UNDERSTANDING KIDNEY TRANSPLANT BONE DAMAGE: A RETROSPECTIVE CROSS SECTIONAL STUDY

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INTRODUCTION AND OBJECTIVES

Kidney transplantation (KT) is the therapy of choice for end stage renal disease (ESRD) and allows more extensive survival than dialysis. bone damage can persist post-transplantation, because immunosuppressants (e. g. glucocorticoid administration) can induce secondary osteoporosis and often hyperparathyroidism persists. These factors affect the turn over of bone tissue and prolong a situation of bone fragility.

Long-term, post-transplant bone pathology is an insidious complication and it is one of the major causes of morbidity [1] because it increases the risk of fractures [2] whose treatment might require immobilization and hospital admission [3]

METHODS

We designed a monocentric cross-sectional retrospective study in a KT population. Patients transplanted between January 1st, 2000 and March 15th, 2016 and on regular follow-up at the kidney transplant unit of San Matteo hospital (Pavia, Italy), as well as patients transplanted elsewhere but on regular follow up at Pavia centre were included in the study. Patients gave infomed consent for their data to be anonymously utilized for scientific scope according to the policy of our institution. The induction treatment consisted of antithymocyte globulins (ATG) or basiliximab, and the maintenance regimen included calcineurin inhibitors (CNI), mTOR inhibitors (imTOR), antiproliferative drugs and steroids. Acute graft-rejection episodes were treated with methylprednisolne pulses. ATG, intra-venous immunoglobulin (IVIG), rituximab and plasma exchange (PE) were also added in steroid resistent rejections.

The hyperparathyroidism therapy included a combination of one or more of the following drugs: calcitriol, colecalciferol, paricalcitol, cinacalcet, calcium-based phosphate chelators, sevelamer, aluminum hidroxyde, lanthanum carbonate. OS treatment was based on biphosphonates or denosumab. Cumulative Steroid dose (CSD) was expressed as total mg of methylprednisolone.

VARIABLE		N (%)
Patients		297
Gender	Male	194 (65.3)
	Female	103 (34.7)
Menopause	Yes	65 (21.9)
	No	35 (11.8)
	unknown	3 (1)
Smoke	Yes	79 (26.7)
	No	187 (63.2)
	unknown	30 (10.1)
Cause of ESRD	glomerulonephritis	87 (29.3)
	vasculitis	4 (1.3)
	diabetic nephropathy	7 (2.3)
	nephroangiosclerosis	27 (9)
	pyelonephritis	19 (6.4)
	ADPKD	47 (15.8)
	amyloidosis/myeloma	5 (1.7)
	nephrolithiasis	19 (6.4)
	other	30 (10.1)
	not known	71 (23.9)
Previous kidney transplant		34 (11.4)
Pre-transplant fracture		31 (10.4)
		Median (IQR)
BMI		24 (15-35)
Age at follow up (years)		55.5 (5.6 - 83)
Time of exposition to immunosuppressants (years)		5.28 (0 – 25.4)

Table 1. Demographic characteristics of the cohort.

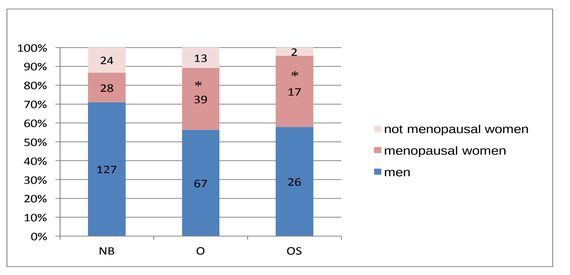

Figure 1. Gender distribution and menopausal status according to the three categories of the study. The numbers reported inside each column represent the absolute number of patients. * p< 0.01 vs menopausal women in NB group.

RESULTS AND CONCLUSIONS

Patients characteristics are summarized in Table 1, The percentage of menopausal women was significantly lower in the NB group (p<0.01) than in the other groups Figure 1. One “single bone” O (femural or vertebral) is more common in patients with longer time lapsed from transplantation (p<0.0001). The patients with “two locations” OS (femural and vertebral) were older than NB patients (p<0.005) (Table 2) The graft function, serum levels of calcium, phosphorus, PTH, 25-OH-vitamin D and 1,25-OH-vitamin D did not differ in the groups. The therapy with imTOR seemed to be a risk factor for OS development (OR 2.76; p<0.05), while the protective effect against OS of mycophenolate mofetil/mycophenolic acid which was pointed out in the univariate analysis, was not confirmed by the multivariate analysis (Tables 3) The only parameters statistically correlated with fractures were the transplantologic age (pointed out by the multivariate analyses p<0.05); the femural OS and imTOR-sirolimus treatment (pointed out by the univariate analysis, p<0.05). (Table 4)

In conclusion, this study reports that bone damage is observed in KT patients, albeit at smaller rates than usually reported in literature. The Centre's guidelines to administer lower doses of steroids might be at the origin of the better bone status. The multi-disciplinary approach aimed at reducing the risk of falling and of metabolic alterations justifies for the low rates of bone fractures consequent to falling.

Last but not least, within the limits of a retrospective cross sectional study, a positive correlation between the use of imTOR and osteoporosis has been noted. This is the first time that such a correlation has been observed in humans. Further prospective and multicentric studies will be necessary to confirm the results and *in vitro* experiments will be necessary to understand the underlying mechanisms.

	NB	Single bone O	Two locations O	p value
Prevalence N (%)	179 (60,3%)	86 (28,9%)	32 (10,8%)	
Time from transplantation (median years)	3,9 (0,06-25,4)	*7,0 (0,55-25,4)	5,6 (0-18,7)	<0,0001
Age at follow up (years)	53±13	53,9±13	57,6±10	0.41
	NB or O	Single bone OS	Two locations OS	p value
Prevalence N (%)	252 (85%)	37 (12%)	8 (3%)	
Time from transplantation (median years)	5,2 (0-23,5)	5,7 (0,55-25,4)	6,7 (1,6-9,4)	0.73
Age at follow up (years)	53,2±12,6	°58,7±13,7	59,3±11,6	0,002

Table 2. Bone status group according to age at follow up and time from transplantation.

* p<0.0001 single bone O vs NB, °p=0.002 single bone OS vs NB or O.

OSTEOPENIA	Odds Ratio	p value	CI 95%	
Sex	3	0.44	0.18	50.59
Age at follow up (years)	1.00	0.82	0.98	1.02
Menopause	2.09	0.12	0.82	5.34
Non menopause	0.32	0.44	0.02	5.88
Smoke	0.79	0.43	0.45	1.41
Sirolimus	0.70	0.25	0.37	1.30
Mycophenolate mofetil	0.70	0.19	0.41	1.20
Time of exposition to immunosuppressants (years)	1.09	0.001	1.03	1.14
OSTEOPOROSI	Odds Ratio	P value	CI 95%	
Sex	0.58	0.72	0.03	11.66
Age at follow up (years)	1.03	0.11	0.99	1.06
Menopause	7.42	0.07	0.84	65.13
Non menopause	6.22	0.32	0.17	231.9
Smoke	1.06	0.89	0.47	2.42
Sirolimus	2.76	0.01	1.27	5.97
Mycophenolate mofetil	0.50	0.07	0.24	1.05
Time of exposition to immunosuppressants (years)	0.99	0.87	0.92	1.07

Table 4. Demografic and post-transplant parameters: multivariate analysis.

	Not fractured	Fractured	p value
Medium Age at follow up (years)	53.7 ± 12.8	62.55 ± 11	0.1
Medium immunosuppressants exposition (years)	6.1 ± 4.6	11 ± 7.2	0.07
Femural osteopenia (%)	54.1	22.2	0.11
Femural osteoporosis (%)	17.8	*44.4	0.04
Lumbar osteopenia (%)	42.3	28.6	0.22
Lumbar osteoporosis (%)	12.1	14.3	0.60
Femural BMD (g/cm2)	0.8 ± 0.2	0.7 ± 0.2	0.31
Femural T-score	1.5 ± 1.1	2.4 ± 1.2	0.16
Femural Z-score	0.8 ± 1.3	0.8 ± 0.5	0.73
Lumbar BMD (g/cm2)	1.01 ± 0.2	0.92 ± 0.3	0.36
Lumbar T-score	1.2 ± 1.4	1.6 ± 2.2	0.70
Lumbar Z-score	0.5 ± 1.4	0.4 ± 1.6	0.94
Medium eGFR (ml/min/1.73 mq)	50.9 ± 23.5	49 ± 23.2	0.75
Medium sCalcium (mg/dl)	9.6 ± 0.6	9.7 ± 0.8	0.37
Medium sPhosphorus (mg/dl)	3 ± 0.8	2.8 ± 0.7	0.88
Medium sPTH (pg/ml)	149.4 ± 121.5	172 ± 62.2	0.24
Medium 1,25-OH-vitamin D (pmol/L)	81.3 ± 46.5	66.2 ± 47.6	0.35
Medium 25-OH-vitamin D (nmol/L)	49.6 ± 31.2	65.9 ± 38.2	0.45
Acute rejection (%)	18.1	10	1
osporin (%)	33.8	40	0.67
olimus (%)	43.5	10	0.08
Sirolimus (%)	17.8	°50	0.02
Everolimus (%)	15.7	10	1
Mofetil mycophenolate (%)	73.9	90	0.61
Azathioprin (%)	3.1	0	1
CSD (g)	6.7 ± 5	6.8 ± 4.7	0.69
BMI (kg/m2)	24.2 ± 3.8	24 ± 3	0.34

Table 6. Post-transplant parameters and risk fractures – univariate analysis.

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