

Original Article

Overweight and body fat are predictors of hypovitaminosis D in renal transplant patients

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Abstract

Background. Hypovitaminosis D has been frequently reported after renal transplantation, but the impact of obesity and other factors in the reduction of vitamin D levels is not well established. We aimed to evaluate risk factors contributing to hypovitaminosis D among nondiabetic renal transplant recipients (RTR) with serum creatinine <2.0 mg/dL, at least 6 months after transplantation.

Methods. One hundred RTR were subjected to anthropometric evaluation and body composition assessment through bioelectrical impedance analysis; blood samples were drawn for biochemical and hormonal determinations and clinical data were retrieved from the medical records.

Results. Hypovitaminosis D was observed in 65% and overweight (body mass index, BMI >25 kg/m²) in 59% of cases with a significant median weight gain after transplantation of 5.1 kg. An inadequate distribution of body fat was evidenced in 50% of males and in 58% of females. Patients with either vitamin D deficiency or insufficiency presented significantly higher median values of body fat and weight gain since transplantation, as well as lower lean mass compared with patients with normal vitamin D levels ($P < 0.001$). Moreover, median values of waist circumference, BMI, serum leptin and parathyroid hormone levels were significantly higher in the group with vitamin D deficiency. A multivariate linear regression analysis then revealed that body fat and leptin levels, but not skin color, gender, age, glucocorticoid use, renal function, microalbuminuria and other confounding factors, were independently associated with low levels of 25 hydroxyvitamin D₃ even after adjustments for seasonal variations.

Conclusion. In conclusion, the present study showed body fat and serum leptin levels to be the only independent risk factors for hypovitaminosis D among RTR.

Keywords: obesity; overweight; renal transplantation; serum leptin; vitamin D

Introduction

Low serum 25 hydroxyvitamin D₃ [25(OH)D] levels are highly prevalent among patients with chronic kidney disease (CKD) worldwide [1–3]. Renal transplant recipients (RTR) are no exception, given that inadequately low levels of 25(OH)D have been found in up to 97% of RTR in Germany, Spain, Denmark and England [4–7]. However, since most of these studies were performed in northern latitudes where solar ultraviolet B exposure is low, generalizing these findings to other regions is questionable. Furthermore, these studies did not consistently identify risk factors associated with hypovitaminosis D.

Vitamin D is recognized to exert effects on kidney allograft function, as vitamin D has known immunomodulatory properties [8]. In addition to the traditional risk factors for hypovitaminosis D (e.g. ageing, skin color, seasonal variation and obesity), particular aspects related to renal transplantation (Tx) may also contribute to the reduction of 25(OH)D, namely the presence of proteinuria,

type of immunosuppressive regimen, reduced sunlight exposure or use of sunscreen to reduce the risk of skin cancer due to immunosuppressive therapy [9].

A high prevalence of overweight and obesity has been recently observed after Tx [10–13] probably because RTR are at risk for increased weight, centripetal obesity and muscle atrophy because of their long-term glucocorticoid requirements and immunosuppressive drugs [14]. However, the effects of these nutritional disorders upon hypovitaminosis D have not been studied in RTR.

Materials and methods

A total of 129 patients who had undergone Tx, a minimum of 6 months prior to enrollment, were recruited from the Renal Transplant Unit of the Nephrology Division from Universidade Federal de São Paulo, Brazil. Exclusion criteria were diabetes mellitus, impaired graft function (serum creatinine level >2.0 mg/dL), acute rejection within the preceding

3 months, current hospitalization, acute infection, patients with metal implants (prostheses or pacemakers) and use of vitamin D supplementation at any time since transplantation. One hundred (100) RTR met eligibility for this cross-sectional study. All patients were receiving immunosuppressive therapy, which consisted of (i) triple associations with calcineurin inhibitor [tacrolimus (Tac) or cyclosporine (CsA)], prednisone (Pred) and mycophenolate agents [mycophenolate mofetil (MMF), mycophenolate sodium (MPS) or azathioprine (Aza)]; (ii) triple associations with Tac or CsA with Pred and sirolimus; and (iii) double associations with Tac or CsA with Pred. A written consent was obtained from all subjects and the local Ethics Committee approved the study.

All RTR were subjected to an anthropometric evaluation and body composition assessment through bioelectrical impedance analysis. A fasting blood sample was drawn for serum biochemical and hormonal determinations, and a spot urine sample was collected to determine albuminuria. The clinical data were retrieved from their medical records.

Biochemical parameters

Serum 25(OH)D, creatinine, calcium, phosphorus, intact-parathormone (iPTH), fibroblast growth factor-23 (FGF-23) and leptin were determined in the blood samples. Creatinine was determined according to a modified Jaffe's reaction in Olympus Clinical Chemistry Analyzer (AU400-America Inc., Pennsylvania, USA), by an isotope dilution mass spectrometry traceable method. Serum estimates of glomerular filtration rate were obtained using the re-expressed four-variable Modification of Diet in Renal Disease equations [15]. Stages of Transplant Chronic Kidney Disease (CKDt) were defined according to the guidelines from Kidney Disease: Improving Global Outcomes (KDIGO) [16]. Serum calcium and serum phosphorus were determined by automated methods. Serum iPTH was measured by chemiluminescence assay (Architect intact PTH, Abbott, Germany). Serum FGF-23 (ELISA, Kainos Laboratories, Japan) and leptin (ELISA, Linco research, USA) were measured by enzymatic immunoassays. Serum concentration of 25(OH)D was measured by chemiluminescence (DiaSorin, Minnesota, USA). Hypovitaminosis D in this population was defined according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) by serum 25(OH)D levels <30 ng/mL, as insufficient when between 15 and 30 ng/mL and deficient if below 15 ng/mL [17]. Albuminuria was determined by enzyme-linked immunosorbent assay (ELISA).

Nutritional assessment

Anthropometric parameters such as body weight (BW), height and waist circumference were obtained from all patients. The BMI was calculated as weight (kg)/height (m²) and classified according to the World Health Organization. A waist circumference >102 cm in males and >88 cm in females was used to define central obesity. Data on pre-operative BW were obtained from their medical records. Post-transplant BW was measured upon enrollment to calculate weight gain since Tx. Body composition was assessed by bioelectrical impedance analysis (BIA). BIA was performed with a portable device model BIA 101 Quantum, RJL Systems (Detroit, MI), and the software provided by the manufacturer calculated total body water, fat-free mass and fat mass. The percent body fat cut-points used to define obesity (Male >25% and Female >30%) were the ones suggested by Okorodudu et al. [18].

Statistical analysis

Categorical variables were compared between three groups using χ^2 or Fisher's exact tests when appropriate. Continuous variables were submitted to a normality test and as most of them did not present a normal curve distribution, nonparametric tests (Kruskal-Wallis complemented by Dunn test) were performed. Data were expressed as mean \pm standard deviations, median and interquartile, or proportions as appropriate. Univariate and multiple linear regression analyses were used to determine factors associated with reduced serum 25(OH)D. Differences with P-values <0.05 were considered as significant. Statistical analyses were performed using the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

The present series consisted of 100 nondiabetics RTR (62 male and 38 female) whose age varied from 19 to 70 years old (42.4 ± 10.5) and the median time after Tx was 18 months [interquartile range (IQR) 8–36]. The etiologies of end-stage renal disease had been hypertensive nephrosclerosis in 38% of the patients, polycystic kidney disease in 13%, chronic glomerulonephritis in 9% and other causes in 9% of the patients. The etiology of CKD was undetermined in 31% of patients. The classification as CKD-t stages showed 52% of RTR to be stage 1 or 2 and 48% as stage CKD 3A (45–59 mL/min). Median BMI of RTR was 26 kg/m² (IQR 23–31), and the median weight gain after transplantation was +5.1 kg (IQR 2.3–7.7). A BMI of >25 kg/m² (overweight) was more prevalent in females than in males (73 versus 50%, $P < 0.05$), and inadequate distribution of body fat (see methods) was evidenced in 50% of males and in 58% of females. The prevalence of abdominal obesity defined by waist circumference was also higher in females (50 versus 14%, $P < 0.05$). The individual data revealed only one patient with hypercalcemia and none with hypophosphatemia. Increased serum leptin levels (>15 ng/mL) were observed in 20% of patients. Seventy percent of patients presented increased serum iPTH levels (>70 pg/mL), and the percentage of elevated parathyroid hormone (PTH) was higher in CKDt 3A versus CKDt 1/2 subgroups (83 versus 56%; $P < 0.05$). Hypovitaminosis D was observed in 65% of patients, with levels indicating insufficiency in 53% and deficiency in 12% of them. Other characteristics of the group as a whole and of patients grouped according to the presence of normal (sufficient) levels of vitamin D (≥ 30 ng/mL), insufficiency (15–30 ng/mL) or deficiency (<15 ng/mL) are shown in Table 1. There was a female preponderance in the group of vitamin D deficiency ($P < 0.001$). Although the percentage of blood collections obtained during the winter season was higher ($P < 0.001$) in either vitamin D-deficient or -insufficient groups, further adjustments were made posteriorly for the multivariate analysis. Patients with either vitamin D deficiency or insufficiency presented significantly higher median values of body fat and weight gain since Tx, as well as lower lean mass compared with patients with normal vitamin D levels ($P < 0.001$). Moreover, median values of waist circumference, BMI, serum leptin and PTH levels were significantly higher in the group with vitamin D deficiency. The median of phosphorus levels was significantly lower in patients with vitamin D deficiency versus those with normal vitamin D levels ($P < 0.015$). The remaining parameters were not statistically different.

Table 1. Main demographic, clinical, and nutritional and laboratorial characteristics of the patients according to the status of vitamin D

Parameters	25(OH)D <15 (n = 12)	25(OH)D 15–30 (n = 57)	25(OH)D ≥30 (n = 31)	P
Male/Female (n)	1/11	33/24	28/3	<0.001
Age (years)	49.6 ± 9.6	41.7 ± 10.3	41.3 ± 10.5	NS
Dialysis vintage (months)	29 (15–42)	18 (9–32)	32 (18–44)	NS
Post-transplant time (months)	28 (13–49)	20 (8–40)	10 (8–24)	NS
Afro-Brazilians [n (%)]	5 (42)	38 (67)	17 (55)	NS
Winter Season [n (%)]	8 (67) ^a	38 (67) ^a	9 (29)	0.001
Cadaver donor [n (%)]	3 (25)	13 (23)	5 (16)	NS
Cumulative prednisone (g)	1.9 (1.6–4.0)	3.4 (1.6–6.4)	4.0 (1.8–7.8)	NS
CsA-based immunosuppression [n (%)]	4 (33)	25 (44)	6 (19)	NS
Body composition				
Weight gain (kg)	5.5 (2.9–10.9) ^a	6.5 (3.8–8.0) ^a	2.4 (1.2–4.9)	0.001
BMI (kg/m ²)	31 (26–41) ^a	27 (24–31)	24 (21–27) ^b	0.001
Body fat (%)	39 (24–50) ^a	30 (22–35) ^a	20 (15–22)	0.001
Waist circumference (cm)	93 (87–99) ^a	92 (84–100)	83 (75–94)	0.044
Lean mass (%)	60 (50–76) ^a	70 (65–77) ^a	79 (78–85)	0.001
Biochemical				
CKD 1/2 [n (%)]	3 (25)	30 (53)	19 (61)	NS
CKD 3A [n (%)]	7 (58)	28 (49)	13 (42)	NS
Creatinine (mg/dL)	1.11 (0.90–1.65)	1.15 (1.00–1.40)	1.20 (1.10–1.50)	NS
Calcium (mg/dL)	9.6 (9.3–10.0)	9.6 (9.3–9.8)	9.7 (9.4–9.9)	NS
Phosphorus (mg/dL)	3.0 (2.6–3.2) ^a	3.1 (2.9–3.5)	3.5 (3.1–3.9)	0.015
FGF-23 (pg/mL)	22 (10–23)	46 (13–55)	46 (11–61)	NS
25(OH)D (ng/mL)	11 (10–13)	23 (16–25)	33 (31–38)	NA
Leptin (ng/mL)	16.7 (8.2–18.9) ^a	9.9 (5.9–14.2)	6.2 (2.8–8.7)	0.001
PTH (pg/mL)	148 (113–235) ^{a,b}	95 (72–160)	98 (69–117)	0.042
Albuminuria [n (%)]	7 (58)	45 (79)	16 (52)	NS

Data expressed as mean ± standard deviation, number (% of total) or median (interquartile range).

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index.

^aP < 0.05 versus ≥30.

^bP < 0.05 versus 15–30 (Dunn's test).

Table 2 shows the univariate and multivariate linear regression analyses involving all of the above parameters, with serum 25(OH)D as a dependent variable. The levels of 25(OH)D were significantly associated with female gender, directly associated with serum phosphorus and creatinine and inversely associated with weight gain, BMI, body fat, waist circumference and serum leptin. The multivariate linear regression analysis showed an independent and inverse association of body fat and serum leptin levels with 25(OH)D levels, adjusted for season of the year.

Discussion

In consideration of the pleiotropic actions of vitamin D recently recognized as well as the clinical relevance of the vitamin D status on renal outcome after renal Tx [8], the need for investigation of the risk factors for hypovitaminosis D in this population is of utmost importance. Hypovitaminosis D [4–7] as well as obesity [10–13] have been frequently described among RTR. Although the association between hypovitaminosis D and obesity has already been described in the general population [19–21] as well as in CKD [22], to the best of our knowledge, no study has hitherto examined the relationship between obesity and hypovitaminosis D in the renal Tx setting. The main findings of the present study were the negative association of fat mass with 25(OH)D serum levels in RTR.

A high prevalence of overweight, a significant median weight gain after Tx and an inadequate distribution of body fat has been observed in the present series of non-diabetic patients, especially among females. These findings are in accordance with Fernandes *et al.* [23], who described higher weight gain and total body adiposity

values in women than in men and with several studies who observed a high prevalence of overweight and obesity after Tx, reaching 60% of the patients after 10 years [13] and a weight gain up to 7.3 kg [10–12].

In the current study, hypovitaminosis D was present among 65% of RTR. Although the prevalence is somewhat lower than that described in the literature [4–7], it is still high and agrees well with the reports from our country in the general population [24] and CKD patients [3, 22]. As expected, the patients who had blood collections during the winter season showed lower levels of 25(OH)D, evidencing that factors limiting sun exposure in RTR may render this condition even worse. Hypovitaminosis D was not more prevalent among dark-skinned patients in the present sample, differing from the findings in the general population [25]. However, the lack of association between skin color and 25(OH)D in our patients might have been ascribed to the broad spectrum of ancestry heterogeneity of the Brazilian population. In the current study, 70% of patients presented elevated serum PTH, and median PTH was significantly higher in the vitamin D deficiency group versus the others, similar to other reports, which found an inverse association [26]. It needs to be further determined whether vitamin D supplementation would decrease serum PTH levels in such patients [4]. Although there have been speculations that elevated BMI and obesity are associated with increased PTH in the general population [21] and in CKD patients [27], PTH levels did not correlate with BMI in our series. However, the percentage of elevated PTH was also higher in CKDt 3a versus CKDt 1/2 subgroups. Therefore, our results suggest that in addition to very low levels of 25(OH)D, high PTH could also be accounted for suboptimal graft and/or deterioration of Tx function [28].

Table 2. Univariate and multivariate linear regression analyses with serum 25(OH)D as dependent variable (n = 100)

Independent variables	Univariate analysis			Multivariate analysis		
	Coefficient β (EP)	P	R ²	Coefficient β (EP)	P	R ²
Dialysis vintage (months) ^a	0.116 (0.100)	0.252	0.013			
Post-transplant time (months) ^a	-0.208 (0.102)	0.044	0.041			
Cadaver donor	-7.11 (7.12)	0.320	0.010			
Cumulative prednisone ^a	-0.164	0.103	0.162			
CsA-based immunosuppression [n (%)]	-10.98 (6.11)	0.076	0.032			
Winter season	-21.56 (5.44)	<0.001	0.138	-15.26 (5.05)	0.004	0.058
Afro-Brazilians	3.78 (5.97)	0.529	0.004			
Gender (female)	-34.61 (4.88)	<0.001	0.339			
Age (years) ^a	-0.109 (0.100)	0.280	0.012			
Weight gain (kg) ^a	-0.402 (0.092)	<0.001	0.162			
BMI (kg/m ²) ^a	-0.450 (0.090)	<0.001	0.203			
Body fat (%) ^a	-0.667 (0.092)	<0.001	0.366	-0.487 (0.130)	0.001	0.318
Waist circumference (cm) ^a	-0.375 (0.114)	0.002	0.1109			
Creatinine (mg/dL) ^a	0.213 (0.099)	0.034	0.045			
Calcium (mg/dL) ^a	-0.045 (0.101)	0.659	0.002			
Phosphorus (mg/dL) ^a	0.264 (0.098)	0.008	0.069			
FGF-23 (pg/mL) ^a	0.107 (0.105)	0.313	0.010			
Leptin (ng/mL) ^a	-0.541 (0.087)	<0.001	0.285	-0.260 (0.117)	0.030	0.0360
PTH (pg/mL) ^a	-0.156 (0.100)	0.120	0.024			
Albuminuria [n (%)]	-6.41 (6.21)	0.305	0.010			

Total R² = 0.497; Constant (EP) = 109.26 (7.75); P < 0.001.

^aVariables converted into ranks.

Of note, we observed in the present series that the vitamin D-deficient and -insufficient groups presented higher weight gain and body fat, and furthermore, the vitamin D-deficient group presented higher BMI, waist circumference and serum leptin levels. Besides, a multivariate linear regression analysis indicated that body fat and serum leptin, known to be correlated [29], represented the strongest predictive factors of low levels of 25(OH)D, even when adjusted for season of the year, corroborating previous reports of association between hypovitaminosis D and obesity in other populations [19–22]. Such an association could be attributed to either the low exposure of obese individuals to sunlight or sequestration and storage of vitamin D in the adipose tissue [30]. Enhanced lipogenesis and reduced lipolysis observed in obese individuals may also reduce vitamin D3 bioavailability [21]. Given that proteinuria has been described as a potential cause of hypovitaminosis D [31] we searched for the presence of albuminuria, but there has been no significant differences among groups with or without hypovitaminosis D.

Our study had primary limitations. Its cross-sectional design did not allow us to determine the timing of weight gain and/or hypovitaminosis D. The sample size may represent another limitation since we have examined RTR from a single medical institution; thus, our results may not apply to the transplant population at large. Unfortunately, we did not measure levels of 1.25(OH)₂D₃, the active vitamin D metabolite. Nevertheless, current data does suggest that fat stores may influence blood levels of 25(OH)D. Further investigation is needed to characterize the specific mechanisms by which adipose tissue of varying types contributes to reduced 25(OH)D concentration in overweight or obese transplant recipients.

In conclusion, the present study showed body fat and serum leptin levels to be the only independent risk factors for hypovitaminosis D among RTR. Considering that RTR are a high-risk group for hypovitaminosis D, well-designed interventional trials are needed for the development of effective strategies aimed at the prevention and treatment of hypovitaminosis D in such patients.

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Conflict of interest statement. A.B.C. is a consultant/lecturer to AMGEN, ABBVIE and SANOFI. These associations had no effect on the research performed in this manuscript. None of the other authors have any conflict of interest to report.

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