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Body mass index and metabolic syndrome impact differently on major clinical events in renal transplant patients

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Abstract. – OBJECTIVE: Kidney transplant recipients (KTRs) are bound to develop cardiovascular disease (CVD), and obesity represents a well-known risk factor for CVD. It has been reported that the metabolic syndrome (MetS) is a frequent finding in KTRs, and MetS could develop even if body mass index (BMI) is only mildly increased. We compared the impact of BMI and MetS on the development of major clinical events (MCEs) in a cohort of 107 KTRs during a follow-up of 63 ± 31 months.

PATIENTS AND METHODS: Clinical characteristics were recorded at the time of enrollment and patients were classified on the basis of MCEs development. In a Cox model, MCEs were the dependent variable while age, sex, history of CVD, glomerular filtration rate, length of dialysis pre-transplantation, BMI classes and diagnosis of MetS were independent variables. Patients were classified into 3 groups: normal (BMI < 25 kg/m^2), overweight (BMI of 25 to 30 kg/m^2) and obese (BMI > 30 kg/m^2).

RESULTS: During follow-up, 55 MCEs were recorded: 16 patients died (15%), 19 (18%) had major cardiovascular events (CVEs), and 20 (19%) started dialysis due to graft failure. KTRs who had MCEs (n = 42) were older, had a lower renal function, longer dialysis vintage pre-transplantation, higher prevalence of history of CVD and higher BMI than those without MCEs. Cox regression analysis showed that length of dialysis pre-transplantation, renal function, previous CVD, and BMI classes (overweight and obesity) were related to MCEs.

CONCLUSIONS: BMI, but not MetS, predicted MCEs in KTRs as well as non-traditional CVD risk factors such as length of dialysis pre-transplantation and graft function. Thus, a simple evaluation during clinic visits could identify KTRs at high risk for MCEs.

Key Words:
Kidney transpnatation, Metabolic syndrome, Body mass index, Graft failure, Cardiovascular disease.

Introduction

In adults aged > 20 years, metabolic syndrome (MetS) is a frequent condition (34% of cases), as reported by the National Health and Nutrition Examination Survey (NHANES) 1999-2006[1]. Similar data were also reported by an Italian report[2]. According to the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATP III) definition, diagnosis of MetS is established by ≥ 3 of the following risk factors: (1) abdominal obesity defined as a waist circumference more than 102 cm in men and 88 cm in women; (2) hypertriglyceridemia (≥ 150 mg/dl); (3) hypertension (blood pressure ≥ 130/85 mmHg); (4) impaired fasting glucose or diabetes (fasting glucose ≥ 100 mg/dl); and (5) low high-density lipoprotein cholesterol (HDL-C) levels (< 40 mg/dl in men or < 50 mg/dl in women)[3].

Moreover, other clinical and metabolic alterations are considered related to MetS such as high triglycerides/HDL-cholesterol ratio, high apolipoprotein B and non-HDL-C levels and low apolipoprotein A level[4].

Obesity is an important feature of MetS and represents a well-known independent risk factor for MetS. Both obesity and MetS are related to an increased risk of cardiovascular disease (CVD) and chronic kidney disease (CKD) in general populations[5]. Moreover, CKD and MetS are strong

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predictors of CVD and they act sinergistically[6]. Similar findings have been reported in kidney transplant recipients (KTRs) in whom risk of CVD has been calculated to be about 50-fold greater than in the general population[7,8]. Also, a Scandinavian study showed that half of the deaths in KTRs were due to ischemic heart disease, and an additional 10% to other vascular complications[9]. However, the prevalence of CVD was higher in KTRs from deceased donors compared with living donors[10]. A long-term study found that events related to CVD were reported in 50% of KTRs; main risk factors were male gender, age, hypertension, history of cardiovascular events before transplantation, longer pre-transplant dialysis, and older era of transplantation. Moreover, also diabetes mellitus, hypertension and hypertriglyceridemia development after transplantation appeared to be related to CVD risk[11]. Obesity impacts negatively heart surgery in hemodialysis-dependent patients[12].

In a previous study, we reported that about one-third of KTRs had MetS, and that body mass index (BMI) above 25 kg/m^2 was related to MetS[13]. The aim of the present study was to evaluate, in the same cohort of KTRs the relationship between Mets, BMI and development of major clinical events (MCEs) such as death due to all causes, CVD events and graft failure.

Patients and Methods

We conducted a prospective, longitudinal, observational study during which 107 KTRs were followed-up for 5 years. The study, in agreement with the terms of the Declaration of Helsinki and approved by local Ethic Committee, included a cohort of Caucasian KTRs outpatients continuously attending the nephrology clinic of the University Hospital of Ferrara between June 2009 and May 2014. The total sample consisted of stable KTRs, and all of them gave their informed consent for participation in the study. Patients' characteristics have been previously reported[13]. Briefly, the following demographic and clinical data were derived from clinical records: age, duration of dialysis treatment before transplantation, time since transplantation, smoking and diabetes mellitus history, therapy and co-morbid conditions. Renal allograft function was evaluated by estimated glomerular filtration rate (eGFR) using the 4-variables Modification of Diet in Renal Disease Study Equation (MDRD) formula[14] that offer a better eGFR prediction in KTRs and in the early CKD stages compared with other equations[15,16]. Also, we measured height, weight, and waist circumference (WC) with the subject standing. WC was measured midway between the iliac crest and the lowest rib. We calculated BMI as weight in kg divided by the square of height in meters; BMI was used to classify KTRs into 3 groups: normal (BMI < 25 kg/m^2), overweight (BMI 25 to 30 kg/m^2), and obese (BMI > 30 kg/m^2), according to the World Health Organization[17]. MetS was defined using the criteria proposed by the NCEP-ATP III [3]. Duration of follow-up was 63 ± 31 months, and MCEs considered as the main end-point included CVD events, graft failure with beginning of dialysis and all-cause death. Data were obtained from Hospital database and clinical notes.

Statistical Analysis

Data are expressed as absolute numbers, percentage and mean ± standard deviation. MCEs, representing our primary outcome, were considered the sum of CVD events, graft failure with beginning of dialysis and all-cause death. Univariate analysis was performed by dividing patients into two groups related to the presence of MCEs. Differences between groups were compared with Student's *t*-test for parametric continuous variables and Mann-Whitney U test for nonparametric continuous variables. Chi-squared test was applied for estimating the occurrence of categorical variables. Cox-regression analysis for Hazard Ratio (HR) calculation was performed in order to evaluate features independently related to MCEs development. Age, sex, history of CVD, eGFR, length of dialysis pre-transplantation, BMI classes and diagnosis of MetS were the independent variables in the analysis. Kaplan-Meier survival curve was drawn analyzing the impact of different BMI classes on MCEs, CVD events, graft failure and all-cause death. All *p*-value were two-tailed, and a p-value < 0.05 was considered significant. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyzes.

Results

During the follow-up, 16 patients died (14.9%), 19 had a CVD event (17.7%), and 20 (18.6%) started dialysis due to graft failure. CVD events were represented by: 10 myocardial infarctions, 6 strokes, and 3 episodes of aortic rupture. Features of KTRs investigated are reported in Table I.

Table I. Characteristic of the 107 kidney transplant recipients.

Male [no. (%)]	72 (67%)
Age (years)	54.6 ± 11.3
Current or ex-smoker [no. (%)]	21 (20%)
Diabetes mellitus [no. (%)]	12 (11%)
Hypertension [no. (%)]	90 (84%)
History of CVD [no. (%)]	17 (16%)
Dyslipidemia [no. (%)]	41 (38%)
Normal weight [no. (%)]	64 (60%)
Overweight [no. (%)]	35 (33%)
Obesity [no. (%)]	8 (7%)
Metabolic syndrome [no. (%)]	37 (34%)
Weight (kg)	71.1 ± 13
Abdominal circumference (cm)	94.2 ± 11.6
BMI (kg/m^2)	25 ± 3.5
eGFR (ml/min/1.73 m^2)	53.4 ± 19.7
Cardiovascular disease events [no. (%)]	19 (18%)
Graft failure [no. (%)]	20 (19%)
Length of dialysis pre-transplantation (month)	28.9 ± 31
Deceased [no. (%)]	16 (15%)

At the univariate analysis, KTRs who suffered a MCEs were older (57.8 ± 11.5 *vs.* 52.5 ± 10.8 years; $p = 0.014$), had a lower eGFR at enrollment (46.9 ± 19.5 *vs.* 57.7 ± 18.8 ml/min/1.73m^2; $p = 0.004$), longer dialysis vintage pre-transplantation (41 ± 39.7 *vs.* 20.9 ± 20.9 month; $p = 0.001$), higher prevalence of history of CVD (29.5 *vs* 6%; $p = 0.001$), and a higher BMI (26 ± 3.8 *vs.* 24.4 ± 3.1 kg/m^2; $p = 0.018$) than those without MCEs (Table II).

Cox regression analysis showed that length of dialysis pre-transplantation (HR = 1.013, 95% CI 1.005-1.021; $p = 0.001$), eGFR (HR = 0.973, 95% CI: 0.955-0.997; $p = 0.004$), previous CVD events (HR = 2.802, 95% CI: 1.317-5.958; $p = 0.007$), and BMI classes (overweight HR = 2.085, 95% CI: 1.050-4.142; $p = 0.036$, and obesity HR 4.773, 95% CI: 1.868-12.195; $p = 0.001$) were related to development of MCEs. Impact of the different classes of BMI on MCEs, CVD events, graft failure and all-cause death as reported in Figure 1.

Discussion

Although the number of patients evaluated in this study was low, we found that only BMI, but not MetS, could predict major clinical events in KTRs. Moreover, we found that non-traditional CVD risk factors, such as length of dialysis pre-transplantation and graft function, were related to MCEs development[18].

In the general population, MetS represents an important CVD risk factor[19], and risk of CVD events appears to be higher in women than in men.

Prevalence of MetS in KTRs has been reported to vary between 20 and 65% , progressively increasing in the post-transplantation period (22.6% after 1 year, 64% after 6 years)[20]. On the other hand, data about this item are not consistent[21-22]. Development of MetS in KTRs has

Table II. Comparison between kidney transplant recipients (KTRs) with and without major clinical events (MCEs). MCEs included major cardiovascular disease (CVD) events, graft failure with beginning of dialysis, all-cause death.

	KTRs without MCEs (n = 65)	KTRs with MCEs (n = 42)	*p*
Male [no. (%)]	45 (69%)	27 (64%)	NS
Female [no. (%)]	20 (31%)	15 (36%)	
Age (years)	52.5 ± 10.8	57.8 ± 11.5	0.014
Current or ex-smoker [no. (%)]	11 (17%)	10 (24%)	NS
Diabetes mellitus [no. (%)]	6 (9%)	6 (14%)	NS
Hypertension [no. (%)]	54 (83%)	36 (85%)	NS
Dyslipidemia [no. (%)]	22 (34%)	19 (45%)	NS
History of CVD [no. (%)]	4 (6%)	13 (31%)	0.001
Weight (kg)	69.9 ± 13.6	72.9 ± 11.9	NS
Abdominal circumference (cm)	93 ± 11.8	96.2 ± 11.2	NS
Body mass insex (kg/m^2)	24.4 ± 3.1	26 ± 3.8	0.018
Normal weight [no. (%)]	45 (69%)	19 (45%)	0.02
Overweight [no. (%)]	18 (27%)	17 (40%)	
Obesity [no. (%)]	2 (3%)	6 (14%)	
Metabolic syndrome [no. (%)]	21 (32%)	17 (60%)	NS
eGFR (ml/min/1.73 m^2)	57.7 ± 18.8	46.9 ± 19.5	0.004
Length of dialysis pre-transplantation (month)	20.9 ± 20.3	41 ± 39.7	0.001

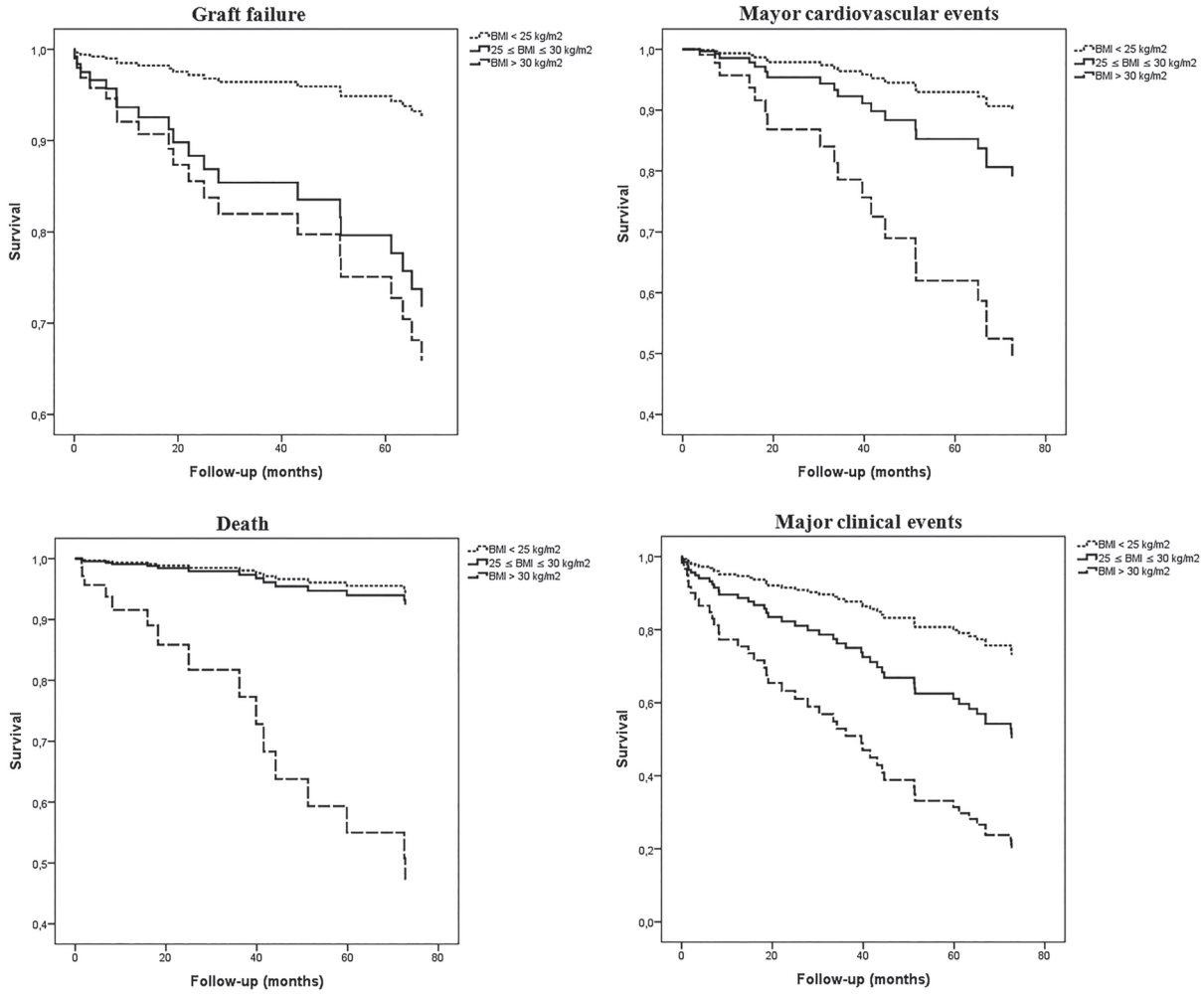

Figure 1. Survival analysis reporting the impact of different classes of body mass index (BMI) on major clinical events (MCEs), cardiovascular disease (CVD) events, graft failure, and all-cause death

been related to different conditions including immunosuppressive drugs; cyclosporine could increase serum uric acid, blood pressure, and LDL cholesterol; sirolimus could induce dyslipidemia, tacrolimus, cyclosporine and prednisolone could contribute to development of diabetes[23-25]. Moreover, Courivaud et al[26] reported that patients who developed MetS during the first year of renal transplantation had older age, were male, and had high BMI. The Kidney Disease Improving Global Outcomes (KDIGO) Transplant Working Group reported that CVD risk is high in KTRs, due to the high prevalence of hypertension, hyperlipidemia, diabetes and obesity after kidney transplantation[27], and that treatment of these clinical conditions could reduce the risk of morbidity and mortality. Obesity represents an important risk factor related to negative outcome, a systematic review[28] on the effects of obesity on kidney transplantation showed that it was related with delayed graft function and cardiovascular mortality. Cannon et al[29] evaluated the impact of obesity on delayed graft function, graft survival and patient survival in 74,983 KTRs. They confirmed that obesity represented an important risk factor for delayed graft function and graft survival. A negative impact of obesity on graft developed very early post-transplantation; however, patient survival was not influenced by this condition. Accordingly, Ditonno et al[30] found an inverse relationship between obesity and worsening graft function at 6 months, 1 year, and 3 years post-transplantation. Moreover, obesity increased the risk of acute rejection and obese patients suffered cardiovascular and metabolic complications in the first 3 years post-transplan-

tation. Furthermore, high BMI has been shown to increase mortality in KTRs with a comparable effect after 2 and 3 years post-transplantation[31]. Also, Grosso et al[32] analyzed survival of obese KTRs and showed that they had lower survival than non-obese ones at 1 year (76.9 *vs.* 35.3%) and 3 years (46.2 *vs.* 11.8%); the main causes of death were myocardial infarction and cardiovascular complications. Again, Lentine et al[33] evaluated the association between BMI and post-transplantation cardiac risk evaluating prevalence of congestive heart failure (CHF), atrial fibrillation (AF), and myocardial infarction. Each 5 units of BMI increase was predictive of a 25% higher risk of cardiac disease.

Both pre- or post-transplant obesity has been reported to negatively affect graft function, independently from time of diagnosis. Pre-transplant obesity was related to development of post-transplant hypertension and hyperlipidemia within 6 months, insulin resistance or diabetes within 3 years, and chronic allograft nephropathy and graft loss[34]. American data showed that about 60% of KTRs were overweight at the time of transplantation; in USA and United Kingdom obese patients were excluded from transplant lists due to higher prevalence of post-procedural complications, such as graft failure or surgical complications[35]. Studies on obesity during pre-transplant period demonstrated higher mortality and graft failure[36]. As demonstrated by Meier-Kriesche et al[37] in 51,927 KTRs. On the other hand, not all authors confirmed these results[38-39]. It has to be underlined that weight frequently increases during post-transplantation period, as reported by Fernandes et al[40] who described higher BMI values, weight gain, prevalence of abdominal obesity and diabetes mellitus in women than men. Also, hypertension and alteration of glycemic control were higher in pediatric obese KTRs[41].

This study has some limitations. First, it is a single-center observational cohort study enrolling a limited number of patients, with a few number of events, and all patients had been followed-up in a single nephrology clinic. We did not take into account therapy, in particular, immunosuppressive therapy, that could impact on weight and CVD risk factors. Also, we did not take into consideration any inflammatory biomarker, whereas it has been reported that in KTRs increasing BMI could be positively related to high levels of high C-reactive protein and interleukin-6, two biomarkers independently associated with MCEs[42]. Moreover, increasing BMI has been associated with secretion of adipokines, adiponectin, leptin, matrix metalloproteinases (in particular matrix metalloproteinases-2), tumor necrosis factor-α and resistin[43-45]. Finally, we did not differentiate KTRs from deceased and living donors; it was reported that prevalence of MCEs was higher in patients receiving a kidney from deceased donors than in those receiving a graft from living ones[10].

Conclusions

Our study suggests that a simple evaluation during clinic visits could identify KTRs at high risk for MCEs. Obesity should be taken into account by physicians, in fact, simple action such as nutritional interventions and lifestyle modification could favor weight reduction, amelioration of lipid profile and glucose tolerance and improving cardiovascular performance[46-47]. These simple actions do not need any pharmacologic intervention, and the improved metabolic profile could ameliorate outcome not only by reducing CVD risk but also by improving graft function[48-49].

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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