantation.

Trabulus S, Apaydin S, Altiparmak MR, Seyahi N, Sariyar M, Serdengeçti K, Erek E.

Department of Nephrology, SSK Istanbul Educational Hospital, Istanbul, Turkey.

This study was performed to determine risk factors associated with osteoporosis that develops after renal transplantation. Sixty-five kidney graft recipients were included in this study. They were divided into four groups according to the time since transplantation: Group 1 (< 1 year; n = 26), group 2 (1-3 years; n = 16), group 3 (3-5 years; n = 12) and group 4 (> 5 years; n = 11). These groups were matched according to probable risk factors for osteoporosis, findings of serum biochemistry, biochemical markers of bone turnover and measurements of bone mineral density. One way ANOVA test and Kruskal-Wallis test were used for statistical analysis. Osteoporosis was found in 22 recipients (33.8%). There were significant differences in recipient age, cumulative steroid dose, and episodes of acute rejection between the four groups. Increasing age, cumulative steroid dose and episodes of acute rejection were found to be risk factors for osteoporosis in our study.

PMID: 12778869 [PubMed - indexed for MEDLINE]

21. Am J Kidney Dis. 2000 Jul;36(1):160-6.

Bone disease in patients with long-term renal transplantation and normal renal function.

Carlini RG, Rojas E, Weisinger JR, Lopez M, Martinis R, Arminio A, Bellorin-Font E.

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Renal osteodystrophy may persist during the early years after renal transplantation. However, information on bone status after a successful long-term renal transplantation is limited. We examined biochemical parameters, bone mineral density (BMD), and bone histomorphometry in 25 asymptomatic men with normal renal function after 7.5 +/- 5.7 years of a renal transplantation. Serum calcium, phosphorus, alkaline phosphatase, and 1,25(OH)(2)D(3) levels and urinary calcium level and cyclic andenosine monophosphate excretion were within normal range in all patients. Serum intact parathyroid hormone (PTH) level was elevated in 11 subjects (133.6 +/- 78 pg/mL) and normal in the other 14 subjects (47.9 +/- 13.6 pg/mL). Mean BMD at the lumbar spine and femoral neck was low in the entire group. However, it progressively increased as time after transplantation increased, approaching normal values after 10 years. Bone histomorphometric analysis showed bone resorption, osteoid volume, and osteoid surface greater than normal range in the majority of patients. Bone formation rate and mineralization surface were low, and mineralization time was delayed in most patients. These lesions were more severe in patients after 3 to 4 years of transplantation but improved with time and approached normal values after a period of 10 years. PTH values did not correlate with bone histological characteristics or BMD. These results show that the bone alterations observed after long-term renal transplantation consist of a mixed bone disease in which features of high bone turnover coexist with altered bone formation and delayed mineralization. These findings may result from the combined effect of preexisting bone disease and immunosuppressive therapy.

PMID: 10873886 [PubMed - indexed for MEDLINE]

22. Ann Transplant. 1999;4(1):46-53.

Disorders of calcium metabolism at various times after renal transplantation.

Babarykin D, Adamsone I, Amerika D, Folkmane I, Rozental R.

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OBJECTIVES: Increased parathyroid hormone (PTH) production and related defects of calcium-phosphorus metabolism could persist even after successful kidney transplantation. Much more serious long term consequences after the transplantation are bone defects caused by immunosuppressive drugs. Many authors consider steroid therapy as one of the factors that maintain this process. Our study aimed to investigate calcium-phosphorus and bone pathological features during the various post transplantation periods, using non-invasive bone research methods (bone ultrasound structurally-densitometric analysis), and also to analyse the risk of hyperparathyroidism and steroid therapy in the development of post transplantation osteopathy.
METHODS: 52 patients after successful kidney transplantation were investigated. All patients were divided in three groups according to the time after transplantation. 1st group-patients in the earlier post transplantation period, up to 1 year (n = 12); 2nd group-patients in the period from 1 to 5 years after transplantation (n = 25); 3rd group-patients in later post transplantation period (more than 5 years after the transplantation, n = 15).
RESULTS: 8 patients from the 1st group (66.7%), 18 patients from the 2nd group (72%) and 8 patients from the 3rd group (53.3%) had an increased level of serum creatinine. The level of corrected serum Ca was increased ($p < 0,05$) in the first year after the transplantation. Hypercalcaemia was noted in 5 patients (41.7%) from the 1st group, in 3 patients (12%) from the 2nd group and in 2 patients (13.3%) from the 3rd group. Urine Ca level was lower ($p < 0.05$) in patients with post transplantation period over 5 years. Serum iPTH level as well as the level of osteocalcin was higher in all groups. The highest iPTH and osteocalcin level ($p < 0.05$) were observed during the first post transplantation year, but in the later post transplantation period they had a tendency to decrease, but never reached the norm for healthy subjects even in later post transplantation period. The decreased speed of ultrasound in the trabecular bones and osteopenia were noted in 6 patients from the 1st group (50%), osteoporosis -- in 1 patient from the 1st group(8.3%). In the 2nd group 8 patients had osteopenia (32%) and 1 patient had osteoporosis (4%), and in the 3rd group 7 patients had osteopenia (46.7%) and 4 patients -- osteoporosis (26.7%). A negative correlation was noted between patient age and speed of sound in all patient populations ($r = -0.39$, $p<0,01$), both in the early post transplantation period ($r = -0.67$, $p<0.01$), and during the period 1-5 years after transplantation ($r = -0.5$, $p <0.01$). The whole patient population showed negative correlation ($r = -0.28$, $p<0.05$) between Z-score and time after the transplantation. Z-score negatively correlates with a cumulative steroid dose in all investigated patients groups($r = -0.35$, $p<0.02$).
CONCLUSIONS: Disorders of calcium metabolism and immunosuppression related bone disease are the most common complications after transplantation, especially in patients with an impaired graft function. The mild hyperparathyroidism is usually noted in these patients at various times after transplantation. We also can note hypocalciuria in the later post transplantation period in these patients, which is based on the parathyroid glands hyperfunction and on the negative effects of the steroid therapy. The cumulative steroid dose and patient age are the determining factors for the

development of osteopenia in transplantation patients at the stage of 5 or more years after transplantation.

PMID: 10850601 [PubMed - indexed for MEDLINE]

23. Nephrol Dial Transplant. 1998 Oct;13(10):2605-11.

Effects of oral phosphorus supplementation on mineral metabolism of renal transplant recipients.

Caravaca F, Fernández MA, Ruiz-Calero R, Cubero J, Aparicio A, Jimenez F, García MC.

S. Nefrología, Hospital Universitario Infanta Cristina, Badajoz, Spain.

BACKGROUND: Persistent hyperparathyroidism (HPT) is frequently observed in kidney transplant recipients. Hypophosphataemia is a common biochemical consequence of HPT. Theoretically, oral phosphorus administration may induce negative effects on the control of HPT, though this point has never been demonstrated in kidney-transplant recipients. This study was designed to evaluate the effects of oral phosphorus supplementation on the mineral metabolism of successful kidney transplant recipients.
METHODS: Thirty-two kidney transplant recipients with serum creatinine < 2 mg/dl and serum phosphate levels <3.5 mg/dl were included in the study. After a washout period in which oral phosphorus supplementation was discontinued, the following parameters were determined (F0 period): serum calcium, phosphate, alkaline phosphatase, uric acid, bicarbonate, PTH, 1,25-dihydroxyvitamin D3 (1,25 (OH)(2)D) and 25-hydroxyvitamin D3 (25OHD). Creatinine clearance, calcium, and phosphate excretion were determined from a 24-h urine sample. The same determinations were repeated (F1 period) after all patients received 1.5 g of oral phosphorus for 15 days. For data analysis, patients were divided into two subgroups (optimal and suboptimal) according to allograft function (Ccr>or < 70 ml/min/1.73 m2).
RESULTS: In the F0 period, only nine of 32 patients had PTH levels within the normal range (<65 pg/ml). The mean concentrations of PTH, 1,25(OH)(2)D and 25OHD were 132+/-97pg/ml, 40.5+16pg/ml and 12.5+/-8.2 ng/ml respectively. Phosphorus supplementation led to significant reductions in serum calcium and 1,25(OH)(2)D concentrations, as well as in urinary calcium excretion in the whole group. On the contrary, serum phosphate, PTH, and urinary phosphate excretion increased significantly. The percentage increase in PTH concentrations after phosphorus supplementation were similar in patients with optimal and suboptimal allograft function (33 vs 36%). The reduction of 1,25 (OH)(2)D concentrations after phosphorus supplementation was observed mainly in the subgroup with optimal allograft function (21% reduction with respect to baseline values), while the mean 1,25(OH)(2)D concentrations in patients with suboptimal allograft function scarcely changed (1.4% increase). Changes in 1,25(OH)(2)D concentrations after phosphorus supplementation, expressed as a percentage of the initial concentrations, correlated positively with the percentage changes in PTH concentrations for the whole group, as well as for each subgroup. The best determinants for the percentage and the absolute increase in PTH concentration after phosphorus supplementation was the final serum phosphate concentration (F=4.84, r=0.37, P=0.035) and the increase in serum phosphate (F=7.69, r=0.45, P=0.009) respectively.
CONCLUSIONS: Oral phosphorus supplementation led to a significant increase in the PTH concentration of kidney transplant recipients. The mean 1,25(OH)(2)D concentration decreased mainly in recipients with optimal allograft function. The counterbalance effect of PTH on 1,25(OH)(2)D production may account for the relative preservation of 1,25(OH)2D levels in recipients with suboptimal allograft function.

PMID: 9794568 [PubMed - indexed for MEDLINE]

24. Transplantation. 1995 Jun 27;59(12):1690-4.

Lack of evidence that cyclosporine treatment impairs calcium-phosphorus homeostasis and bone remodeling in normocalcemic long-term renal transplant recipients.

Dumoulin G, Hory B, Nguyen NU, Henriet MT, Bresson C, Regnard J, Saint-Hillier Y.

Explorations Fonctionnelles Rénales Métaboliques et Endocriniennes, Centre Hospitalier Universitaire, Besançon, France.

Since the effects of cyclosporine on mineral and bone metabolism are controversial, we studied calcium regulating hormones, calcium-phosphorus (Ca-P) metabolism, and bone remodeling, assessed by serum osteocalcin, in long-term renal transplant recipients (RT). Forty-seven normocalcemic patients with good renal function receiving cyclosporine (CT, n = 27) or not (NC, n = 20) were studied at baseline and after an oral Ca load. CT and NC had similar age, daily dose of steroids, GFR level, and duration of transplantation. Baseline evaluation included 24-hr urinary Ca, P, TRP, TmP/GFR, fasting serum intact PTH, 1,25-(OH)2D, 25OHD, osteocalcin, Ca, and P. Subjects of the two groups had excessive secretion of PTH, tubular P wasting, and high serum osteocalcin level, as is usual in RT. However, there was no difference between CT and NC regarding any baseline variable. Ten CT and ten NC, matched for duration of transplantation and serum PTH level, ingested 1g Ca to achieve an acute dynamic study of PTH secretion and Ca-P metabolism. In both CT and NC, this Ca load caused the same decreases in serum PTH ($P < 0.001$), NcAMP ($P < 0.05$), and urinary P ($P < 0.001$) and the same increases in serum and urinary Ca ($P < 0.001$), and in both TmP/GFR and TRP ($P < 0.001$). These results strongly suggest that cyclosporine treatment had no significant effect on calcium-regulating hormone secretion, P-Ca metabolism, and bone remodeling level. We therefore consider that cyclosporine is unlikely to have any prominent role in the abnormalities of bone endocrine and mineral metabolism that are common in long-term kidney recipients.

PMID: 7604439 [PubMed - indexed for MEDLINE]

25. Transplant Proc. 1994 Oct;26(5):2646-8.

Bone mineral content in cyclosporine-treated renal transplant patients.

Massari PU, Garay G, Ulla MR.

Renal Transplant Program, Hospital Privado-Centro Medico de Córdoba, Argentina.

PMID: 7940826 [PubMed - indexed for MEDLINE]

26. Transplant Proc. 1994 Aug;26(4):2009-11.

Bone mineral density profile in uremic and renal transplant patients.

Chao SH, Tsai KS, Chieng PU, Lee PH, Lee CJ, Lee CS.

Department of Surgery, National Taiwan University Hospital, Taipei, Republic of China.

PMID: 8066651 [PubMed - indexed for MEDLINE]

27. Scand J Urol Nephrol. 1994 Mar;28(1):21-7.

Sequential changes in vitamin D and calcium metabolism after successful renal transplantation.

Saha HH, Salmela KT, Ahonen PJ, Pietilä KO, Mörsky PJ, Mustonen JT, Lalla ML, Pasternack AI.

Division of Transplantation, Helsinki University Central Hospital, Finland.

A prospective study was made of sequential changes in the metabolism of vitamin D and calcium in 19 allograft recipient during the first year after successful renal transplantation. All but one of the patients received cyclosporine A combined with corticosteroids and azathioprine as immunosuppressive therapy. Shortly after transplantation most patients showed transient hypocalcemia and hypophosphatemia. At the time of transplantation 17 of 19 patients had an elevated plasma intact parathyroid hormone (PTH) level, and at the close of follow-up one in four patients. In six other patients intact PTH was within the reference range, but high in relation to simultaneously measured serum ionized calcium. According, one year after transplantation less than half of the patients showed complete resolution of hyperparathyroidism. The change towards normal in the metabolism of vitamin D began within the first post-transplantation week irrespective of the onset of diuresis. One to two weeks after transplantation 1,25(OH)2D3 and 24,25(OH)2D3 reached the lower limit of normal range. In these renal allograft recipients who received cyclosporine A the long-term values of serum 1,25(OH)2D3 did not differ from those of normal subjects.

PMID: 8009188 [PubMed - indexed for MEDLINE]

28. Ann Clin Biochem. 1994 Mar;31 (Pt 2):125-8.

Calcium metabolism following renal transplantation.

Straffen AM, Carmichael DJ, Fairney A, Hulme B, Snell M.

Department of Chemical Pathology, St Mary's Hospital, London, UK.

Comment in:
Ann Clin Biochem. 1995 Mar;32 (Pt 2):234.
Ann Clin Biochem. 1994 Nov;31 (Pt 6):587.

Abnormalities of calcium homeostasis are a recognized feature of end-stage renal disease. The treatment of choice is renal transplantation, but this does not always result in normalization of the biochemical profile. Persistent hypercalcaemia is well documented and our study was undertaken to investigate the status of the calcium regulating hormones in renal patients post-transplantation. Serum calcium, parathyroid hormone, 1,25-dihydroxyvitamin D (1,25(OH)2D) and osteocalcin concentrations were measured in post-transplant patients. Twenty per cent of the patients had subnormal 1,25(OH)2D concentrations while 55% had biochemical evidence of hyperparathyroidism but only 5% were hypercalcaemic. Time elapsed since transplantation was not correlated with any of the analytes investigated and there was no relationship between persistent impairment of renal function and abnormalities of calcium homeostasis.

PMID: 8060089 [PubMed - indexed for MEDLINE]

29. Clin Nephrol. 1989 Jun;31(6):316-22.

Serum osteocalcin and bone mineral metabolism following successful renal transplantation.

Boiskin I, Epstein S, Ismail F, Thomas SB, Raja R.

Albert Einstein Medical Center, Philadelphia, PA 19141.

Serum osteocalcin (bone gla protein, BGP), a vitamin K-dependent non-collagenous bone protein and its relationship to other markers of bone and mineral metabolism were studied cross-sectionally in varying numbers of patients before and over 240 days following renal transplantation. Marked elevation of serum creatinine (11.9 +/- 0.76 mg/dl), osteocalcin (216.9 +/- 7 ng/ml), parathyroid hormone (PTH, mid-molecule fragment) (24.5 +/- 3.6 ng/ml), alkaline phosphatase (255.2 +/- 54.7 IU/l) and phosphorus (5.6 +/- 0.3 mg/dl) were noted preoperatively. Serum calcium levels remained normal throughout the study period while phosphate levels normalized within one week after transplantation. PTH levels progressively decreased postoperatively over the study period but were still elevated well above normal. Serum osteocalcin decreased to near normal values at 60-90 days after surgery. Both PTH and alkaline phosphatase correlated significantly with osteocalcin preoperatively and postoperatively. The relatively depressed values of osteocalcin in the face of still elevated PTH levels post-transplantation was attributed to the effect of immunosuppressive corticosteroid therapy. The significant correlation between PTH and osteocalcin suggests that osteocalcin may be as or more sensitive a measurement of bone turnover than alkaline phosphatase pre- and post-transplantation.

PMID: 2665993 [PubMed - indexed for MEDLINE]

30. Miner Electrolyte Metab. 1985;11(3):167-72.

Disturbances in mineral metabolism after successful renal transplantation.

Sakhaee K, Brinker K, Helderman JH, Bengfort JL, Nicar MJ, Hull AR, Pak CY.

Abnormalities of mineral metabolism remain a clinical problem after successful renal transplantation. These disturbances may be the result of derangements in divalent ion, parathyroid hormone (PTH) and/or vitamin D metabolism. We therefore measured serum Ca, phosphorus, PTH and 1,25-dihydroxyvitamin D [1,25(OH)2D] levels and fractional intestinal Ca absorption (alpha) in 6 patients before and after successful transplantation (early, less than or equal to 6 months). 3 were reexamined later (late, greater than or equal to 24 months after transplantation). The patients exhibited decreased serum levels of 1,25(OH)2D and alpha before the renal transplantation. In the early stages, renal transplantation reduced serum phosphorus from 5.55 +/- (SD)1.96 to 2.96 +/- 0.95 mg/dl (p less than 0.02); this was accompanied by a rise in serum 1,25(OH)2D from 8.7 +/- 1.5 to 26.3 +/- 8.4 pg/ml (p less than 0.005). The calcemic response to PTH infusion became normal, since the increment in serum Ca rose from 0.45 +/- 0.21 mg/dl before transplantation to 1.03 +/- 0.18 mg/dl early after transplantation. Although the mean value for alpha increase significantly from 0.263 +/- 0.048 to 0.402 +/- 0.175 (p less than 0.05), alpha was subnormal in 3 patients (alpha less than 0.37). Urinary Ca was high in 3 patients, and it exceeded absorbed Ca (from intestines) in 4 patients (indicative of negative Ca balance). Serum PTH fell significantly but remained above normal. It was hoped that late after transplantation, when patients were maintained on smaller doses of oral glucocorticoids, these abnormalities would be ameliorated. However, hypercalciuria was found in 2 of 3 patients.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 3892264 [PubMed - indexed for MEDLINE]

31. Adv Nephrol Necker Hosp. 1983;12:331-40.

Disorders of calcium and phosphorus metabolism after successful kidney transplantation.

Ulmann A, Chkoff N, Lacour B.

Systematic study undertaken of 44 transplant patients with plasma creatinine below 0.11 mmol/L indicated renal phosphorus leak in approximately two-thirds of them and increased plasma PTH in all but one. Plasma 1,25(OH)2D was elevated in half the patients in whom it was measured. The lack of correlation found between plasma 1,25(OH)2D and plasma PTH or phosphorus probably indicates tubular lesions resulting in decreased production of 1,25(OH)2D. A phosphorus restriction test in 12 hypophosphatemic patients demonstrated that the reduced renal phosphorus reabsorption probably was due to both persisting hyperparathyroidism and a PTH-independent phosphorus leak.

PMID: 6404142 [PubMed - indexed for MEDLINE]

32. Nephron. 1980;26(5):225-9.

Factors influencing the intestinal absorption of calcium and phosphorus following renal transplantation.

Walker GS, Peacock M, Marshall DH, Giles GR, Davison AM.

After successful renal transplantation there is continuing malabsorption of calcium and phosphorus. This is due in part to impaired glomerular filtration rate, and in part to the action of steroid on calcium and phosphorus absorption. The effect of steroids is most marked over the first 18 months after transplantation and causes significant malabsorption of calcium and phosphorus even though good graft function is established. Calcium and phosphorus malabsorption can be improved by exogenous 1,25-dihydroxy vitamin D (oral 1 alpha-OH D3 or 1,25-[OH]2D3).

PMID: 6999370 [PubMed - indexed for MEDLINE]

33. Am J Surg. 1976 Jul;132(1):83-9.

Hypercalcemia of seven years' duration after kidney transplantation.

Bigos ST, Neer RM, Goar WT.

A case is reported of hypercalcemia persisting for seven years after kidney transplantation, with normocalcemia being achieved after subtotal parathyriodectomy. The finding of post-transplantation hyperparathyroidism of this extreme duration, in association with several other reports of hyperparathyroidism persisting for years after kidney transplantation, raises serious questions about the completeness of parathyroid involution after kidney transplantation. Extensive review of the literature reveals that little is really known about the natural history of parathyroid function and involution after kidney transplantation.

PMID: 782270 [PubMed - indexed for MEDLINE]

34. Aust N Z J Med. 1976 Jun;6(3):214-7.

Calcium metabolism after renal transplantation.

Duggin GG, Dale NE, Johnson JR, Evans RA, Whittlestone AL, Tiller DJ.

Calcium metabolism was studied in four patients who had undergone renal transplantation from eight to 19 months previously. The studies included conventional biochemical and radiological parameters, undecalcified bone histology and metabolic balances. The only abnormality found was biochemical and histologic evidence of mild hyperparathyroidism. All patients were in approximate calcium balance, and there was no evidence of osteoporosis, osteomalacia or osteitis fibrosa. It is suggested that transplantation patients with stable, well functioning grafts and normal biochemical and radiologic parameters are unlikely to have or to be at risk of developing metabolic bone disease.

PMID: 788696 [PubMed - indexed for MEDLINE]

35. Transplantation. 2005 Mar 27;79(6):629-34.

Posttransplantation bone disease.

Cunningham J.

Source

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Abstract

Transplanted patients experience rapid loss of bone, high fracture rates, and increases in morbidity and mortality as a consequence of a posttransplant scenario that is highly deleterious to the skeleton. Immune suppressive drugs, especially glucocorticoids, are toxic to bone, often acting on a background of preexisting osteodystrophy resulting from long-standing renal, hepatic, cardiac, or pulmonary disease. Cyclosporin and tacrolimus lead to a severe osteopenic state in rats, but the skeletal toxicity of the calcineurin inhibitors in the clinical environment is less clear. Nor is it clear whether cyclosporin and tacrolimus differ in their skeletal actions. Mycophenolate mofetil and sirolimus do not appear to have important skeletal toxicity. Preventative strategies include minimizing glucocorticoid exposure and implementing therapies to counter the increase in bone resorption and decrease in bone formation that follows transplantation. Antiresorptive agents, especially bisphosphonates, appear capable of retarding or halting the early bone loss and possibly reduce fracture rates also. Vitamin D and calcium are ineffective, but calcitriol has utility in some reports. Bone anabolic agents, such as synthetic parathyroid hormone and growth hormone, have potential, but data are lacking.

PMID: 15785362 [PubMed - indexed for MEDLINE]

36. Nephrol Dial Transplant. 2008 Feb;23(2):450-8. Epub 2007 Dec 1.

Bone disease after renal transplantation.

Kunzendorf U, Krämer BK, Arns W, Braun J, Grossmann J, Pietruck F, Schmidt-Gayk H, Schwarz A, Ziegler E, Sperschneider H, Wüthrich RP, Nonnast-Daniel B, Schindler R, Renders L.

PMID: 18056071 [PubMed - indexed for MEDLINE]

37. Nat Rev Nephrol. 2010 Jan;6(1):32-40. Epub 2009 Nov 17.

Bone disease after renal transplantation.

Malluche HH, Monier-Faugere MC, Herberth J.

Source

Division of Nephrology, Bone and Mineral Metabolism, University of Kentucky, UK Medical Center, 800 Rose Street, Lexington, KY 40508, USA. hhmall@uky.edu

Abstract

In light of greatly improved long-term patient and graft survival after renal transplantation, improving other clinical outcomes such as risk of fracture and cardiovascular disease is of paramount importance. After renal transplantation, a large percentage of patients lose bone. This loss of bone results from a combination of factors that include pre existing renal osteodystrophy, immunosuppressive therapy, and the effects of chronically reduced renal function after transplantation. In addition to low bone volume, histological abnormalities include decreased bone turnover and defective mineralization. Low bone volume and low bone turnover were recently shown to be associated with cardiovascular calcifications, highlighting specific challenges for medical therapy and the need to prevent low bone turnover in the pretransplant patient. This Review discusses changes in bone histology and mineral metabolism that are associated with renal transplantation and the effects of these changes on clinical outcomes such as fractures and cardiovascular calcifications. Therapeutic modalities are evaluated based on our understanding of bone histology.

PMID: 19918255 [PubMed - indexed for MEDLINE]

38. Clin J Am Soc Nephrol. 2006 Nov;1(6):1300-13. Epub 2006 Aug 23.

Bone disease after renal transplantation.

Weisinger JR, Carlini RG, Rojas E, Bellorin-Font E.

Source

Division of Nephrology, Hospital Universitario de Caracas, Universidad Central de Venezuela, Caracas, Venezuela. jweising@telcel.net.ve

Abstract

It has been well established that a rapid decrease in bone mineral density (BMD) occurs in the first 6 to 12 mo after a successful renal transplantation and persists, albeit at a lower rate, for many years. This rapid BMD loss significantly increases the fracture risk of these patients to levels that are even higher than those of patients who have chronic kidney disease stage 5 and are on dialysis. The presence of low BMD in renal transplant patients as a predictor of risk fracture is controversial. Indeed, as has been suggested also for patients with postmenopausal osteoporosis, there is not a compelling correlation between the decline in BMD and skeletal fractures. However, bone disease after renal transplantation probably represents a unique bone disorder that must encompass underlying renal osteodystrophy. In fact, this syndrome results from multiple factors that include pretransplantation bone status, use of glucocorticoids and other immunosuppressive drugs, hypophosphatemia, and alterations of the calcium-vitamin D axis. Recent studies have demonstrated decreased osteoblast number, reduced bone formation rate, delayed mineralization, and increased osteoblast and osteocyte apoptosis. Bisphosphonates and vitamin D metabolites may be valuable in preventing or diminishing early bone loss. However, clinicians should be careful with the use of bisphosphonates and oversuppression of bone, especially in patients with low bone turnover. New prospective, controlled trials are required to confirm the real efficacy of these drugs, particularly in long-term renal transplant patients.

PMID: 17699362 [PubMed - indexed for MEDLINE]

39. Clin J Am Soc Nephrol. 2010 Oct;5(10):1887-92. Epub 2010 Jul 15.

Fibroblast growth factor-23 and parathyroid hormone are associated with post-transplant bone mineral density loss.

Kanaan N, Claes K, Devogelaer JP, Vanderschueren D, Depresseux G, Goffin E, Evenepoel P.

Source

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Abstract

BACKGROUND AND OBJECTIVES:

Among the multiple factors contributing to bone mineral density (BMD) loss after renal transplantation, hypophosphatemia is increasingly recognized to play an important role. Hypophosphatemia occurs in up to 90% of the renal transplant recipients in the early post-transplant period and is caused by renal phosphate wasting. We hypothesized that a high pretransplant level of the recently described phosphaturic hormone fibroblast growth factor 23 (FGF-23) is a risk factor for accelerated BMD loss occurring within the first post-transplant year.

DESIGN, SETTING, PARTICIPANTS, & MEASUREMENTS:

We performed a two-center observational retrospective cohort study in 127 incident renal transplant recipients. Serum full-length FGF-23, parathyroid hormone (PTH), and parameters of mineral metabolism were determined at the time of transplantation. BMD was assessed by osteodensitometry at the time of transplantation and 1 year later.

RESULTS:

A moderate decrease of BMD was observed during the first post-transplant year. High FGF-23 levels were associated with BMD loss at the lumbar spine and total hip region, whereas low PTH levels were associated with BMD loss at all three regions. Cumulative doses of prednisone and post-transplant serum phosphate level were not correlated with BMD changes.

CONCLUSION:

Our data indicate that patients with a high serum FGF-23 level and/or a low PTH level at the time of transplantation are at risk for increased BMD loss during the first post-transplant year.

40. Am J Transplant. 2007 May;7(5):1193-200. Epub 2007 Mar 12.

Tertiary 'hyperphosphatoninism' accentuates hypophosphatemia and suppresses calcitriol levels in renal transplant recipients.

Evenepoel P, Naesens M, Claes K, Kuypers D, Vanrenterghem Y.

Source

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Abstract

Hypophosphatemia and inappropriately low calcitriol levels are frequently observed following successful renal transplantation. Fibroblast growth factor-23 (FGF-23) is a recently characterized phosphaturic hormone that inhibits renal 1 alpha-hydroxylase activity and may be involved in the pathogenesis of both phenomena. The following hypotheses were tested: pretransplant FGF-23 predicts posttransplant FGF-23, FGF-23 predicts posttransplant hypophosphatemia and FGF-23 is associated with decreased calcitriol levels independent of renal and parathyroid function. Serum biointact parathyroid hormone (PTH), calcidiol, calcitriol, full-length FGF-23, calcium and phosphate were monitored in 41 renal transplant recipients at the time of transplantation (pre) and 3 months thereafter (post). In addition, serum phosphate nadir in each individual patient was identified and urinary fractional excretion of phosphate (FE(PO4)) at month 3 was calculated. High FGF-23(post) levels were independently associated with high FGF-23(pre), low calcitriol(post) and high calcium(post) levels. FGF-23, but none of the other mineral metabolism indices, was an independent predictor of the phosphate nadir in the early posttransplant period. A high FGF-23(post) level was independently associated with a high FE(PO4). High FGF-23(post) and creatinine levels and low PTH(post) levels were independently associated with low calcitriol(post) levels. In conclusion, our data indicate that persistence of FGF-23 contributes to hypophosphatemia and suboptimal calcitriol levels in renal transplant recipients.

PMID: 17359508 [PubMed - indexed for MEDLINE]

Proyecto Prometeo

Referencias Bibliográficas

Grupo III

Tratamiento Alteraciones Óseas

Con el patrocinio de:

Sociedad Española de Nefrología

UAM UNIVERSIDAD AUTONOMA DE MADRID
CÁTEDRA DE TRASPLANTE
UAM-ROCHE

Roche

1. Transplant Proc. 2010 Dec;42(10):4078-82.

Treatment of hyperparathyroidism with cinacalcet in kidney transplant recipients.

Borstnar S, Erzen B, Gmeiner Stopar T, Kocjan T, Arnol M, Kandus A, Kovac D.

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BACKGROUND: After successful kidney transplantation, hyperparathyroidism can persist in 10% 50% of patients and can harmfully affect bone metabolism. Calcimimetic cinacalcet is a new treatment option in the management of persistent hyperparathyroidism in these patients.
METHODS: This prospective, clinical study of 11 patients included those who had a serum intact parathyroid hormone (iPTH) concentration >65 ng/L, a serum creatinine concentration was <200 μmol/L, stable kidney graft function, and were >1 year since transplantation. Patients were not treated with drugs other than calcitriol that could influence bone metabolism. During the 6-month observation period, in which the stability of measured parameters was determined, and in the 12-month treatment period (cinacalcet 30 mg/d), we followed serum concentrations of calcium, phosphate, iPTH, creatinine, vitamin 25OH D(3), bone-specific alkaline phosphatase (ALP), osteocalcin, collagen degradation fragments (CTX), urinary calcium excretion, and bone mineral density (BMD).
RESULTS: During the treatment period, the serum calcium concentration decreasedsignificantly (from 2.50 ± 0.12 to 2.32 ± 0.12 mmol/L; P < .01). Serum iPTH concentration decreased significantly (from 247 [range, 199-362] at time 0 to 198 [range, 165-233] ng/L after 1 month of treatment; P < .05), but increased slightly thereafter. After 6 months of treatment, the serum concentration of ALP and CTX increased significantly, but decreased thereafter. There were no significant changes in the other parameters assessed. Renal function remained stable during the treatment period. The BMD of the lumbar spine, hip, and forearm did not change during the 12 months of treatment.
CONCLUSION: Cinacalcet was effective in treating posttransplant hyperparathyroidism, resulting in decreased calcemia and transient decreased iPTH. ALP and CTX transiently increased during therapy, but other markers of bone metabolism remained unchanged. Twelve months of cinacalcet treatment did not result in a change in BMD. Cinacalcet seems to be a safe drug with no negative effect on renal function.

PMID: 21168632 [PubMed - in process]

2. J Nephrol. 2010 Nov-Dec;23 Suppl 16:S175-81.

Calcium and phosphate changes after renal transplantation.

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Hypercalcemia and hypophosphatemia are frequently observed in recipients of a kidney transplant (KTx). Hypercalcemia has been reported in up to 66% of KTx patients. Many factors have been suggested as the putative causal factors; however, the persistence of moderate-severe secondary hyperparathyroidism, associated with a change in the set-point of the Ca-controlled parathyroid hormone (PTH) secretion, is considered to play a prominent role. Hypercalcemia can negatively impact on both the graft and patient outcome, increasing the incidence of nephrocalcinosis, which can induce a worse graft outcome, inducing vascular calcifications, and increasing the incidence of pancreatitis. In addition, severe hypercalcemia after KTx often requires parathyroidectomy, which is not universally considered a safe medical solution in this clinical setting. After KTx, phosphate levels often fall below the normal range, with hypophosphatemia being observed in up to 40% of patients. The putative causal factors for this metabolic alteration are persistent hyperparathyroidism, increased levels of FGF-23, tubular damage secondary to the immunological effects, and toxic and vascular effectors. Hypophosphatemia can negatively impact on either skeletal or muscular systems, contributing to the increased incidence of bone fractures in KTx patients. The current therapeutic options should take into account an accurate pretransplant treatment and screening of the waiting-list patient and should also evaluate the efficacy and safety profile of the new pharmacological tools (calcimimetics) in comparison with the classical surgical approach (parathyroidectomy).

PMID: 21170877 [PubMed - in process]

3. Transplant Proc. 2010 Oct;42(8):2917-20.

Vitamin D deficiency in a renal transplant population: safe repletion with moderate doses of calcidiol.

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BACKGROUND: Deficits of vitamin D are a common finding in the general population, especially among patients with chronic kidney disease. However, there are not much data about its prevalence after renal transplantation. Our aim was to analyze the calcidiol status among a cohort of kidney transplant recipients, in a region of Spain with a high number of annual sunshine hours, as well as the effects of supplementation with oral calcidiol.
PATIENTS AND METHODS: We included 110 kidney transplant recipients in a retrospective observational study. Measurements of 25-hydroxyvitamin D (25OHD), calcium, phosphate, intact parathyroid hormone (iPTH), serum creatinine and albumin, 24-hour microalbuminuria, and proteinuria were performed at the same time. Patients were classified based on their serum 25OHD levels: normal (>30 ng/mL); insufficiency (16-30 ng/mL); and deficiency (<16 ng/mL). In a second analysis, we included 63 patients with 25OHD<30 ng/mL with adjusted calcium levels below 10.2 mg/dL for treatment with oral calcidiol to approach target levels of 30 to 40 ng/mL. Mineral metabolism parameters were monitored at baseline as well as 6 and 12 months after beginning treatment.
RESULTS: Insufficient or deficient 25OHD levels were present in 106/110 patients (96.3%); they were normal in just four patients (3.6%). Patients with calcidiol deficiency were older. We observed no differences in sex, posttransplant follow up, serum calcium, phosphate, iPTH, glomerular filtration rate, or 24- hour albuminuria or proteinuria. The 63 patients treated with oral calcidiol received a mean dose of 8044±4087 IU/wk at baseline. The 61.3% of them with deficient 25OHD levels at baseline decreased to 2.1% at 6 months and 7.5% at 12 months after treatment. No significant changes in calcium, phosphate or iPTH were observed during the treatment.
CONCLUSIONS: Deficits of 25 OHD was frequent after renal transplantation but improved safely with moderate doses of oral calcidiol without negative secondary effects.

PMID: 20970570 [PubMed - in process]

4. Transplant Proc. 2010 May;42(4):1148-55.

Immunosuppressive agents and bone disease in renal transplant patients with hypercalcemia.

Sessa A, Esposito A, Iavicoli GD, Lettieri E, Dente G, Costa C, Bergallo M, Rossano R, Capuano M.

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Renal transplantation is the definitive treatment for many metabolic abnormalities of uremic patients, although it is only partially effective for renal osteodystrophy, which may interact with posttransplant renal osteopathy. Osteopenic-osteoporotic syndrome represents, together with fractures secondary to osteoporosis and osteonecrosis, the bone complication most related to renal transplantation. Several factors contribute to the pathogenesis of posttransplantation osteoporosis, particularly immunosuppressive treatment. In this study, we evaluated the prevalence of factors related to posttransplant renal osteopathy and the clinical impact of immunosuppressive protocols. We studied 24 renal transplant recipients with hypercalcemia. Glomerular filtration rate was >50 mL/min. Mean age, time on dialysis, and time from transplantation were 49.6, 5.4, and 6.9 years, respectively. We evaluated serum and urine calcium and phosphorus, calcitonin, parathormone, bone-specific alkaline phosphatase, osteocalcin, urine deoxypyridinoline, telopeptide of type 1 procollagen, 1,25-(OH)(2) and 25-OH vitamin D, parathyroid ultrasound, and computerized bone mineralometry. The combination of sirolimus and steroids resulted in the most disadvantageous outcomes regarding alkaline phosphatase and mineralometry. Calcineurin inhibitors did not significantly influence bone metabolism markers; mycophenolate mofetil evidenced no effect on bone. According to the literature, steroids account for the abnormalities found in our patients and in severe osteopenia. Several factors may contribute to the development of osteoporosis and fractures in transplantation patients, although they are overcome by the prominent effect of steroids. In patients at high risk of osteoporosis, steroid-free therapy should be considered. Everolimus is indicated for diseases with bone loss. Combined therapy with everolimus and mycophenolic acid without cyclosporine and steroids, seemed to be particularly indicated. Prophylactic treatments should be commenced early. No single marker was useful to diagnose posttransplant renal osteopathy. The definitive diagnosis should be made by bone biopsy during transplantation, and noninvasive procedures, such as densitometry and evaluation of biologic markers, may be useful during follow-up.

PMID: 20534247 [PubMed - indexed for MEDLINE]

5. Transplant Rev (Orlando). 2010 Apr;24(2):79-88.

Treatment with calcimimetics in kidney transplantation.

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Graft and patient survival in renal transplantation has increased with better immune suppression treatment, leading to the appearance of new complications such as posttransplant bone disease. After renal transplantation and the recovery of renal function, mineral metabolism disorders secondary to renal failure could be expected to normalize. However, both immediately after transplantation and later, and even with good renal graft function, we see bone disorders associated to renal osteodystrophy, a high incidence of osteopenia, persistent hyperparathyroidism, hypercalcemia, hypophosphoremia, and less commonly, aseptic bone necrosis. The causes potentially responsible for these disorders have basically been identified as different degrees of renal insufficiency in the graft, persistent posttransplant secondary hyperparathyroidism, and negative impact of immunosuppression treatment, particularly corticosteroids. The most important factor in the evolution of metabolic and bone disorders after renal transplantation, however, is pretransplant bone status. Special attention should be paid to other osteoarticular complications such as loss of bone mass and fractures, leading to significant morbidity. In the therapeutic approach to these patients, as well as encouraging physical exercise and advice about diet or other habits, the use of drugs such as calcium and vitamin D supplements, bisphosphonates, and more recently, calcimimetics have made significant improvements in the prevention and treatment of bone-mineral metabolism. It has been shown that calcimimetic agents can control the parathyroid hormone, reduce episodes of hypercalcemia, and improve hypophosphatemia. Their properties have to be assessed in broader studies to establish the basis for their widespread use among renal transplant recipients.

PMID: 20303456 [PubMed - indexed for MEDLINE]

8. Transplant Proc. 2009 Jul-Aug;41(6):2144-7.

Calcimimetics and bone mineral density in renal transplant patients with persistent secondary hyperparathyroidism.

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BACKGROUND: The persistence of secondary hyperparathyroidism plays an important role in posttransplant bone loss. Calcimimetics are efficient to control metabolic alterations associated with this problem, but there are few publications that assess their effects on bone density.
PATIENTS AND METHODS: This prospective study assessed the effects of a single daily dose of cinacalcet on calcemia, phosphatemia, parathyroid hormone (PTH), and bone densitometry (femur and spine) values of 27 renal transplant patients with stable kidney function, calcium > 10.5 mg/dL, and PTH > 65 pg/mL.
RESULTS: A preliminary study after 6 months showed decreased calcemia (11.05 +/- 0.5 to 10.18 +/- 0.6 mg/dL; P < .0001), reduced levels of intact PTH (iPTH; 258 +/- 104 to 209.61 +/- 127 pg/mL; P < .05), and increased phosphatemia (2.38 +/- 0.45 to 2.54 +/- 0.3 mg/dL; P < .05). We also observed an increase in femoral neck bone mass with improved T score (-1.36 +/- 1.19 to -1.05 +/- 0.84 g/cm(2); P < .05).
CONCLUSIONS: Cinacalcet was effective in the management of posttransplant persistent secondary hyperparathyroidism, resulting in decreased calcemia and iPTH, while also improving femoral neck bone loss. Longer-term studies with control groups are needed to determine the drug's influence on overall bone mineral density.

PMID: 19715857 [PubMed - indexed for MEDLINE]

9. J Clin Endocrinol Metab. 2009 May;94(5):1483-90.

Approach to the patient with transplantation-related bone loss.

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Transplantation is an established therapy for end-stage diseases of the kidney, endocrine pancreas, heart, liver, lung, intestines and for many hematological disorders. Current immunosuppressive regimens with glucocorticoids and calcineurin inhibitors produce excellent patient and graft survival rates. This has resulted in both increases in transplant numbers and an increased recognition of previously neglected long-term complications of transplantation such as fractures and osteoporosis. Both pretransplantation bone disease and immunosuppressive therapy result in rapid bone loss and increased fracture rates. Patients are particularly at risk early after transplantation. The bone health of candidates for organ transplantation should be assessed with bone densitometry of the hip and spine. Spinal x-rays should be performed to diagnose prevalent fractures. Any secondary causes of osteoporosis should be identified and treated. Vitamin D deficiency should be corrected with vitamin D doses selected to achieve a serum 25-hydroxyvitamin D concentration of at least 20 ng/ml. All patients should receive calcium. Patients with kidney failure should be evaluated and treated for chronic kidney disease-mineral and bone disorder, including renal osteodystrophy. Secondary hyperparathyroidism, in particular, should be treated. Treatment is indicated in the immediate posttransplantation period irrespective of bone mineral density because further rapid bone loss will occur in the first several months after transplantation. Long-term organ transplant recipients should also have bone mass measurement and treatment of osteoporosis. Oral and iv bisphosphonates are the most promising approach for the management of transplantation osteoporosis. Active vitamin D metabolites may have additional benefits in reducing hyperparathyroidism, particularly after kidney transplantation.

PMID: 19420272 [PubMed - indexed for MEDLINE]

11. Transplantation. 2008 Oct 15;86(7):919-24.

Cinacalcet increases calcium excretion in hypercalcemic hyperparathyroidism after kidney transplantation.

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BACKGROUND: Cinacalcet reduces serum calcium in kidney transplant recipients with hypercalcemic hyperparathyroidism. The mechanism of action is not fully understood. We hypothesized that cinacalcet increases renal elimination of calcium, thereby improving hypercalcemia in kidney transplant recipients.
METHODS: We prospectively examined the effect of cinacalcet (30 mg/d) during the first 6 weeks of treatment on serum and 24 hrs urinary calcium concentration and calculated fractional calcium excretion in 32 patients with sustained hypercalcemic hyperparathyroidism (Ca >2.6 mmol/L [10.4 mg/dL], intact parathyroid hormone >60 pg/mL). Secondary endpoints were serum phosphate and tubular maximum of phosphate corrected for glomerular filtration rate, intact parathyroid hormone and serum creatinine.
RESULTS: Serum calcium concentrations decreased in all patients (from 2.77 to 2.51 mmol/L; P<0.0001), fractional calcium excretion increased rapidly in the first 2 weeks of treatment from 1.06 to 1.78% (P<0.0001), and decreased thereafter to 1.37% (P<0.05 vs. early treatment). Simultaneously serum phosphate and tubular maximum of phosphate corrected for glomerular filtration rate increased significantly from 0.79 to 0.85 to 0.88 mmol/L (P<0.05), and from 0.52 to 0.61 (P<0.005) and 0.62 (P<0.0001 vs. baseline), respectively. Intact parathyroid hormone did not decrease significantly. Serum creatinine remained stable.
CONCLUSION: We provide evidence that the calcium lowering effect of cinacalcet in patients with persistent hyperparathyroidism after kidney transplantation is caused, at least in part, by increased urinary calcium excretion.

PMID: 18852656 [PubMed - indexed for MEDLINE]

12. Am J Transplant. 2008 Sep;8(9):1864-70.

Effect of teriparatide on early bone loss after kidney transplantation.

Cejka D, Benesch T, Krestan C, Roschger P, Klaushofer K, Pietschmann P, Haas M.

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Kidney transplantation is associated with bone loss and a high risk of fractures. Prophylactic treatment of bone is therefore recommended in the early posttransplant period. As a large number of transplant recipients develop adynamic renal osteodystrophy, recombinant parathyroid hormone (rPTH) could be a promising therapeutic option. In a 6-month double-blind, randomized trial, 26 kidney transplant recipients were treated with daily subcutaneous injections of 20 microg teriparatide (PTH 1-34) or placebo. Bone mineral density (BMD) of the femoral neck, lumbar spine and radial bone was measured at transplantation and after 6 months. Paired bone biopsies for histomorphometric analysis were obtained in six, and for measurement of bone matrix mineralization in five patients of each group. Serologic bone markers were measured at baseline and every 3 months. A total of 24 out of 26 patients completed the study. Femoral neck BMD was stable in the teriparatide group, but decreased significantly in the placebo group. Lumbar spine and radial BMD, histomorphometric bone volume and bone matrix mineralization status remained unchanged in both groups. Serologic bone markers were similarly reduced in both groups throughout the study. We conclude that teriparatide does not improve BMD early after kidney transplantation. Neither histological analysis nor bone markers provide evidence of improved bone turnover or mineralization.

PMID: 18786230 [PubMed - indexed for MEDLINE]

13. Transplantation. 2008 Aug 15;86(3):413-7.

Effect of cinacalcet on hypercalcemia and bone mineral density in renal transplanted patients with secondary hyperparathyroidism.

Bergua C, Torregrosa JV, Fuster D, Gutierrez-Dalmau A, Oppenheimer F, Campistol JM.

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BACKGROUND: Persistent secondary hyperparathyroidism (SHP) is the most frequent cause of hypercalcemia observed in approximately 10% of renal transplanted (RT) patients 1 year after surgery. Persistent SHP with hypercalcemia is an important factor of bone loss after renal transplantation. This study prospectively evaluates the effects of cinacalcet therapy on serum calcium (SCa) and parathyroid hormone (PTH) blood levels, and basically on bone mineral density (BMD) in RT patients with persistent hyperparathyroidism.
METHODS: Nine RT patients (eight women, one man) with allograft function more than 6 months were included based on total SCa more than 10.5 mg/dL and intact parathyroid hormone (iPTH) concentration more than 65 pg/mL. After inclusion, patients started on a single daily oral dose of 30 mg of cinacalcet. At inclusion and every study visit blood levels of creatinine, Ca, P, alkaline phosphatase, iPTH 1,25- dihydroxyvitamin D3, and 25-hydroxyvitamin D3 were assessed. Baseline and at the end of study radial BMD were measured. Study follow-up was 12 months.
RESULTS: During the study period, SCa decreased from 11.72+/-0.39 to 10.03+/-0.54 mg/dL (P<0.001). iPTH decreased from 308.85+/-120.12 to 214.66+/-53.75 mg/dL (P<0.05). The mean serum creatinine decreased from 1.58+/-0.34 to 1.25+/-0.27 mg/dL (P=0.03) and the mean radial BMD increased from 0.881+/-0.155 to 0.965+/-0.123 gr/cm2 (P<0.05). There were no significant changes in the other parameters assessed. One patient was excluded for gastrointestinal intolerance.
CONCLUSIONS: In RT patients with hypercalcemia secondary to persistent SHP, cinacalcet corrects hypercalcemia and PTH, simultaneously improving BMD.

PMID: 18698244 [PubMed - indexed for MEDLINE]

14. Transpl Int. 2008 Jul;21(7):615-24. Epub 2008 Mar 13.

Bone disease after kidney transplantation.

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Post-transplant renal osteopathy (ROP) remains a serious problem, which contributes to substantial long-term morbidity of the graft recipients. Bone loss is most pronounced during the first months after engraftment; concerning bone density development in long-term transplant recipients, controversial data exist. The clinical impact of ROP is a marked increase in fracture rate following kidney transplantation compared with both general population and patients on dialysis treatment. The following review will focus on post-transplant ROP and discuss its epidemiology, the clinical features, factors contributing to the pathogenesis of this complication, as well as the evaluation, prevention and treatment options available for kidney allograft recipients.

PMID: 18346011 [PubMed - indexed for MEDLINE]

15. Expert Opin Pharmacother. 2008 Apr;9(5):795-811.

New strategies for the treatment of hyperparathyroidism incorporating calcimimetics.

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BACKGROUND: Hyperparathyroidism (HPT), characterised by increased parathyroid hormone (PTH) secretion and parathyroid hyperplasia, can be caused by physiologic defects in the parathyroid gland (primary HPT [PHPT]) or as a consequence of declining renal function (secondary HPT [SHPT]).
OBJECTIVE: To review the safety and efficacy of cinacalcet in the treatment of SHPT and PHPT.
METHODS: Studies indexed in NLM/PubMed investigating the safety, efficacy, and pharmacokinetics of cinacalcet for PHPT and SHPT and supporting preclinical evidence.
RESULTS/CONCLUSION: Recent evidence has demonstrated the efficacy of the calcimimetic cinacalcet in the treatment of PHPT and SHPT. Compared with traditional therapies such as vitamin D sterols and phosphate binders, cinacalcet treatment can allow an increased proportion of patients with SHPT to improve Kidney Disease Outcomes Quality Initiative (KDOQI) Bone Metabolism and Disease laboratory parameter target attainment. Recent evidence suggests that improvements in these biochemical parameters with cinacalcet can translate into improved morbidity and mortality. Cinacalcet lowers PTH and calcium in patients following renal transplantation, and also normalises serum calcium in patients with PHPT. Ongoing studies are focusing and future studies are likely to focus on the effect of cinacalcet on clinical outcomes and on novel strategies for the integration of cinacalcet with traditional therapies to improve serum PTH and mineral metabolism control.

PMID: 18345956 [PubMed - indexed for MEDLINE]

18. Ren Fail. 2008;30(10):992-9.

The effect of low-dose cholecalciferol and calcium treatment on posttransplant bone loss in renal transplant patients: a prospective study.

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BACKGROUND/AIM: Posttransplant steroid doses have been reduced with the use of new and potent immunosuppressive agents. However, posttransplant osteoporosis is still a serious problem. Our aim in this study was to investigate the effect of low-dose cholecalciferol and calcium supplementation on bone loss after transplantation in renal transplant patients.
METHODS: Fifty-eight renal transplantation patients were included in the study. Fourteen newly transplanted patients (group 1) and 44 renal transplantation patients with a graft age of at least six months (group 2) were involved. All patients received 400 IU/day orally cholecalciferol (vitamin D3) and 600 mg/day orally calcium replacement starting from the second day posttransplantation. All patients baseline serum and urine biochemistry, serum 25-hydroxy vitamin D3 (25(OH)D3), and bone mineral density (BMD) tests were performed. Also, the same measurements were performed at the 12th month in group 1.
RESULTS: After one year of treatment, BMDs were improved in group 1. Patients in group 1 had a nonsignificant increase of lumbar spine (8.12 +/- 18.64% of baseline BMD) and femoral total (7.10 +/- 13.48% of baseline BMD) BMD at the end of the first year. On the other hand, there was a significant increase in femoral neck (10.06 +/- 15.70% of baseline BMD, $p < 0.05$) measurements. The baseline results of group 2 were similar to group 1. In group 1, 25 (OH)D3 levels were increased while PTH levels were decreased at the end of the year.
CONCLUSION: In renal transplant patients who use low-dose metilprednisolon and new immunosuppressive agents together, low doses of vitamin D3 and calcium replacement for one year provides a reduction in lumbar spine, femoral neck, and femoral total bone loss and prevents bone loss in group 2. In addition, it contributed to the normalization of PTH levels.

PMID: 19016151 [PubMed - indexed for MEDLINE]

20. Transpl Int. 2007 Aug;20(8):708-11. Epub 2007 Jun 6.

Weekly risedronate in kidney transplant patients with osteopenia.

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Daily bisphosphonate is effective in preventing and treating corticosteroid-induced osteoporosis in renal transplant recipients, although it frequently has gastrointestinal side effects. The aim was to assess efficacy and side effect profile of weekly oral risedronate. Eighty-four renal transplant patients, receiving either cyclosporin A or tacrolimus and steroids were prospectively included. The study group (39 patients) received 35 mg risedronate weekly, vitamin D and calcium, while control group (45 patients) only vitamin D and calcium. At baseline, 6 and 12 months, creatinine, calcium, phosphorus, alkaline phosphatase and iPTH were determined. Fractures and bone mineral densities were assessed by X-rays and dual-energy X-ray absorptiometry, respectively. Pain was assessed by clinical interview. Mineral bone density score increased significantly in risedronate group after 1 year. There were no differences in the incidence of fractures, although, anamnestic pain assessment revealed that 3% of treatment group reported to have bone pain compared with 18% in nontreatment group ($P < 0.05$). Follow-up calcium, phosphorus, alkaline phosphatases, and iPTH levels showed no differences from basal measures. Risedronate was well tolerated with no major side effects. Weekly oral risedronate in renal transplanted patients reduces bone mineral loss and bone pain and has an excellent side effect profile.

PMID: 17555530 [PubMed - indexed for MEDLINE]

22. Nephrol Dial Transplant. 2006 Aug;21(8):2275-81. Epub 2006 Mar 30.

Effects of bisphosphonates on bone loss in the first year after renal transplantation--a meta-analysis of randomized controlled trials.

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Comment in:
Nat Clin Pract Nephrol. 2006 Dec;2(12):676-7.

BACKGROUND: Bone loss remains a serious problem after kidney transplantation and is most pronounced during the first months after engraftment. Bisphosphonates are frequently used to treat post-transplant osteodystrophy, but data of large randomized controlled trials (RCTs) are missing.
METHODS: We, therefore, conducted this systematic review of the literature, searching electronic databases, reference lists and abstracts from scientific meetings to identify RCTs in all languages. The primary outcome assessed was the change in bone mineral density (BMD) during the early post-transplantation period. Based on the mean BMD change presented in the identified publications, the authors were asked for the individual BMD results of all randomized patients, determined at lumbar spine and femoral neck before and after bisphosphonate therapy. Data were pooled for summary estimates by using weighted mean differences of absolute change in BMD. An analysis of covariance was performed, adjusted for individual baseline values, treatment arm and individual trial.
RESULTS: Five studies involving 180 participants were included in our meta-analysis. Treatment with bisphosphonates showed a substantial effect in preventing post-transplant osteodystrophy. BMD decline at the lumbar spine within 6-12 months after transplantation was significantly reduced by 0.06 g/cm(2) in patients treated with bisphosphonates (95% CI 0.05-0.08 g/cm(2)). At the femoral neck, the loss of BMD was reduced by 0.05 g/cm(2) during this period (95% CI 0.0-0.11 g/cm(2)), reaching just non-statistical significance. This benefit of bone loss prevention could be reached without major side effects.
CONCLUSION: Bisphosphonates are effective in preventing bone loss in the early post-transplant period.

PMID: 16574684 [PubMed - indexed for MEDLINE]

25. Treat Endocrinol. 2006;5(5):297-318.

Metabolic bone disease in children : etiology and treatment options.

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Metabolic bone disease in children includes many hereditary and acquired conditions of diverse etiology that lead to disturbed metabolism of the bone tissue. Some of these processes primarily affect bone; others are secondary to nutritional deficiencies, a variety of chronic disorders, and/or treatment with some drugs. Some of these disorders are rare, but some present public health concerns (for instance, rickets) that have been well known for many years but still persist. The most important clinical consequences of bone metabolic diseases in the pediatric population include reduced linear growth, bone deformations, and non-traumatic fractures leading to bone pain, deterioration of motor development and disability. In this article, we analyze primary and secondary osteoporosis, rickets, osteomalacia (nutritional and hereditary vitamin D-dependent, hypophosphatemic and that due to renal tubular abnormalities), renal osteodystrophy, sclerosing bony disorders, and some genetic bone diseases (hypophosphatasia, fibrous dysplasia, skeletal dysplasia, juvenile Paget disease, familial expansile osteolysis, and osteoporosis pseudoglioma syndrome). Early identification and treatment of potential risk factors is essential for skeletal health in adulthood. In most conditions it is necessary to ensure an appropriate diet, with calcium and vitamin D, and an adequate amount of physical activity as a means of prevention. In secondary bone diseases, treatment of the primary disorder is crucial. Most genetic disorders await prospective gene therapies, while bone marrow transplantation has been attempted in other disorders. At present, affected patients are treated symptomatically, frequently by interdisciplinary teams. The role of exercise and pharmacologic therapy with calcium, vitamin D, phosphate, bisphosphonates, calcitonin, sex hormones, growth hormone, and thiazides is discussed. The perspectives on future therapy with insulin-like growth factor-1, new analogs of vitamin D, strontium, osteoprotegerin, and calcimimetics are presented.

PMID: 17002489 [PubMed - in process]

28. Kidney Int. 2005 May;67(5):2039-45.

A prospective randomized study for prevention of postrenal transplantation bone loss.

El-Agroudy AE, El-Husseini AA, El-Sayed M, Mohsen T, Ghoneim MA.

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Comment in:
Kidney Int. 2005 Nov;68(5):2403.

BACKGROUND: We aimed to investigate different treatment drugs for the prevention of post-transplant bone loss.
METHODS: Sixty adult male recent renal transplant recipients were enrolled into the study. Patients were randomized into 4 groups: group I received daily alfacalcidol 0.5 microg PO; group II received oral alendronate 5 mg/day; group III received intranasal salmon calcitonin 200 IU every other day; and group IV was considered a control group. Every patient was supplemented with daily 500 mg oral calcium carbonate. Parameters of bone metabolism were measured before and at 12 months after starting treatment. Bone mineral density (BMD) was measured by (DEXA) at lumber spine, femoral neck, and forearm before and after treatment period.
RESULTS: BMD was increased at lumber spine by 2.1%, 0.8%, 1.7%, by 1.8%, 0.6%, 1.6% at femoral neck, and by 3.2%, 1.9%, 2.6% at forearm in groups I, II, and III, respectively, while it decreased by 3.2%, 3.8%, and 1.8% at the same sites, respectively, in control group (P= <0.05). iPTH level decreased significantly in group I, while the decrease was insignificant in other groups (P= 0.003). All other parameters were not statistically significant between treatment groups. Apart from transient hypocalcaemia in 3 patients in group II, and 2 patients in group III, no other significant adverse effects were noted.
CONCLUSION: This study proves that early bone loss that occurs during the first 12 months after renal transplantation could be prevented by alfacalcidol, calcitonin, or alendronate. Among the treatment groups, alfacalcidol significantly improved the hyperparathyroidism. All treatment drugs are safe and tolerable.

PMID: 15840055 [PubMed - indexed for MEDLINE]

29. Am J Kidney Dis. 2005 Apr;45(4):638-49.

Interventions for preventing bone disease in kidney transplant recipients: a systematic review of randomized controlled trials.

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BACKGROUND: Before renal transplantation complex abnormalities of bone metabolism exist and lead to increased risk for fracture after transplantation. This study was conducted to assess the evidence available to guide targeted treatment to reduce bone disease in transplant recipients.
METHODS: The Cochrane CENTRAL Registry, MEDLINE, and EMBASE were searched for randomized trials of interventions for bone disease after renal transplantation. Data were extracted on fracture, bone mineral density (BMD) by means of dual-energy X-ray absorptiometry, acute graft rejection, and adverse events. Analysis was performed with a random-effects model, and all results are expressed as relative risk with 95% confidence intervals (CIs).
RESULTS: Twenty-three eligible trials (1,209 patients) were identified. No trial found a reduction in risk for fracture. Bisphosphonates (7 trials; 268 patients; weighted mean difference [WMD], 7.66; 95% CI, 4.82 to 10.50), vitamin D analogues (2 trials; 51 patients; WMD, 6.13; 95% CI, 4.97 to 7.29), and calcitonin (1 trial; 31 patients; WMD, 5.00; 95% CI, 0.88 to 9.12) favorably affected the percentage of change in BMD at the lumbar spine compared with no treatment. Bisphosphonates (4 trials; 149 patients; WMD, 7.18; 95% CI, 6.22 to 8.13) and vitamin D analogues (2 trials; 51 patients; WMD, 3.73; 95% CI, 2.71 to 4.75), but not calcitonin (1 trial; 31 patients; WMD, -0.30; 95% CI, -5.00 to 4.40), had a favorable effect on BMD measured at the femoral neck compared with no treatment. The incidence of reported toxicity was low.
CONCLUSION: The trials were inadequately powered to show a reduction in risk for fracture. Bisphosphonates and vitamin D have a beneficial effect on BMD at the lumbar spine and femoral neck. With increasing survival after renal transplantation, this study stresses the importance of randomized controlled trial evidence of interventions of bone disease after renal transplantation.

PMID: 15806466 [PubMed - indexed for MEDLINE]

30. Transplantation. 2005 Jan 15;79(1):108-15.

A controlled study of vitamin D3 to prevent bone loss in renal-transplant patients receiving low doses of steroids.

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BACKGROUND: New and potent immunosuppressive regimens allow for reduced doses of corticosteroids after renal transplantation. The aims of our study were to investigate whether the use of low-dose corticosteroids is associated with a reduction in posttransplant bone loss and to assess the ability of cholecalciferol supplementation to further decrease bone loss in this setting.
METHODS: Ninety patients admitted for renal transplantation and scheduled to be treated per protocol with low doses of prednisolone were randomized to receive either 400 mg daily oral calcium (Ca group, n=44) or the same dose of calcium in association with a monthly dose of 25,000 IU of vitamin D3 (CaVitD group, n=46). Bone mineral density (BMD) was measured by dual energy absorptiometry at baseline and at 1 year.
RESULTS: The overall population experienced a moderate but significant -2.3+/-0.9% loss of lumbar spine BMD ($P<0.01$) but no bone loss at the femoral neck and shaft during the first posttransplant year. Bone loss tended to be slightly higher in the CaVitD group, but the difference did not reach statistical significance. Patients in the CaVitD group had significantly higher 25(OH) but not 1,25(OH)2 vitamin D levels. We observed a highly significant negative correlation between 25(OH) vitamin D and intact parathyroid hormone (iPTH) serum levels.
CONCLUSIONS: Kidney-transplant recipients receiving modern immunosuppressive regimens with low doses of corticosteroids experience only minimal loss of BMD during the first posttransplant year. Cholecalciferol supplementation did not prevent posttransplant bone loss but contributed to the normalization of iPTH levels after renal transplantation.

PMID: 15714177 [PubMed - indexed for MEDLINE]

33. Pediatr Transplant. 2004 Aug;8(4):357-61.

Treatment of osteopenia and osteoporosis in renal transplant children and adolescents.

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Successful renal transplantation corrects many of the metabolic abnormalities associated with the development of renal osteodystrophy, but despite a well-functioning graft osteopenia, growth failure, spontaneous fractures, and avascular necrosis remain prevalent in adult and pediatric kidney recipients. A paucity of information exists regarding the effects of different therapies to prevent and treat bone loss in the renal transplant recipients. We constructed a design to study the effect of different modalities of treatment on bone mass in our renal transplant children. Among 93 patients who underwent renal transplantation at the age of 17 yr or less and were subjected to dual-energy X-ray absorptiometry (DEXA), we blindly randomized 60 patients who had osteopenia or osteoporosis (T-score = -1 by DEXA) in a prospective study. Their mean age at time of transplantation was 13.4 +/- 4.3 yr. The mean duration after transplantation was 48 +/- 34 months. The patients were classified randomly into four groups. Each group consisted of 15 patients: group 1 was the control group, group 2 received oral alfacalcidol 0.25 microg daily, group 3 received oral alendronate 5 mg daily, and group 4 received 200 IU/day nasal spray calcitonin. Parameters of bone turnover, calcium metabolism, and DEXA were measured before and after 12 months of treatment duration. The characteristics of all groups were comparable at the beginning of the study. At the lumber spine, bone mass density decreased from -2.4 to -2.8 in group 1, increased from -2.3 to -0.5 in group 2, from -2.3 to -1.9 in group 3, and from -2.3 to -1.0 in group 4. The four groups had similar patient profiles, serum creatinine, intact parathyroid hormone, osteocalcin, and deoxypyridinoline. This study confirmed the value of alfacalcidol and antiresorptive agents in the treatment of osteopenia and osteoporosis in young renal transplant recipients.These therapies were safe, tolerable, simple to administer and potentially applicable to other renal transplant patients.

PMID: 15265162 [PubMed - indexed for MEDLINE]

34. Kidney Int. 2004 Feb;65(2):705-12.

Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation.

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BACKGROUND: Bone loss occurs during the first 6 months after renal transplantation (RT), and corticosteroid therapy plays an important role. Although calcium plus vitamin D administration prevents corticosteroid-induced osteoporosis, its use in RT recipients is limited by the risk of hypercalcemia.
METHODS: This double-blind, randomized, and controlled prospective intervention trial examined the effect of intermittent calcitriol (0.5 microg/48 h) during the first 3 months after RT, plus oral calcium supplementation (0.5 g/day) during 1 year with calcium supplementation alone. The primary outcome measure was the change in bone mineral density (BMD) at 3 and 12 months after RT; we also explored whether the effect of calcitriol on BMD was different among vitamin D receptor (VDR) genotypes (BsmI). Forty-five recipients were randomized to calcitriol therapy (CT) and 41 were randomized to placebo (PL).
RESULTS: Both groups had a similar degree of pre-existing hyperparathyroidism (197 +/- 229 vs. 191 +/- 183 pg/mL), but a more pronounced decrease of parathyroid hormone (PTH) levels after RT was observed in CT patients (at 3 months: 61.4 +/- 42.2 vs. 85.7 +/- 53.1 pg/mL, P= 0.02; at 12 months: 67.3 +/- 33.7 vs. 82.6 +/- 37 pg/mL; P= 0.08). CT patients preserved their BMD at the total hip significantly better than those on PL (3 months: 0.04 +/- 3.3 vs. -1.93 +/- 3.2%, P= 0.01; 12 months: 0.32 +/- 4.8 vs. -2.17 +/- 4.4%, P= 0.03); significant differences were noted at the intertrochanter, trochanter, and Ward's triangle. Differences did not reach significance at the femoral neck. Two CT patients (4.4%) and 4 PL patients (9.8%) developed a hypercalcemic episode during the first 3 months after RT. The effect of CT on BMD at 3 months was more prominent in recipients with the at-risk allele of the VDR gene (P= 0.03).
CONCLUSION: Therapy with low-dose calcium supplements during 1 year, plus intermittent calcitriol for 3 months after RT, is safe, decreases PTH levels more rapidly, and prevents bone loss at the proximal femur; a more pronounced effect is seen in recipients with at least one at-risk allele of the VDR genotype.

PMID: 14717945 [PubMed - indexed for MEDLINE]

36. J Am Soc Nephrol. 2003 Nov;14(11):2975-9.

Preventing bone loss in renal transplant recipients with vitamin D.

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Very rapid bone loss, osteopenia, and osteoporosis have been documented in the first 6 to 12 mo after renal transplantation. Investigated was the effect of treatment with active vitamin D on the prevention of posttransplantation bone loss. Forty adult men who were recent renal transplant recipients were enrolled onto the study. Patients were randomized into two groups: group 1 received daily alfacalcidol 0.5 micro g by mouth, and group 2 (control) received placebo. Every patient in both groups received daily 500-mg calcium carbonate supplements. Parameters of bone metabolism and bone mineral density measured at three sites were assessed before and after the study period. Bone mineral density was increased by 2.1%, 1.8%, and 3.2% at lumbar spine, femoral neck, and forearm, respectively, in group 1, whereas it decreased by 3.2%, 3.8%, and 1.8% at the same sites in the control group ($P < 0.05$). Serum intact parathyroid hormone level decreased significantly in group 1 compared with the control group ($P = 0.003$). Early bone loss that occurs during the first 1 yr after renal transplantation could be prevented by alfacalcidol. Use of alfacalcidol early after transplantation is safe and well tolerated.

PMID: 14569109 [PubMed - indexed for MEDLINE]

37. J Am Soc Nephrol. 2003 Oct;14(10):2669-76.

Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate.

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Renal transplant recipients are at risk of developing bone abnormalities that result in bone loss and bone fractures. These are related to underlying renal osteodystrophy, hypophosphatemia, and immunosuppressive treatment regimen. Although bisphosphonates are useful in ameliorating bone mineral loss after transplantation, it is not known whether their use in renal transplant patients leads to excessive suppression of bone turnover and increased incidence of adynamic bone disease. A randomized, prospective, controlled, clinical trial was conducted using the bisphosphonate pamidronate intravenously in patients with new renal transplants. Treatment subjects (PAM) received pamidronate with vitamin D and calcium at baseline and at months 1, 2, 3, and 6. Control (CON) subjects received vitamin D and calcium only. During months 6 to 12, the subjects were observed without pamidronate treatment. Biochemical parameters of bone turnover were obtained monthly and, bone mineral density (BMD) was obtained at baseline and months 6 and 12. Bone biopsies for mineralized bone histology were obtained at baseline and at 6 mo in a subgroup of subjects who underwent scheduled living donor transplantation. PAM preserved bone mass at 6 and 12 mo as measured by bone densitometry and histomorphometry. CON had decreased vertebral BMD at 6 and 12 mo (4.8 +/- 0.08 and 6.1 +/- 0.09%, respectively). Biochemical parameters of bone turnover were similar in both groups at 6 and 12 mo. Bone histology revealed low turnover bone disease in 50% of the patients at baseline. At 6 mo, all of PAM had adynamic bone disease, whereas 50% of CON continued to have or developed decreased bone turnover. Pamidronate preserved vertebral BMD during treatment and 6 mo after cessation of treatment. Pamidronate treatment was associated with development of adynamic bone histology. Whether an improved BMD with adynamic bone histology is useful in maintaining long-term bone health in renal transplant recipients requires further study.

PMID: 14514747 [PubMed - indexed for MEDLINE]

38. Osteoporos Int. 2003 Jun;14(5):412-7. Epub 2003 Apr 16.

Comparison of calcium and alfacalcidol supplement in the prevention of osteopenia after kidney transplantation.

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The aim of this observational study was to compare the effect of calcium and alfacalcidol supplementation on the regression of hyperparathyroidism and on prevention of osteopenia in patients up to 3 years after renal transplantation. Two historical cohorts were compared for that purpose. One hundred and fifty-nine patients received calcium carbonate supplement (group 1), while 81 patients were treated with alfacalcidol (group 2). Serum Ca, phosphate (P), Mg, creatinine, alkaline phosphatase (AP) and parathyroid hormone (PTH) levels were determined before and after transplantation in the two groups, for 3 years. Femoral neck and lumbar spine bone mineral density (BMD) was measured only at 3 and 6 months and 1, 2 and 3 years after transplantation. At baseline there was no difference in age or sex ratio, but prevalence in post-menopausal women was higher in group 1 (6.9% versus 1.2%). Duration on dialysis was comparable but prevalence of interstitial and undetermined nephropathies was higher in group 1. Baseline serum concentrations of PTH, Ca and P were comparable in both groups. After transplantation, plasma creatinine decreased to comparable levels in both groups. Immunosuppression by triple therapy was more prevalent in group 2, so that cumulative dose of steroid was higher in group 1, especially at 1 month because of higher incidence of acute rejections (51% versus 13%). Mean intact PTH levels decreased in both groups, from 18 pmol/l to 8.4 and 7.9 at 3 years, but the decrease was significantly greater with alfacalcidol at 6 and 12 months. At 3 months, BMD were comparable at both sites. From 3 months to 3 years after kidney transplantation, mean lumbar spine BMD significantly increased from 0.963 to 1.054 g/cm(2) in group 1, whereas there was no significant decrease (1.048 to 1.006 g/cm(2)) in group 2, the difference in changes being significant ($P<0.05$). Femoral neck BMD was not significantly increased in either group (0.932 to 0.993 g/cm(2) in group 1, and 0.850 to 0.907 g/cm(2) in group 2). Expressed as percentages, these changes were +9.4% and -4% for lumbar BMD and +6.5% and +6.7% for femoral neck, for groups 1 and 2, respectively. Prevalence of osteopenia was not significantly lower at 3 years in group 1 (45% and 51%) than in group 2. During the follow-up period, osteonecrosis was diagnosed in six patients (3.8%) in group 1 and in nine (11%) in group 2. In conclusion, alfacalcidol compared to CaCO3 supplement suppressed hyperparathyroidism more rapidly and strongly. In spite of higher osteopenia risk in the CaCO3 group, lumbar BMD increase was greater and incidence of osteonecrosis higher in this group, suggesting better bone protection with CaCO3 than with alfacalcidol.

PMID: 12730763 [PubMed - indexed for MEDLINE]

40. Kidney Int. 2003 Mar;63(3):1130-6.

Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation.

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BACKGROUND: Bisphosphonates can prevent bone mineral density loss after renal transplantation, but their effect on trabecular mineralization and bone morphology, two key factors of bone stability, remains unknown.
METHODS: In a 6-month, randomized, placebo-controlled study, 20 kidney transplant recipients received either 4 mg zoledronic acid or placebo twice within 3 months after engraftment. At transplantation and after 6 months, mean trabecular calcium concentration and trabecular morphometry were measured in bone biopsies. Bone mineral density (BMD) of the femoral neck and the lumbar spine were evaluated by dual-energy x-ray absorptiometry, and serum biochemical markers of bone metabolism were determined monthly.
RESULTS: Trabecular calcium content increased significantly in the zoledronic acid group, but remained unchanged in the placebo group. BMD at femoral neck showed no change in the zoledronic acid group, but decreased in the placebo group. BMD of the lumbar spine was increased in the zoledronic acid group without change in the placebo group. High-turnover bone disease resolved similarly in both groups, as evidenced by a significant decrease of eroded bone surface, osteoclast and osteoblast surface. Serologic markers of bone formation and resorption were significantly lower in zoledronic acid-treated patients throughout the study. Kidney transplant function was stable after zoledronic acid therapy.
CONCLUSIONS: Our results show that administration of zoledronic acid improves the calcium content of cancellous bone after kidney transplantation. The beneficial effect of bisphosphonate therapy is further evidenced by an increase of lumbar spine BMD, and stabilization of femur BMD.

PMID: 12631097 [PubMed - indexed for MEDLINE]

43. Am J Transplant. 2002 Jan;2(1):62-7.

Treatment of osteoporosis and osteopenia in long-term renal transplant patients with alendronate.

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Bone mineral density (BMD) and biochemical markers of bone-turnover were evaluated in a 2-year study in 58 long-term renal transplant recipients with good renal function. In the first year of study, data were collected and patients with osteoporosis and parameters of high bone turnover were classified as being at high risk for on-going bone loss (Group A; n = 29). Patients with lesser degrees of bone loss or without biochemical parameters of high bone turnover were followed longitudinally (Group B; n = 29). Group A patients were then placed on alendronate 10mg/day and both groups were followed for an additional year. Changes in regional BMD and bone-turnover markers between the first and second year within each group were analyzed using paired tests. BMD in Group A, which had declined at the lumbar spine (- 1.6 +/- 0.5%) and total femur (-1.5 +/- 0.4%) during the first year of the study, increased on alendronate therapy at both the lumbar spine (+3.4 +/- 0.6%, p = 0.001) and total femur (+1.6 +/- 0.6%, p <0.001). These patients also experienced a significant decline in levels of serum alkaline phosphatase, osteocalcin, urinary levels of deoxypyridinoline and pyridinoline. In contrast, neither BMD nor biochemical markers changed significantly over 2 years in Group B. The current results demonstrate that renal transplant patients with osteoporosis and biochemical parameters of high bone turnover are at continued risk for bone loss. Therapy with a bisphosphonate can reverse this bone loss and even increase bone mass in these patients. Whether patients with lesser degrees of bone loss and/or patients without parameters of high bone turnover can also benefit from bisphosphonate therapy deserves further study.

PMID: 12095058 [PubMed - indexed for MEDLINE]

45. J Am Soc Nephrol. 2001 Jul;12(7):1530-7.

Effect of ibandronate on bone loss and renal function after kidney transplantation.

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Severe osteoporosis frequently is observed after organ transplantation. In kidney transplantation, it adds to pre-existing renal bone disease and strategies to prevent osteoporosis are not established. Eighty kidney recipients were included in a randomized controlled prospective intervention trial. Treated patients (n = 40) received an injection of ibandronate, a bisphosphonate, immediately before and at 3, 6, and 9 mo after transplantation. The primary outcome measured was the change in bone mineral density. Secondary measures included graft outcome, spinal deformities, fracture rate, body height, and hormonal and metabolic data. Loss of spongy and cortical bone after transplantation was prevented by ibandronate. Changes of bone mineral density (ibandronate versus controls) were as follows: lumbar spine, -0.9 +/- 6.1% versus -6.5 +/- 5.4% (P < 0.0001); femoral neck, +0.5 +/- 5.2% versus -7.7 +/- 6.5% (P < 0.0001); and midfemoral shaft, +2.7 +/- 12.2% versus -4.0 +/- 10.9% (P = 0.024). Fewer spinal deformities developed with ibandronate (7 patients with 7 deformities versus 12 patients with 23 deformities; P = 0.047). Loss of body height was 0.5 +/- 1.0 cm versus 1.1 +/- 1.0 cm in control subjects (P = 0.040). Two bone fractures occurred in each group. There were fewer acute rejection episodes with ibandronate (11 versus 22; P = 0.009). Graft function after 1 yr was comparable. Bone loss, spinal deformation, and loss of body height during the first year after kidney transplantation are prevented by injection of ibandronate at intervals of 3 mo. The smaller number of rejection episodes of the ibandronate-treated group should be confirmed and its mechanism should be explored in additional studies.

PMID: 11423583 [PubMed - indexed for MEDLINE]

55. Transplant Proc. 2011 Apr;43(3):858-62.

Risk factors for osteoporosis after renal transplantation and effect of vitamin d receptor bsm I polymorphism.

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OBJECTIVE: Rapid loss of vertebral or hip mineral density after renal transplantation is a major complication which occurs within 6-12 months. The aim of this study was to evaluate risk factors contributing to bone disease in the early stage after renal transplantation and the effect of vitamin D receptor (VDR) gene polymorphisms. METHODS: We prospectively followed for up to 12 months 44 patients (29 men and 15 women) with end-stage renal disease who underwent kidney transplantation. All patients received prednisone with either cyclosporine (CsA)/mycophenolate mofetil (MMF) or tacrolimus (Tac)/MMF therapy. Spine, hip, and whole body bone mineral density (BMD) was measured at 12 months after transplantation. According to World Health Organization recommendations, our patients were categorized as normal, osteopenic, or osteoporotic BMD levels. VDR alleles were genotyped as BB, Bb, or bb by polymerase chain reactions based on polymorphism at the Bsm I restriction site. RESULTS: Forty-six percent of patients were normal, 43% osteopenic, and 11% osteoporotic. Significant risk factors for osteoporosis among renal transplant recipients were younger age and pretransplant high intact parathyroid hormone (iPTH) levels. (P values .045 and .027, respectively). According to polymorphic group categorization, posttransplant serum Ca was significantly higher in patients with BB or Bb genotype than in those with bb genotype (P = .012). Although there was no statistical significance regarding iPTH levels, it was higher among Bb+BB than the bb genotype group. Also, first-year BMD analysis after transplantation according to Bsm I polymorphism showed significant differences in femur BMD levels according to the dual classification of polymorphism (P < .05). The BMD levels in the bb group was higher than in the Bb+BB group. CONCLUSIONS: Although high pretransplant iPTH levels and younger age enhanced posttransplant bone loss, functionally different alleles of the VDR gene may modulate bone turnover during the first year after renal transplantation.

PMID: 21486615 [PubMed - in process]

56. Nephrol Dial Transplant. 2011 Mar 25. [Epub ahead of print]

Mineral abnormalities and long-term graft function in pediatric renal transplant recipients: a role for FGF-23?

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BACKGROUND: Although current guidelines recommend the evaluation of mineral and bone metabolism in patients with all stages of chronic kidney disease (CKD), the prevalence of altered mineral ion homeostasis in the pediatric posttransplant population is unknown. Moreover, the contribution of abnormal mineral ion metabolism to graft outcomes in this population has not been evaluated. METHODS: Serum calcium, phosphorus, 25(OH)vitamin D, 1,25(OH)(2)vitamin D, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF-23) levels were evaluated 4.9 ± 0.5 years after transplantation in 68 stable pediatric renal allograft recipients. Patients were subsequently followed for 2 years. RESULTS: At baseline, mean estimated glomerular filtration rate (GFR) was 60 ± 2 mL/min/1.73m(2). Serum calcium and phosphorus values were within the reference interval. PTH values were elevated but did not differ by CKD stage. 25(OH)vitamin D levels were low in nearly half of all subjects. Tubular reabsorption of phosphate and 1,25(OH)(2)vitamin D values were lower, while FGF-23 and PTH values were higher in more advanced stages of CKD. Thirty percent of patients with FGF-23 values >110 RU/mL had a decrease in GFR of >50% ($P < 0.05$) and FGF-23 values predicted future episodes of rejection. CONCLUSIONS: Despite normal serum calcium and phosphorus levels in the majority of prevalent pediatric renal transplant recipients, abnormalities in PTH, 25(OH)vitamin D and FGF-23 are common. FGF-23 levels may be associated with increased risk for deterioration of kidney function and episodes of rejection.

PMID: 21441401 [PubMed - as supplied by publisher]

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