Evaluation of metabolic syndrome and associations with inflammation and graft function in renal transplant recipients

Avaliação da síndrome metabólica e suas associações com inflamação e função do enxerto em pacientes receptores de transplante renal

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ABSTRACT

Introduction: Cardiovascular disease (CVD) is a major determinant of mortality in renal transplant recipients (RTR). Metabolic syndrome (MS) and chronic inflammation are currently considered non traditional risk factors for cardiovascular disease. This study evaluates the frequency of these conditions their associations with graft function. **Objective:** To evaluate the prevalence of metabolic syndrome (MS) and inflammation and their associations with graft function in renal transplant recipients. **Methods:** A cross-sectional study was carried out with 200 RTR. MS was defined by the NCEP-ATP III criteria. Inflammation was assessed by CRP levels. Renal function was assessed by GFR estimation using the MDRD equation. **Results:** MS occurred in 71 patients (35.5%). Patients with MS had higher CPR and decreased GFR levels. Inflammation was present in 99 patients (49.5%). Mean waist perimeter, body mass index, triglycerides and serum total cholesterol were significantly higher in inflamed patients. An association between MS and inflammation was demonstrated, 48 (67.6%) patients with MS were inflamed and among those without MS the rate of inflamed patients was 39.5% (51 patients) ($p < 0.001$). A significantly higher percentage of patients with MS in the group of patients in chronic renal disease stages III and IV was observed. **Conclusion:** In RTR there is a significant association among MS and inflammation. MS is negatively associated with graft function. The clinical implications of these findings must be evaluated in longitudinal studies.

Keywords: C-reactive protein; inflammation; kidney transplantation; metabolic syndrome X; obesity.

RESUMO

Introdução: A doença cardiovascular (DCV) é um dos principais determinantes da mortalidade em receptores de transplante renal (RTR). A síndrome metabólica (SM) e a inflamação crônica atualmente são considerados fatores de risco não tradicionais para doença cardiovascular. **Objetivo:** Avaliar a frequência da SM e da inflamação e suas associações com a função do enxerto em receptores de transplante renal. **Métodos:** Foi realizado um estudo transversal com 200 RTR. A SM foi definida pelos critérios do NCEP-ATP III. A inflamação foi avaliada por meio dos níveis de PCR. A função renal foi avaliada pela estimativa da TFG por meio da equação MDRD. **Resultados:** A SM ocorreu em 71 pacientes (35,5%). Pacientes com SM apresentaram maior PCR e diminuição dos níveis de TFG. A inflamação esteve presente em 99 pacientes (49,5%). A circunferência abdominal, índice de massa corporal, triglicérides e colesterol total foram significativamente maiores em pacientes com inflamação. Foi demonstrada associação entre MS e inflamação, 48 (67,6%) pacientes com SM estavam inflamados e entre aqueles sem SM a taxa de inflamados foi de 39,5% (51 pacientes) ($p < 0,001$). Uma porcentagem significativamente maior de pacientes com SM foi observada no grupo de pacientes de doença renal crônica estágios III e IV. **Conclusão:** Em RTR há associação significativa entre MS e inflamação. A SM está negativamente associada com a função do enxerto. As implicações clínicas destes achados devem ser avaliadas em estudos longitudinais.

Palavras-chave: inflamação; obesidade; proteína c-reativa; síndrome X metabólica; transplante de rim.

Introduction

Renal transplantation has become the treatment choice for a significant proportion of patients with terminal chronic renal disease (CRD). Over the last decades, the advances in the field lead to significant reduction of the acute rejection rates and improvements in short-term survival of patients and grafts. However in the long term the results still need to improve and most of the losses occur due to chronic allograft failure, mainly chronic rejection and death with functioning graft.[1] Among the causalities, cardiovascular disease (CVD) is the leading cause accounting for approximately half of the observed mortality,[2] Many risk factors for CVD in the general population are present in renal transplant recipients. The most prevalent are hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking and anemia.[2] In addition, other risk factors have been suggested in the pathogenesis of CVD in renal transplant recipients (RTR), among these factors proteinuria and inflammation have being described.[3,4]

The components of the metabolic syndrome (MS) namely, hypertension, diabetes mellitus, dyslipidemia and obesity, are independent risk factors for CVD. MS is an evolving concept, however its relevance in the renal transplant population has already being shown.[5,6] Its prevalence has been evaluated and reported to be as high as 63% in one study.[7] Recent studies report that MS may be associated with impaired long-term graft function, cardiovascular events, new onset diabetes after transplantation, graft loss and patient's death.[7-10]

Inflammation, as in the general population and uremic patients, is associated to cardiovascular events in RTR. In clinical practice it is diagnosed by the increment of acute phase proteins, and the C-reactive protein (CRP) is the clinically used parameter for such purpose.[11] CRP is produced by hepatocytes in response to infections, inflammation, injury and other stimuli. Its increment is well correlated to other inflammation markers, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).[12] It has been identified as a predictor of cardiovascular events in the general population, patients undergoing dialysis, and in RTR.[13-15] Moreover, there is evidence that increased post-transplant CRP levels are associated with a higher risk of chronic graft disease.[16]

After transplantation, appetite restoration, end of alimentary restrictions and the side effects of the immunosuppressive agents commonly lead to weight gain and obesity, a major problem after renal transplantation, occurring in up to 50% of the patients. The average weight gain is reported to be of 10 kg during the first post-transplant year.[17] Previous studies suggested that obesity is associated with an increased cardiovascular morbidity and mortality, and reduced survival of patients and grafts.[18]

The present study was undertaken to evaluate the prevalence and associations of metabolic syndrome and inflammation in a population of RTR in southern Brazil.

Methods

A cross-sectional study was conducted including RTR followed at the kidney transplant clinic at Hospital de Clínicas de Porto Alegre. The study was approved by the *Hospital de Clínicas de Porto Alegre* - Federal University of *Rio Grande do Sul* Institutional Review Board (IRB) and Ethics Committee, in adherence with the Declaration of Helsinky.

Outpatient RTR that met the following criteria: (a) transplant time between one and ten years; (b) stable graft function in the last three months defined by the variation of serum creatinine ≤ 0.3 mg/dL and; (c) accepting to participate in the study by signing the written informed consent, were included in the study. Patients with clinical or laboratorial evidence of infection, inflammation, auto immune diseases and with estimated glomerular filtration rate (GFR) ≤ 15 mL/minute were excluded.

Demographic data including age, gender, ethnicity, post-transplant time, organ source (living/deceased), primary renal disease, immunosuppressive treatment and medication use were recorded. The comorbidities evaluated included hypertension, hyperlipidemia, obesity, pre transplant and posttransplant diabetes mellitus and smoking. Laboratory data including the CRP levels were obtained in a routine clinic appointment in conjunction with measurements of the blood pressure, body weight, height, and waist perimeter. Body weight was measured in a 0.1 kg precision scale and the height was measured by using a 0.5 cm precise stadiometer. Body mass index was calculated as body weight (kilograms) divided by the squared height (meters). Patients were classified, according to BMI: undernourished (BMI < 18.5 kg/m^2), eutrophic (BMI 18.5 to 24.9 kg/m^2), overweight (25 to 29 kg/m^2), obesity class I (30 to 34.9 kg/m^2), obesity class II (35 to 39.9 kg/m^2) and obesity class III (≥ 40 kg/m^2).[19] The waist perimeter was measured by using an inelastic

metric tape, positioning half way between the lower rib and the superior iliac crest.

Metabolic syndrome

The National Cholesterol Education Program's Adults Treatment Panel III (NCEP-ATP III) definition criteria was used and include: central obesity, measured by waist circumference (WC), (> 102 cm for men and > 88 cm for women); triglycerides (TG) ≥ 150 mg/dL; HDL cholesterol (HDL-c), (< 40 mg/dL for men and < 50 mg/dL for women); systolic pressure (SP) ≥ 130 mmHg or diastolic pressure (DP) ≥ 85 mmHg and fasting glucose ≥ 100 mg/dL. Patients were diagnosed with MS when presenting at least three of the components.[20]

Inflammation

The inflammatory state was accessed by the measurement of CRP that was analysed by nephelometry, using the reagent CardioPhase hsCRP (Dade Behring, Germany). In the absence of validated values for the renal transplant recipients population, the median value observed in the sample of this study was used as a cutoff for defining inflammation.

Renal function

Renal function was estimated through creatinine based GFR estimation, according to MDRD (Modification of Diet in Renal Disease) equation: GFR = 175 x $(\text{creatinine})^{-1.154}$ x $(\text{age})^{-0.023}$ x (0.742 woman) x (1.210 black race).[21] After calculating the GFR, patients were classified according to CRD stages: stage I: > 90 mL/min/1.73m²; stage II: 60-89 mL/min/1.73m², stage III: 30-59 mL/min/1.73m²; stage IV: 15-29 mL/min/1.73m²; and stage V: < 15 mL/min/1.73m² (excluded).[22]

Statistical analysis

Statistical analyses were performed by using the SPSS (Statistical Package for the Social Sciences) software, for Windows 16 version. Normality was tested by using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation. Median and quartile interval were used for variables without normal distribution. Paired data were compared by Student´s *t* test, ANOVA was used for multiple comparisons and unpaired variables through by Mann-Whitney U test. The categorical variables were associated according to chi square test with Yates' correction. Poisson's regression with robust variance was used for the estimation of the prevalence ratios. The continuous variables were correlated by the Spearman's test. Multiple comparisons of continuous variables with asymmetric distribution were made by using the Kruskal-Wallis test. A rank transformation of the variables with asymmetric distribution was performed and used for comparison between groups through Tukey's test. *p* values lower than 0.05 were considered statistically significant.

Results

Two hundred renal transplant recipients were evaluated, 113 (56.5%) men, mean age 45.7 ± 11.5 years. The median of transplant time was 44 (19-71) months, and 135 patients (67.5%) received organs from deceased donors. Primary renal diseases were hypertension in 49 patients (24.5%), primary glomerular disorders in 36 patients (18%), adult polycystic kidney disease in 27 patients (13.5%) diabetic nephopathy in 15 (7.5%) chronic pyelonephritis in 14 (7%), other causes in 14 (7%) and in 52 patients (26%) the etiology of the renal disease was unknown. The more frequent co-morbidities were: hypertension in 159 patients (79.5%), hyperlipidemia in 56 (28%), obesity in 35 (17.5%) and hepatitis C virus (HCV) infection in 33 (16.5%). Sixteen patients (8%) were diabetic before transplantation and new onset diabetes after transplantation occurred in 18 patients (9%). Eleven patients (5.5%) were current smokers.

All patients were using low dose of prednisone (5 mg/day), calcineurin inhibitors were used by 179 patients (89.5%) and mycophenolate sodium or mofetil in 168 patients (84%), azathioprine in 15 (7.5%) and rapamycin in 7 (6.0%). The main non-immunosuppressive medications used were: antihypertensive drugs in 158 patients (79%), proton pump inhibitors in 123 (61.5%), diuretics in 73 (36.5%), statins in 56 (28%), low dose aspirin in 26 (13%), insulin in 25 (12.5%), and other diabetes controlling drugs in 6 (3%).

The nutritional assessment, according to BMI categories, revealed that 82 patients (41%) were eutrophic, 83 (41.5%) were overweight and 35 (17.5%) obese, being 24 (12%) classified as class I obesity, 9 (4.5%) class II obesity and 2 (1%) class III obesity. There were no undernourished patients.

The mean estimated GFR was 52.0 ± 19.9 mL/min/1.73m². Ten patients (5%) were classified as

CRD stage I, 49 (24.5%) stage II, 116 (58%) stage III and 25 (12.5%) stage IV.

Demographic and laboratory data of patients with and without MS and inflammation are shown in Table 1. MS occurred in 71 patients (prevalence 35.5%). Apart from variables involved in the definition of MS, which were expectedly higher in patients with MS, it was also found that patients with MS were older, presented significantly higher serum urea, CRP and BMI. They also presented significantly lower estimated GFR values (Table 1).

According to the criteria established for this analysis inflammation was defined by a serum CRP level higher than 1.6 mg/L. Ninety nine patients were considered inflamed (49.5% prevalence). Among the variables shown in Table 1, it was observed that the mean waist circumference, BMI, TG and serum total cholesterol were significantly higher in this group.

An association between MS and inflammation was observed. Forty-eight (67.6%) patients with MS were inflamed and among patients without MS the percentage of inflamed patients was 39.5% (51 patients) ($p < 0.001$). As shown in Figure 1 median and quartile CRP serum values were significantly higher in the group of patients with MS [3.2 (1.2-5.4)] as compared to the group of patients without MS [1.2 (0.6-3.8)] ($p < 0.001$).

A significant association was found between increased BMI and inflammation. As shown in Table 2, firstly considering all patients, the prevalence rate of inflammation significantly increased in the overweight group and further increased significantly in the obese group. In patients with CRD stages I + II (excellent and good graft function) a significant effect of weight in the prevalence rate of inflammation was observed only in the obese group. However in the group of patients in CRD stages III + IV (fair and poor graft function) this prevalence rate increased significantly in the overweight and in the obese subgroups uncovering a possible association between loss of graft function and inflammation.

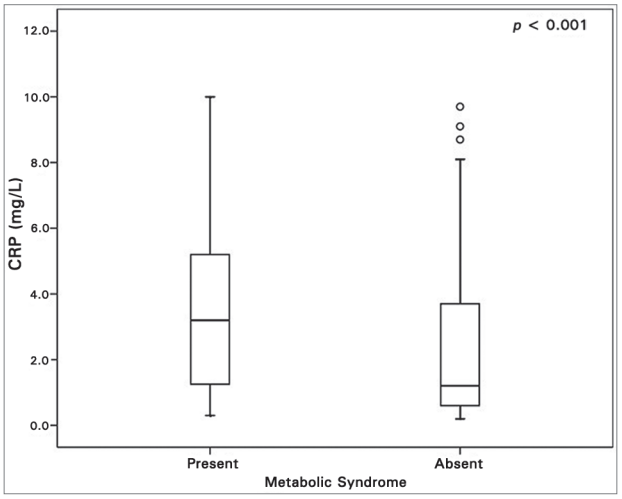
The presence of inflammation was tested against MS individual components. Positive and significant correlations between CRP with waist circumference ($r_s = 0.270$; $p < 0.001$), with fasting glucose ($r_s = 0.174$; $p = 0.014$) and with serum triglycerides ($r_s = 0.229$; $p = 0.001$) were found. No correlation was found between inflammation and blood pressure, either systolic or diastolic, or inflammation and HDL-cholesterol. To further investigate the

Table 1 Comparison of the groups with and without metabolic syndrome and inflammation

	MS present (n = 71)	MS absent (n = 129)	*p*	Inflamed (n = 99)	Not Inflamed (n = 101)	*p*
Age (years)[a]	48.45 ± 10.08	44.13 ± 11.98	0.007	47.01 ± 11.11	44.35 ± 11.78	0.102
Ethnicity (caucasian/non-caucasian)	57/14	107/22	0.702	84/15	80/21	0.400
Time post-renal tranplantation (months)[b]	37 (16-75)	45 (19-71)	0.486	44 (19-88)	44 (18-61)	0.384
Donor (living/deceased)	20/51	45/84	0.349	28/71	37/64	0.207
Waist Circumference (cm)[a]	99.87 ± 13.21	87.16 ± 11.43	< 0,001	94.81 ± 12.97	88.59 ± 13.37	< 0.001
Serum triglycerides (mg/dL)[a]	236.01 ± 72.85	145.52 ± 61.33	< 0.001	195.26 ± 80	160.38 ± 73.37	0.002
HDL-c (mg/dL)[b]	41 (35-49)	53 (42-65)	< 0.001	46 (37-57)	49 (40.5-62)	0.146
Hemoglobin (mg/dL)[a]	13.29 ± 1.98	12.91 ± 1.64	0.147	13.12 ± 1.74	12.97 ± 1.80	0.541
Hematocrit (mg/dL)[a]	40.72 ± 5.86	40.07 ± 4.85	0.403	40.54 ± 5.23	40.06 ± 5.23	0.520
Serum total cholesterol (mg/dL)[a]	207.31 ± 43.50	193.73 ± 48.62	0.051	209.35 ± 48.53	187.96 ± 43.56	< 0.001
Glucose (mg/dL)[b]	109 (92-128)	91 (86-99.5)	< 0.001	96 (89-109)	93 (86,5-99)	0.070
Creatinine (mg/dL)[b]	1.52 (1.19-2.06)	1.48 (1.16-1.76)	0.189	1.47 (1.11-1.91)	1.5 (1.23-1.90)	0.487
Serum urea (mg/dL)[b]	63 (46-90)	56 (43-69)	0.031	58 (45-79)	59 (43.5-72.5)	0.516
eGFR (mL/min/1.73m²)[a]	48.17 ± 18.88	54.17 ± 20.14	0.041	52.06 ± 21.78	52.03 ± 17.89	0.992
Body Mass Index (Kg/m²)[a]	28.93 ± 4.23	25.14 ± 3.99	< 0.001	27.77 ± 4.65	25.23 ± 3.88	< 0.001
C-reactive Protein (mg/L)[b]	3.2 (1.2-5.4)	1.2 (0.6-3.8)	< 0.001	4,2 (3-6.7)	0.8 (0.4-1.15)	< 0.001

[a] Values expressed as mean ± SD; [b] Values expressed as median and interquartile interval (p25-75); HDL-c: Serum HDL cholesterol; eGFR: Estimated glomerular filtration rate.

Figure 1. CRP (mg/L): Values distribution among the group of patients with and without metabolic syndrome. Box-plot graphs presenting the median values 25-75. percentiles 10-90 and outliers.



association between inflammation and the individual components of MS Poisson´s regression was used to analyze the prevalence ratios of each component against the presence of inflammation (Table 3). Here we found that the waist circunference, and HDL cholesterol are the components that significantly impact in the association. Further analyses showed that CRP positively correlated with BMI (r_s = 0.315; p < 0.001) and with total cholesterol (r_s = 0.173; p = 0.015).

The comparisons of median and quartile CRP serum levels in eutrophic, overweight and obese groups of patients are shown in Figure 2. Significant differences were found between the group of eutrophic [CRP = 1.15 mg/L (0.4-3.0)] and overweight patients [CRP = 2.3 mg/L (0.8-4.1)] (p < 0.042) and between eutrophic and obese patients [CRP = 3.6 mg/L (1.5-5.7)]; (p < 0.001).

An evaluation of the serum creatinine, BMI, estimated GFR and metabolic syndrome was made according to CRP quartiles and is shown in Table 4. BMI values where higher in the third and fourth quartiles and the percentages of patients with metabolic syndrome were higher in the third quartile as compared to the first quartile.

To explore a possible association between renal function and MS and renal function and inflammation we grouped the patients at CRD stages I and II (59 patients), and the patients at CRD stages III and IV (141 patients). MS was present in 14 patients (23.7%) and in 57 patients (40.4%) respectively in the first and second groups (p = 0.037). However, the prevalences of inflammation were 49.1% (29 patients) and 49.6% (70 patients) in the respective groups (p = 0.949).

Discussion

Several factors contribute to the elevated prevalence of MS observed in RTR. Among them factors related to the use of immunosuppressive drugs including weight gain, altered lipid profiles, effects on blood pressure, glucose metabolism and possibly the renal graft function have being described.[8] Immunosuppressive therapy with corticosteroids, calcineurin inhibitors and rapamycin is associated important modifications in lipid and glucose metabolism and may impact on *de novo* MS.[23,24] Furthermore correction of uremia and the use of corticosteroids lead to increased appetite and to development of post-transplant overweight and obesity.[25]

An elevated prevalence of MS was previously reported in studies with RTR.[7,9,26] Studies adopting the NCEP-ATP III diagnostic criteria reported a prevalence

Table 2 Association between the body mass index classifications and the prevalence ratio of inflammation in all patients and in the chronic renal disease (CRD) stage III + IV group

	All patients (n = 200)			Patients with CRD Stage I+II (n = 59)			Patients with CRD Stage III+IV (n = 141)		
	Inflammation n (%)	PR - CI 95%	p*	Inflammation n (%)	PR - CI 95%	p*	Inflammation n (%)	PR - CI 95%	p*
Eutrophic (n = 82/25/57)	30 (36.6)	1	-	10 (40)	1	-	20 (35.1)	1	-
Overweight (n = 83/26/57)	44 (53.0)	1.45 (1.02-2.05)	0.038	12 (46.2)	1.1 (0.61-2.18)	0.659	32 (56.1)	1.6 (1.05-2.44)	0.029
Obese (n = 35/8/27)	25 (71.4)	1.95 (1.37-2.78)	0.000	7 (87.5)	2.187 (1.27-3.78)	0.005	18 (66.7)	1.9 (1.22-2.96)	0.004

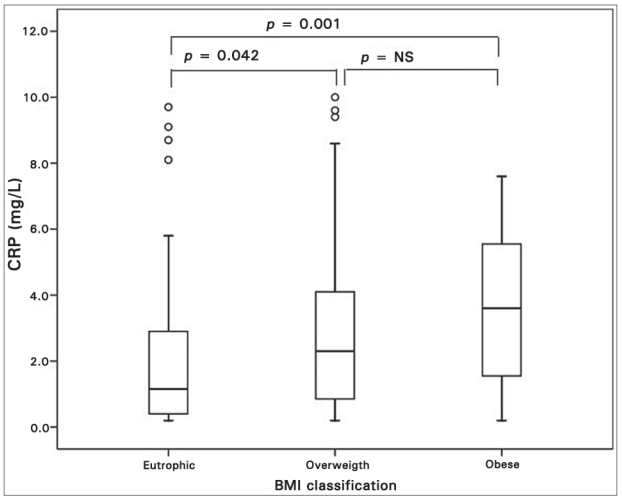
* Prevalence ratio (Poisson's regression); PR: Prevalence ratio; CI: Confidence interval; CRD: Chronic renal disease. The first number in each category corresponds to the general sample, the second corresponds to the sample of patients with I+ II CRD and the third corresponds to the sample of patients with III + IV CRD. The statistical comparisons were made against the group of eutrophic patients.

Table 3 Impact on inflammation of the metabolic syndrome components. Prevalence ratios

Metabolic Syndrome component	Prevalence Ratio (PR) (95% CI)	Adjusted PR (95% CI)	*p**
Serum triglycerides	1.59 (1.16-2.21)	1.37 (0.98-1.91)	0.058
Waist circunfewrence	1.71 (1.31-2.23)	1.47 (1.08-1.99)	0.013
Blood pressure	0.98 (0.74-1.31)	0.90 (0.68-1.18)	0.448
Serum glucose	1.39 (1.04-1.86)	1.03 (0.78-1.36)	0.823
HDL cholesterol	1.53 (1.17-2.01)	1.35 (1.02-1.78)	0.033

* Poisson's regression; CI: Confidence interval.

Figure 2. CRP (mg/L) values distribution among the BMI classification categories. Box-plot graphs presenting median values. percentiles 25-75. percentiles 10-90 and outliers. Eutrophic: BMI (18.5-24.9kg/m²); Overweight: BMI (25-29.9 kg/m²), Obese: BMI (≥ 30 kg/m²).



of around 60%.[7,27] Other reports with the same criteria, but using BMI instead of waist circumference, reported prevalence between 22.6% and 32.0% one to six years after renal transplantation.[9,28] In the present study the prevalence of 35.5% was found. The observed variation is most possibly explained by the design of the studies, time of evaluation after transplantation and perhaps by population differences in the frequency of the MS components in each study. The time of transplant is also an important variable to be taken into consideration.[7,9] In addition, other variables in the composition of study populations including previous time of dialysis therapy, rate of preemptive transplantation, donor type (deceased or living) and the immunosuppressive drug regimen can potentially influence the MS prevalence.[7,9,23]

Obesity is a frequent post-transplant complication and a well established risk factor for atherosclerotic disease. Besides, it is associated to an increased risk for diabetes, dyslipidemia and hypertension.[29] In this study, 41.5% of patients were overweight and 17.5% were obese. These frequencies are similar to those reported in another studies.[15]

Inflammation is currently considered a risk factor for cardiovascular disease in RTR.[4] In the clinical practice it is detected by the increased CRP levels. However, the values correlated to cardiovascular outcomes are different in the general population and in uremic patients, and there are no validated cutoffs for renal transplant recipients. Cueto-Manzano *et al.* measured CRP before and at different moments after renal transplantation, and found a significant decrease until one year after the transplant, leveling off around 3.2 mg/L afterwards.[30] Another study found a similar mean for the CRP levels.[31] Besides, CRP and other biomarkers of inflammation such as interleukin-6 and tumor necrosis factor alpha as well as markers of oxidative stress presented a fast decrease after transplantation.[31] In the present study, the cutoff

Table 4 Evaluation of body mass index, serum creatinine, estimated GFR and metabolic syndrome according to C-reactive protein quartiles

	Quartile (CPR levels)				
	1 (< 0.8 mg/L) (n = 49)	2 (0.8-1.6 mg/L) (n = 52)	3 (> 1.6-4.17 mg/L) (n = 49)	4 (> 4.17 mg/L) (n = 50)	*p*
Body Mass Index	24.51 ± 3.83[a]	25.92 ± 3.84[b]	27.30 ± 4.60[c]	28.22 ± 4.69[d]	< 0.001*
serum creatinine	1.66 ± 0.57	1.55 ± 0.49	1.74 ± 0.83	1.47± 0.50	0.133*
eGFR	51.31 ± 18.68	52.70 ± 17.23	51.80 ± 26.96	52.31 ± 15.38	0.987*
Metabolic Syndrome	5 (10.2%)[e]	18 (34.6%)	25 (51%)[f]	23 (46%)	< 0.001**

eGFR: Estimated glomerular filtration rate); CRP: C-Reactive Protein; * ANOVA; ** Chi square test; n: Number of patients. a *versus* [c] ($p = 0.007$); [a] *versus* [d]: ($p < = 0.001$); [b] *versus* [d]: ($p = 0.035$) and e *versus* [f] ($p < 0.001$).

used in the analyses was the median value of the CRP (1.6 mg/dL) found in our study population. In support to this approach a previous robust study found that CRP levels higher than 1.54 mg/L are associated with increased mortality in RTR.[32] Using this cut off to categorize inflammation resulted in half of the patients being considered inflamed and higher levels of CRP were associated to increased weight, abdominal circumference and serum triglycerides. Also, in the evaluations of the BMI and MS according to the CRP quartiles, it was found that the groups of patients with CRP higher than 1.6 presented significantly higher BMI values and percentages of patients with MS.

The pro-inflammatory state has been considered one component of MS.[33] Inflammation markers, such as CRP, tumor necrosis factor, fibrinogen, interleukin-6, among others, are associated to MS.[34,35] In the present study significantly increased levels of CRP were found in patients with MS. These finding supports the association, possibly clinically relevant, between metabolic syndrome and inflammation in the population of RTR.

A significant correlation between CRP and BMI was found. Also, as the CRP levels were analyzed according to the BMI classification (Figure 2) significant differences were observed between the eutrophic and overweight and between the eutrophic and obese groups of patients. These data suggest that as the BMI increment after transplantation is paralleled by the increment of CRP levels.

In the regression analysis we found that waist circumference is the MS component with the strongest association to the inflammatory state. Previously Van Ree *et al*. reported the association between waist circumference and CRP.[36] From these findings, it is possible to suggest that in RTR the MS component most importantly associated with inflammation is obesity. The implication of this finding is perhaps relevant to the prevention and management of MS.

Similarly the evaluation of the BMI categories and the presence of MS and inflammation disclosed significant associations (Table 2). The overweight group of patients presented a higher prevalence of MS as compared to the eutrophic and obese group. Somehow these results are expected since obesity is one of the components of the MS. However, due to its relevance, different weights for the metabolic syndrome components should perhaps be established, especially obesity, should probably have a higher value in the definition. As for inflammation, overweight patients presented 1.4 times the prevalence of inflammation when compared to the eutrophic group, in the obese group the increase in the prevalence was of 2.1 times. Again, these data support the notion that inflammation is significantly associated with obesity.[37]

Decreased GFR is an independent risk factor for cardiovascular events.[38] In keeping with our findings, previous studies in the unselected prevalent population of RTR showed that half of these patients were at CKD stage III.[39] Additionally we also found that GFR is significantly decreased in patients with metabolic syndrome, possibly due to the impact of conditions present in the syndrome that may contribute to the loss of renal function. Also the prevalence of patients with MS is significantly higher in the group of patients at CKD stages III and IV, supporting the hypothesis that MS and inflammation may be involved in the deterioration of renal function in these patients.

The study data allows the conclusion that in renal transplant recipients there are associations among MS, inflammation and graft function. In the late post-transplant period, complications such as hypertension, dyslipidemia, diabetes and obesity and even graft loss are frequent and toxicities of the immunosuppressive therapy, sedentary life style and unhealthy diet may contribute to these outcomes.[40] MS may represent the sum of these factors that lead to increased mortality risk due to cardiovascular events.

Conclusion

In conclusion we believe that a more precise definition of the inflammatory state in RTR is clearly needed. Longitudinal studies that correlate CRP levels, and perhaps other inflammation markers, to outcomes such as mortality and cardiovascular events are necessary to establish adequate prognostic indexes in this population.

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