Serum Leptin, Body Fat, and Nutritional Markers During the Six Months Post-Kidney Transplantation

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Leptin is a 16-kd protein that is thought to be a regulator of food intake and body weight. Many previous studies have reported elevated serum leptin levels in renal failure. In this study, we investigated the outcome of serum leptin and its relationship to body fat (BF), dietary intake, nutritional, and inflammatory markers after kidney transplantation (KTx). A total of 41 kidney transplant recipients were followed-up prospectively during 6 months posttransplantation. Serum leptin, albumin, transferrin, and C-reactive protein (CRP) were measured at KTx, 15 days, 3, and 6 months later. Dietary intake and BF were determined at KTx, 3, and 6 months later. A decrease in serum leptin was observed early at day 15 after KTx; this decrease was significant only in patients with BF ≥ 30% of body weight. The decrease was maintained at 3 and 6 months after KTx. In multivariate analysis, an independent impact of higher percentage BF at KTx on the decrease of serum leptin was observed. Serum leptin correlated positively with BF. Conversely, no correlation was found between changes of serum leptin and changes of dietary intake. Leptin correlated positively with CRP at KTx, but not after normalization of renal function. Changes of serum leptin levels were not correlated with those of serum albumin levels. In summary, hyperleptinemia at KTx is manifest in patients with a high percentage of BF. An early and maintained correction follows KTx. Serum leptin levels did not appear to affect alimentary intake at and after KTx.

LEPTIN, THE HORMONAL product of the *ob* gene, a 16-kd protein, plays an important part in the regulation of food intake, energy expenditure, and body weight.[1,2] Many reports have demonstrated elevated serum leptin in end-stage renal disease (ESRD) patients compared with healthy adults matched for gender and body mass index (BMI). This has been reported in predialysis, hemodialysis, and peritoneal dialysis patients,[3-12] whereas fewer cross-sectional reports have dealt with renal transplant patients.[13-17] Some investigators speculated that hyperleptinemia could contribute to the decrease in appetite in ESRD patients. However, to date, no clear proof of a relationship of loss of appetite with an increase in serum leptin has been reported in renal patients. The present study was conducted to examine the impact of successful kidney transplantation (KTx) on serum leptin concentrations and particularly to analyze the effect of leptin levels on food intake and chemical nutritional markers at KTx and during the 6 months after KTx.

MATERIALS AND METHODS

Patients

We investigated prospectively 47 consecutive cadaver kidney transplant recipients over 6 months posttransplantation. Six patients did not complete the study due to a nonfunctioning graft by the end of the sixth month. Thus, 41 patients (28 men, 13 women) were analyzed. Before KTx, patients had been on hemodialysis treatment for 45 ± 42 months. Patient characteristics at KTx and the underlying causes of ESRD are provided in Table 1. At the end of the sixth month, serum creatinine was below 180 μmol/L in all patients; mean serum creatinine and urea levels in the overall group were 134 ± 31 μmol/L and 9.2 ± 3.2 mmol/L, respectively, and creatinine clearance calculated by the Cockroft and Gault formula[18] was 55.1 ± 17.8 mL/min.

Immunosuppressive Treatment

A triple immunosuppressive protocol using glucocorticoids (methylprednisolone, prednisone), cyclosporine-A (CsA; Neoral, Novartis, Reuil Malmaison, France) or FK506 (Prograf, Fujisawa, La Celle Saint-Cloud, France), and mycophenolate mofetil (MMF; Cellcept, Roche, Neuilly-sur-Seine, France) was used in all patients. Methylprednisolone was administered during the first 3 days then substituted with oral prednisone, which was progressively tapered to reach a daily dose of 5 mg at the end of the third month. In 14 patients, CsA was given orally with a mean dose of 5 to 10 mg/kg/d to result in whole blood levels of 150 to 200 ng/mL. In 27 patients FK506 was given with a mean dose of 0.1 to 0.3 mg/kg/d to result in whole blood levels of 5 to 10 ng/mL. All patients were given MMF with a mean dose of 2 g/d.

Cumulative steroid dose was calculated from oral and intravenous doses and was expressed by milligram of prednisone/kg/d. During the first 3 months, the mean daily dose of prednisone was 0.58 ± 0.43 mg/kg (0.61 ± 0.51 in men, 0.51 ± 0.25 in women, $P = .02$) and during the 6 months, it was 0.34 ± .11 mg/kg (0.36 ± 0.26 in men, 0.31 ± 0.13 in women, $P = .06$).

Measurements

Serum leptin was measured by radioimmunoassay (Immunotech, Marseille, France) using a polyclonal antibody raised in rabbits against purified recombinant human leptin. The first measure was performed immediately before KTx (M0); the other measures were performed after an overnight fast 15 days (D15) later, then 3 (M3) and 6 (M6) months later. Serum albumin, transferrin, C-reactive protein (CRP), and creatinine were assayed by standard techniques, at M0, D15, M3, and M6.

Mean daily total energy and protein intakes were assessed from average of 3-day food records. Patients wrote down everything eaten during 2 weekdays and 1 weekend day, including food portion sizes, and this was followed by an interview with a specialized dietitian to ensure accurate reporting. Calculation was completed with a computerized nutrient analysis program (Bilnut 4.0 SCDA Nutrisoft; Le

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Table 1. Patient Characteristics

	Patients	Controls
No.	41	22
Age (yr)	43.7 ± 10.4	48.2 ± 9.4
Gender (M/F)	28/13	15/7
Age (M/F)	44.8 ± 12/41.9 ± 6.8	49.8 ± 12/44.9 ± 6.8
Race (white/black)	40/1	22/0
BMI (kg/m^2)	23 ± 4.1	24.4 ± 3.9
BMI (M/F)	23.7 ± 3.4/21.6 ± 4.8	24.3 ± 3.9/22.5 ± 3.8
Body fat (kg)	24.4 ± 6.7	25.3 ± 6.3
Body fat M/F	27.4 ± 6.7/24.2 ± 4.8	24.2 ± 6.7/26.8 ± 4.8
Duration of dialysis prior to KTx (mo)	45 ± 42	
Underlying nephropathy		
Chronic glomerulophritis	13	
Interstitial nephritis	10	
Benign nephrosclerosis	8	
Polycystic kidney disease	3	
Hereditary nephritis	2	
Diabetes	2*	
Unknown	3	

*One patient was taking oral sulfonylurea and the other was taking insulin.

Hallier, Cerelles, France). The first record was performed 2 days after KTx to note in retrospect dietary intake at KTx (M0). Later records were achieved at M3 and M6. Weight and BMI (kg/m^2) were also assessed at KTx (M0), then at M3 and M6.

Dual Energy X-Ray Absorptiometry

The first investigation was performed 7 ± 6 days after KTx (M0), then at M3 and M6. A whole-body scan (software 8.19 a: 3) was performed using a fan beam model QDR-4500A-DEXA densitometer (Hologic, Waltham, MA). The scan time was 3 minutes and the radiation dose approximately 2 μSv per scan. The precision error of dual-energy x-ray absorptiometry (DEXA) is quite low, allowing accurate longitudinal studies of body composition. The coefficients of variation for DEXA measure are 1.1% for total fat mass and 0.8% for long-term reproducibility of percentage of body fat (BF) (% fat). The effect of hydration on percentage of fat is negligible: less than 0.6% when the lean mass hydration varies between 78.2% and 68.2%.[19]

Serum leptin and leptin/BF ratio values were compared with those of 22 gender-matched, healthy, control subjects with mean BMI comparable to those of transplant recipients at M0 (Table 1). The subjects were divided into 2 categories according to percent BF (BF $\geq$ 30% or $<$ 30%), and plasma leptin levels and leptin/BF ratio values were compared in the 2 groups. The study was approved by the hospital ethics committee, and all subjects gave informed consent.

Statistical Analyses

All statistical analyses were performed using software Stat View version 5 for Windows (Abascus Concept, Berkeley, CA). Data are expressed as means ± SD. To compare paired data at different times, the Wilcoxon's test was used. Unpaired data were analyzed using the Mann-Whitney *U* test. Simple correlations were studied using Spearman rank test. Lastly, a multiple regression analysis model was performed to examine the predictors of changes in serum leptin levels. $P \leq .05$ was considered significant.

RESULTS

Leptin

In the whole group, a rapid decline in serum leptin level was observed by the 15th day from 22.1 ± 45.2 to 8.7 ± 7.5 ng/mL ($P = .03$), at the same time the serum creatinine level decreased from 873 ± 297 to 287 ± 214 μmol/L. Leptin levels in the overall patients after KTx became comparable to the control group (Fig 1).

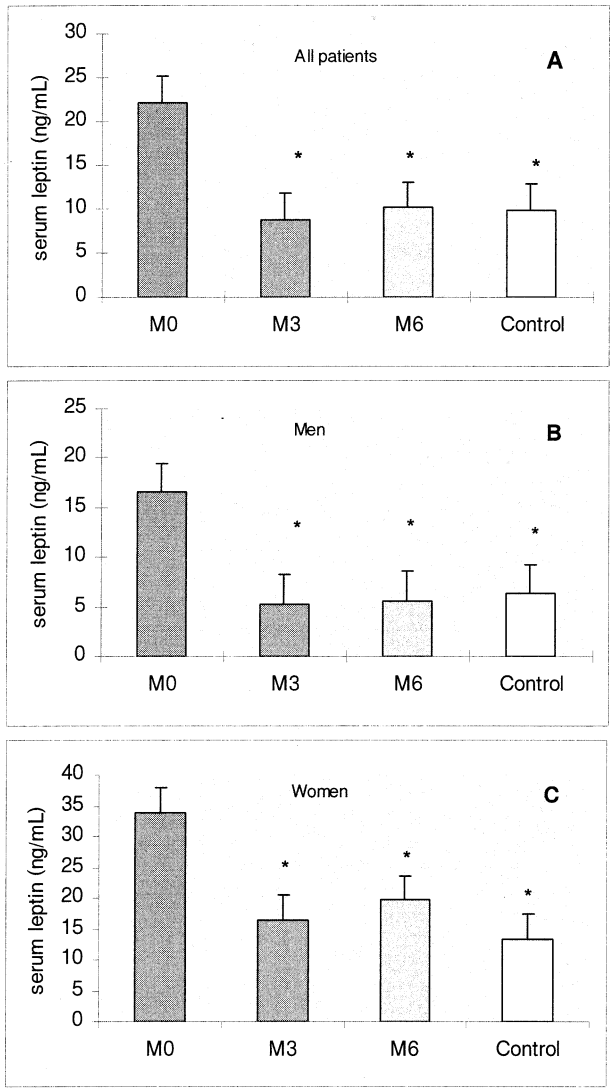

Fig 1. Changes in serum leptin in transplant patients from baseline value at KTx (M0) and 3 and 6 months after KTx (M3, M6), in (A) all patients, (B) men, and (C) women. The results include control subjects. The mean values of BMI in control subjects were similar to those of transplant recipients. Serum leptin (ng/mL): all patients (n = 41); M0: 22.1 ± 43.2; M3: 8.8 ± 10; M6: 10.1 ± 11.3; control: 9.9 ± 7.8 (n = 22). Men (n = 28), M0: 16.5 ± 35.1; M3: 5.3 ± 8.3; M6: 5.6 ± 7.3; control: 6.3 ± 3.9 (n = 15). Women (n = 13), M0: 33.9 ± 61.1; M3: 16.4 ± 13.7; M6: 19.7 ± 20.2; control: 13.4 ± 9.1 (n = 7). *$P \leq .05$ *v* M0.

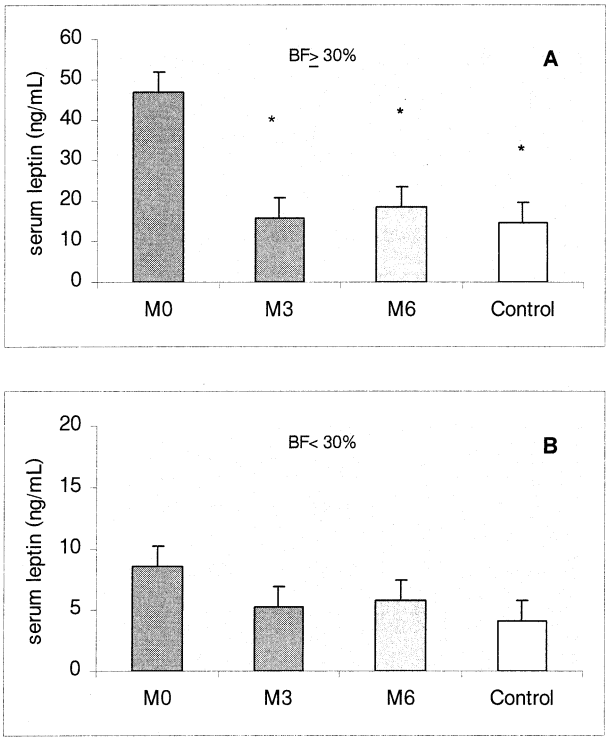

Fig 2. Changes in serum leptin in transplant patients and control subjects from baseline value at KTx (M0) and 3 and 6 months after KTx (M3, M6). The patients and the control subjects are separated by BF (A) ≥ 30% and (B) BF < 30%. Serum leptin (ng/mL): BF ≥30% (n = 15); M0: 47.1 ± 68.6; M3: 15.8 ± 17.6; M6: 18.3 ± 20.8; control: 14.7 ± 6.8 (n = 10). BF < 30% (n = 26); M0: 8.6 ± 8.5; M3: 5.2 ± 5.3; M6: 5.8 ± 5.7; control: 4.1 ± 3.8 (n = 12). *$P < .05$ *v* M0.

When separating patients by gender at M3, the decrease was significant in men ($P = .04$) and in women ($P = .05$). However, leptin levels in female patients tended to remain higher at M3 and M6 than female controls ($P = .32$, $P = .21$, respectively) (Fig 1). Regarding BF percentage, the decrease was significant only in patients whose BF was ≥ 30% of body weight ($P = .011$); these findings were maintained at M6 (Fig 2).

BMI and BF

In the whole group, a decrease in BMI was observed at M3 from 23 ± 4.1 to 22.4 ± 3.7 kg/m^2 ($P = .03$) followed by an increase to 22.9 ± 3.7 kg/m^2 at M6 (not significant [NS] *v* M0). The decrease was observed only in patients with BF ≥30%. Regarding BF, in all patients changes were −4.8% at M3 (NS) and −4.7% at M6 (NS) compared with M0.

When separating patients by gender, fat mass decreased in males −6.8% at M3 and −6.9% at M6 ($P = .038$ and .04, respectively), however, it did not change significantly in females (+1% at M3 and +2% at M6).

Leptin/BF Ratio

Significant decreases in leptin/BF ratio were observed at M3 and M6 in both men ($P = .041$ and .045, respectively) and women ($P = .048$ and .05, respectively). However, leptin/BF ratio in female patients remained higher at M3 and M6 than female controls ($P = .049$, $P = .046$, respectively) (Fig 3).

In the whole group, only patients with BF ≥ 30% decreased significantly leptin/BF ratio at M3 ($P = .008$), and the decrease was maintained at M6 ($P = .009$). There was no significant change in leptin/BF ratio in patients with BF less than 30% at M3 or M6. However, leptin/BF ratio in the later group tended to remain higher at M3 and M6 than controls ($P = .29$, $P = .18$, respectively) (Fig 4).

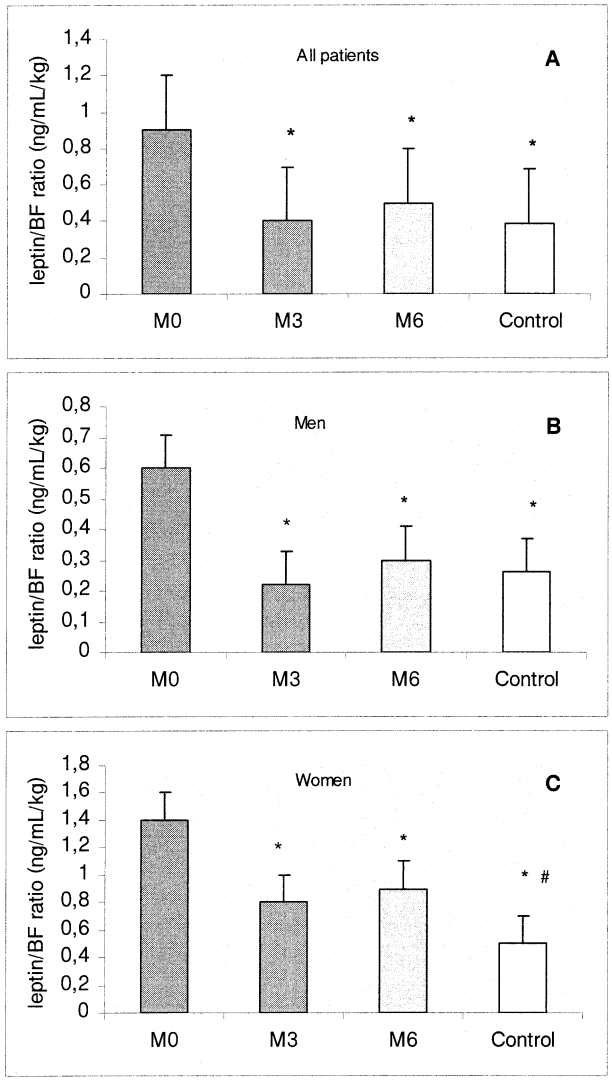

Fig 3. Changes in leptin/BF ratio in transplant patients from baseline value at KTx (M0) and 3 and 6 months after KTx (M3, M6), in (A) all patients, (B) men, and (C) women. The results include control subjects. Leptin/BF (ng/mL/kg): all patients (n = 41); M0: 0.9 ± 1.5; M3: 0.4 ± 0.4; M6: 0.5 ± 0.6; control: 0.39 ± 0.3 (n = 22). Men (n = 28), M0: 0.6 ± 1.2; M3: 0.22 ± 0.2; M6: 0.3 ± 0.2; control: 0.26 ± 0.15 (n = 15). Women (n = 13), M0: 1.4 ± 2.1; M3: 0.8 ± 0.5; M6: 0.9 ± 0.9; control: 0.5 ± 0.3 (n = 7). *$P < .05$ *v* M0, #$P < .05$ *v* M3 and M6.

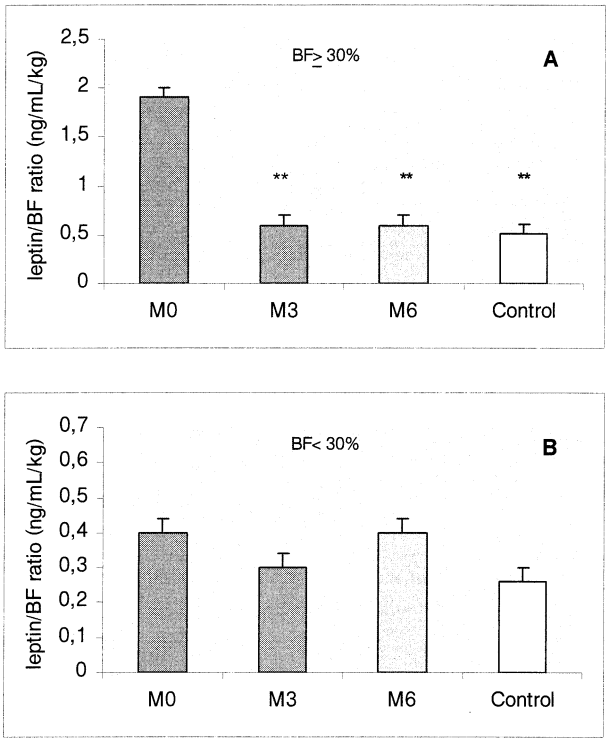

Fig 4. Changes in leptin/BF ratio in transplant patients and control subjects from baseline value at KTx (M0) and 3 and 6 months after KTx (M3, M6). The patients and the control subjects are separated by BF (A) ≥ 30% and (B) BF < 30%. Leptin/BF (ng/mL/kg): BF ≥ 30% (n = 15), M0: 1.9 ± 2.2; M3: 0.6 ± 0.5; M6: 0.6 ± 0.5; control: 0.52 ± 0.2 (n = 10). BF < 30% (n = 26), M0: 0.4 ± 0.4; M3: 0.3 ± 0.3; M6: 0.4 ± 0.3; control: 0.26 ± 0.16 (n = 12). **$P < .01$ *v* M0.

Dietary Intake

In the overall patients, energy and protein intakes, which were, respectively, 29.6 ± 7.5 kcal/kg/d and 1.1 ± 0.4 g/kg/d at M0, increased to 31.2 ± 7.4 and 1.21 ± 0.27 ($P = .06$ and $P = .04$, respectively) at M3, then to 32.5 ± 6.8 kcal/kg/d and 1.36 ± 0.33 g/kg/d at M6 ($P = .03$ and $P = .02$, respectively *v* M0).

Patients with BF ≥ 30% increased energy and protein intake from 28.9 ± 4.5 kcal/kg/d and 1 ± 0.41 g/kg/d at M0 to 30.7 ± 8.4 and 1.22 ± 0.24 ($P = .05$ and $P = .03$, respectively) at M3, then to 32.8 ± 8 kcal/kg/d and 1.38 ± 0.4g/kg/d at M6 ($P = .02$ and $P = .008$, respectively *v* M0).

Likewise, patients with BF less than 30% increased energy and protein intake from 30.1 ± 8.8 kcal/kg/d and 1.16 ± 0.39 g/kg/d at M0 to 31.5 ± 6.9 and 1.21 ± 0.28 ($P = .04$ and $P = .05$, respectively) at M3, then to 32.3 ± 6.1 kcal/kg/d and 1.34 ± 0.3 g/kg/d at M6 ($P = .03$ and $P = .01$, respectively *v* M0).

Chemical Markers

Serum albumin, which was 43.4 ± 6.5 g/L at M0 decreased dramatically during the first 2 weeks, then increased to reach pretransplant values at M3 and remained stable at M6.

Serum transferrin decreased abruptly in the first 2 weeks, then increased to exceed pretransplant values at M3 and stabilized thereafter (Table 2).

CRP remained above normal range during the first 2 weeks, and then stabilized at near normal level thereafter (Table 2).

Correlations

A strong correlation was observed between leptin and BF through the whole study; M0, $r = .85$ ($P < .0001$); M3, $r = .77$ ($P < .0001$); and M6, $r = .81$ ($P < .0001$).

Also, as expected, leptin correlated with BMI; M0, $r = .5$ ($P = .001$); M3, $r = .4$ ($P = .01$); and M6, $r = .46$ ($P = .002$). The decrease in serum leptin correlated positively with the improvement of creatinine clearance in patients with BF ≥ 30% ($r = .76$, $P = .003$), but not in patients with BF <30% of body weight.

Leptin correlated positively with CRP at KTx (M0) and early (15 days) after KTx ($r = .33$, $P = .02$ and $r = .7$, $P = .009$, respectively), but not later after KTx (M3 and M6).

No correlation was found between leptin and both energy and protein intakes at M0, M3, and M6. Additionally, no correlation was found between changes in leptin levels and changes in energy and protein intakes from M0 to M3 and M6. Also, no correlation was found between changes in leptin levels and changes in serum albumin.

Lastly, to examine the predictors of changes in serum leptin levels, a stepwise multiple regression analysis model was performed; changes in leptin between M0 and M3 were used as dependent variable beside 7 independent variables including: gender, cumulative steroid dose, average creatinine clearance between M0 and M3, changes in CRP levels, %BF at M0, changes of BMI and changes in BF between M0 and M3. The decrease in serum leptin levels was highly associated with the %BF higher than 30% at M0 ($R^2 = .48$, $P = .007$). However, a trend of influence of the increase in creatinine clearance

Table 2. Changes in Chemical Markers in the Overall Group (41 patients)

	M0	D15	M3	M6
Alb (g/L)	43.4 ± 6.5	36.2 ± 4.6‡	42.2 ± 3.7	42.7 ± 3.2
Trf (g/L)	1.92 ± .39	1.61 ± .4‡	2.2 ± .48‡	2.2 ± .47†
CRP (mg/L)	17.2 ± 10.2	20.6 ± 13.9	7.8 ± 7.1*	6.4 ± 7.7*
Crt (μmol/L)	873 ± 297	287 ± 214‡	132 ± 44‡	134 ± 31‡
Crt Cl (mL/min)	5.8 ± 1.9	22.3 ± 15.2‡	55.8 ± 18.6‡	55.1 ± 17.8‡

Abbreviations: M0, at transplantation; D15, 15 days after transplantation; M3, M6, 3, 6 months after transplantation; Alb, albumin; Trf, transferrin; CRP, C-reactive protein; Crt, serum creatinine; Crt Cl, creatinine clearance.

*$P \leq .05$, †$P < .001$, ‡$P < .0001$ *v* M0.

between M0 and M3 on the decline in leptin levels ($R^2 = .12$, $P = .09$) was noticed.

DISCUSSION

Many previous investigators have taken interest in leptin metabolism in predialysis, hemodialysis, and peritoneal dialysis patients, whereas fewer reports have dealt with the course of leptinemia after renal transplantation. In this longitudinal study of 41 kidney recipients with a functioning graft, an early decrease of serum leptin was observed and was maintained during the 6-month follow-up. Serum leptin was closely related to fat mass, but only patients with BF higher than 30% decreased significantly leptin/BF ratio after KTx. Lastly, no correlation was observed between leptin and energy and protein intakes.

In our study, the early decrease in serum leptin was found at day 15 posttransplantation; this decrease was maintained at M3 and M6 and was observed in both men and women. This finding is in agreement with those of Landt et al[13] and Kokot et al,[14] who also reported a posttransplant decrease in serum leptin 6 and 23 days, respectively, after KTx. This rapid decrease in serum leptin could be attributed to the improvement of graft function, because the kidney has been considered as the major site of leptin clearance.[20-22] However, our results demonstrated that such a decrease was only significant in patients with BF $\geq$ 30% of body weight; simultaneously, no significant change was observed in those with BF less than 30%. The multivariate analysis confirmed the independent impact of higher %BF on the decrease of serum leptin observed at M3. These observations further support the hypothesis suggesting that ESRD patients may be able to maintain a relatively average leptin/BF ratio due to a possible compensatory mechanism in extrarenal leptin degradation sites. An oversaturation of such degradation sites would occur after a threshold of increased leptin production due to excessive adiposity.[13,20] On the other hand, while leptin/BF ratio in female patients remained to some extent higher at M3 and M6 than female controls, in male patients, it became comparable to male controls at M3 and M6. These findings differ from those of Kokot et al[15,16] and Kagan et al,[17] who reported in prior trans-sectional studies considerably higher leptin levels in both male and female KTx patients compared with healthy controls.

Previous studies have reported that increased leptin/BF ratio in ESRD patients is associated with a decrease in dietary intake.[23,24] In contrast, Parry et al[25] did not observe any correlation between leptin levels and dietary protein intake. In the present study, we did not find any correlation between leptin values and both energy and protein intake either at or after KTx. Moreover, the increase in energy and protein intake at M3 and M6 compared with M0 was observed in both patients who decreased significantly their leptin/BF ratio, as well as in patients who did not. Furthermore, no correlation was found between changes in leptin levels and changes in energy and protein intakes from M0 to M3 and M6. Additionally, the changes in serum albumin levels were not associated with changes in serum leptin levels. This fact also agrees with prior studies[10,12,25] in which no correlation between leptin levels and serum albumin levels in renal failure patients was observed. All of these findings could argue against a relationship between elevated leptin levels and patients' anorexia at or after KTx.

In conclusion, we suggest that hyperleptinemia at KTx is manifest in patients with a high percentage of BF. An early and sustained correction follows KTx. However, female KTx patients maintained moderately higher leptin/BF ratio than healthy controls. Leptin levels did not appear to be affected by inflammation markers after normalization of renal function. Lastly, the presumed relationship between leptin and alimentary intake was not found either at or after KTx.

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