META-ANALYSIS

Effects of metabolic syndrome on kidney transplantation outcomes: a systematic review and meta-analysis

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SUMMARY

Metabolic syndrome (MS) has been associated with proteinuria and reduced glomerular filtration rate. Immunosuppressive agents increase the incidence of traditional risk factors for cardiovascular disease (CVD) and have known effects on MS components after kidney transplantation. The purpose of this meta-analysis was to evaluate the impact of MS on relevant outcomes after kidney transplantation. MEDLINE, EMBASE, and Cochrane Library were searched up to November 7, 2015. Papers that compared patients with and without MS and assessed one of the following outcomes, graft loss, death by cardiovascular disease, and all-cause mortality, were included. Of 585 studies identified, five studies including 1269 patients were evaluated. MS was identified as a risk factor for graft loss [relative risk, 3.06; 95% confidence interval (CI), 2.17, 4.32; I^2 = 0%; P heterogeneity = 0.72] and death by CVD (relative risk, 3.53; 95% CI, 1.27, 9.85; I^2 = 0%; P heterogeneity = 0.40). Results on the association between MS and all-cause mortality were inconclusive (relative risk, 2.61; 95% CI, 0.70, 9.81; I^2 = 58%; P heterogeneity = 0.09). Graft loss and death by CVD were associated with the presence of MS after transplantation. Randomized clinical trials should be conducted to define whether interventions on each MS component would result in better outcomes after transplantation.

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Introduction

Kidney transplantation provides best survival compared to other forms of renal replacement treatments (RRT) [1]. This therapy is also the most cost-effective for a significant portion of patients with end-stage renal disease (ESRD) [2–4]. Although long-term allograft and patient survival after kidney transplant have improved over the past decades, cardiovascular disease (CVD) still importantly limits patient survival and death with a

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functioning graft, mainly by CVD, remains the leading cause of late renal allograft loss [5–9].

Metabolic syndrome (MS) is defined by clinical dysfunctions and biochemical abnormalities, which include obesity, hypertension, dyslipidemia, and impaired glucose metabolism [10,11]. MS results of a complex association among different environmental, genetic, and metabolic factors interconnected by energy homeostasis pathways [12,13] and is a well-defined risk factor for CVD and mortality. Moreover, it has been associated with proteinuria and reduced glomerular filtration rate (GFR) [14,15], suggesting a link with chronic kidney disease (CKD). Diabetes mellitus (DM), CVD, and proteinuria are all often observed after renal transplantation, and recently, MS has attracted a great deal of interest in the kidney transplant setting [16–19].

The prevalence of MS after kidney transplantation has varied between 20% and 65%, probably reflecting differences in study populations and perhaps in diagnostic criteria [20–24]. Even though the individual elements of MS, mainly hypertension and obesity, also have a negative effect on kidney transplant outcomes [23–27], it is not clear whether the MS is a better predictor of outcomes then its individual components [28].

Currently, employed immunosuppressive agents are associated with increment in the incidence and severity of traditional cardiovascular risk factors, mainly obesity, hypertension, diabetes mellitus, and dyslipidemia. Moreover, in kidney transplant recipients, the MS has been shown to be associated with CVD and post-transplant diabetes mellitus (PTDM), deteriorating graft function and graft loss [16,17,19].

The assessment of prevalence and the impact of MS on relevant outcomes after renal transplantation may provide useful information regarding the syndrome and the management of its risk factors in renal transplant recipients. We therefore performed a systematic review and meta-analysis to evaluate the impact of the MS after kidney transplantation on renal graft loss, cardiovascular mortality, and mortality by all causes.

Materials and methods

Search strategy and study selection

Papers were identified using Medical Subject Heading (MeSH) terms and searching MEDLINE (accessed by PubMed), EMBASE and Cochrane Library, gray literature, and hand searching (through reference lists of obtained articles) up to November 7, 2015. The Medline strategy is presented on Appendix S1. All retrieved papers were evaluated regardless its language. This systematic review and meta-analysis is described according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [29].

Eligibility criteria

We included observational studies that evaluated the association between MS after kidney transplantation with one or more of the following outcomes: graft loss, cardiovascular death, and death by all causes. MS was defined based on *National Cholesterol Education Program/Adult Treatment Panel* III (NCEP/ATPII) [10], International Diabetes Federation (IDF) [30], or World Health Organization (WHO) criteria [31].

Articles were excluded when other organ transplants recipients besides kidney transplant (i.e., pancreas, liver, heart, or multi-organ transplant recipients) were analyzed, as well as those reporting outcomes in the pediatric population. Replicated data and articles using database populations were not considered, as these databases may share patients that have already been assessed original reports.

Data extraction

Titles and abstracts of retrieved studies were separately assessed by two researchers (E.F.P. and C.C). Neither of them was blinded to article journals, institutions, and authors. Abstracts with scantly information concerning the eligibility criteria were retrieved for full-text evaluation. Data extraction was performed separately by the reviewers. In case of persistent doubt or possible contrariety, a third reviewer assessed the paper (G.C.S).

The following data were collected: author's name, year of publication, sample size, study design, MS prevalence before and after transplantation, follow-up since kidney transplantation until MS diagnoses and to evaluation of outcomes. Demographic and transplant related variables were also extracted: age, gender, ethnicity, primary kidney disease, weight, abdominal circumference, body mass index (BMI), blood pressure, time on dialysis, smoking status, retransplantation, donor type (living or deceased), immunosuppressive therapy, cold ischemia time, panel-reactive antibodies, human leukocyte antigen (HLA) mismatches, glucose level, total cholesterol, high-density lipoprotein cholesterol (HDL-c), triglycerides (TGL), GFR, C-reactive protein (CRP),

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prevalence of pretransplant DM, hypertension, and CVD.

Quality assessment

The Newcastle Quality Assessment Scale for cohort studies was used to identify risk of bias [32]. For the evaluation of comparability, it was observed whether study groups were controlled by the following variables: gender, age, ethnicity, and donor type. A total score of 5 or less was deemed as low; 6 and 7, moderate; and 8 and 9, high level of quality.

Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines [33] were used to assess the quality of evidence for each outcome under consideration. The quality was classified as high, moderate, low, and very low based on limitations of design or implementation (risk of bias), indirectness of evidence, inexplicable heterogeneity, inconsistent results or presence of publication bias.

Data analysis

The relative risk (RR) of post-transplant outcomes was assessed in patients with MS compared to non-MS patients using the REVIEW MANAGER Software version 5.3 (REVIEW MANAGER; REVMAN, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration 2014 available at http://tech.cochrane.org/news/revman-53-beta-now-live). Calculations were performed using Mantel–Haenszel equation. Heterogeneity was identified using the Cochrane Q test, with a threshold P value of 0.1 considered statistically significant, and the inconsistency I^2 test was applied, with values higher than 50% considered indicative of high heterogeneity. The RR with 95% confidence interval (CI) was calculated using the fixed-effects model, and the random effect model was used in case of heterogeneity. Publication bias was assessed using funnel plot analysis, with asymmetry evaluated by Beeg and Eggers tests. A significant publication bias was considered if the P value was less than 0.1. Funnel plot analyses were conducted using STATA software version 11.0 (STATA Inc., College Station, TX, USA). For meta-analysis with significant risk for publication bias, we used trim-and-fill method to evaluate whether it could influence the results [34]. We used Trial Sequential Analysis software (TSA, Copenhagen, Denmark: Copenhagen Trial Unit 2011 available at http://www.ctu.dk/tsa/downloads.aspx) to access the power of the combined sample size in order to minimized β-error.

Results

Literature search and study characteristics

The databases search identified 585 applicable citations that could be included. Initially, 81 duplicated studies were recognized, and excluded from analysis, remaining a total of 504 to be evaluated. Of those, 461 were removed by reading of title and abstract. The remaining 43 studies were chosen for full-text assessment, and only five fulfilled all inclusion and exclusion criteria, providing data on 1269 kidney transplant recipients. The flowchart is shown in Fig. S1.

The main characteristics of the five articles included in the meta-analysis are displayed in Table 1. Several characteristics that were *a priori* selected to be extracted from original articles were not available, they included the following: primary kidney disease, panel-reactive antibodies, total cholesterol, history of dyslipidemia, HLA mismatches, cold ischemia time, hepatitis C virus serology, abdominal circumference, and weight. TGL level was reported in three studies [23,35,36], and HDL-c, pretransplant DM diagnoses, and cytomegalovirus serology in only two studies [35,36].

C-reactive protein levels were referred in two studies [23,25], while immunosuppressive therapy [23], glucose levels [23], and previous CVD [35] were reported in only one article.

Information on abdominal circumference was not available in the majority of the reports; therefore, all included papers in this meta-analysis used the BMI as one of the MS criterion. In addition, all studies used the NCEP/ATP III to define MS [10]. Consequently, MS was defined as any combination of three or more of the following five factors: overweight or obesity (BMI >25 kg/m^2); fasting plasma glucose >110 mmol/l, including pretransplant diabetes or PTDM; hypertension (blood pressure >135/85 mmHg); hypertriglyceridemia (TGL >150 mg/dl), and low HDL-c (<40 mmol/l for men and <50 mmol/l for woman). MS diagnoses were assessed 12 months after kidney transplantation.

In agreement with the Newcastle Quality Assessment Scale for cohort studies [32], all the studies evaluated were classified as articles with a high-quality level (see quality scores for each domain in Table S1), considering that two studies [23,37] scored 9 points and the other 3 [25,35,36] scored 8 points, indicating a low risk of bias. Considering that this systematic review includes only observational studies, the overall GRADE quality rating [33] has to be considered very low.

Table 1. Main Characteristics.

Study, year (reference)	Post-transplant MS prevalence (%)	Groups	Patients, *n*	Ethnicity, (%) Caucasian	Age, years mean ± SD	Men (%)	Deceased donor (%)	Re-tx (%)	Dialysis duration (months)	BMI, kg/m^2 mean ± SD	Smoking status (%)	Hypertension (%)
Courivaud *et al.* (2007) [35]	32	MS	12	NA	50 ± 9	67	NA	NA	NA	24.6 ± 4.6	23	99
		Non-MS	229		43 ± 11							76
Ducloux *et al.* (2005) [36]	32	MS	93	NA	45 ± 13	67	NA	NA	NA	24.4 ± 4.4	22.3	72
		Non-MS	199									
Faenza *et al.* (2007) [25]	16.7	MS	50	NA	43.5 ± 10.9	68	100	NA	31.2 ± 2.4	NA	NA	61
		Non-MS	248		44.7 ± 13.3	62.9			36 ± 3.48			
Ozdemir *et al.* (2009) [37]	28.6	MS	32	NA	29.1 ± 8.9	NA	NA	NA	32.9 ± 8.87	22 ± 3.0	69.7	NA
		Non-MS	80		30.9 ± 9.1	NA			30.9 ± 9.14	22 ± 3.5	20	
Porrini *et al.* (2006) [23]	22.6	MS	52	NA	52 ± 11	71.2	100	NA	22.5 ± 2.0	32 ± 4.2	NA	NA
		Non-MS	178		43 ± 13	70.0			24.5 ± 2.4	26.1 ± 5.2		

Ref, reference; SD, standard deviation; BMI, body mass index; Re-tx, retransplantation; non-MS, presence of metabolic syndrome; non-MS, absence of metabolic syndrome; NA, not available.

Metabolic syndrome and kidney transplant outcomes

Graft loss

A total of four studies assessed graft loss, including 932 kidney transplant recipients. MS was associated with an increased risk of graft loss (RR: 3.06; 95% CI: 2.17–4.32; I^2 = 0%; P heterogeneity = 0.72) (Fig. 1a).

Death by cardiovascular disease

Three studies evaluated cardiovascular death, accounting for 865 patients. No heterogeneity was observed, and an association between MS after kidney transplantation and death by cardiovascular disease was found (RR: 3.53; 95% CI: 1.27–9.85; I^2 = 0%; P heterogeneity = 0.40) as it is shown in Fig. 1b.

All-cause mortality

Three studies assessed all-cause mortality, with a total of 865 subjects included. A statistically significant association between MS post-transplantation and this outcome could not be found (RR: 2.61; 95% CI: 0.70–9.81; I^2 = 58%; P heterogeneity = 0.09) (Fig. 1c).

Publication bias

Contour-enhanced funnel plots and Egger regression test revealed no publication bias for graft loss (P = 0.268) and cardiovascular death (P = 0.613). All-cause mortality revealed a borderline significance of publication bias (P = 0.067). However, it did not influence the results based on trim-and-fill analysis. The funnel plot for each meta-analysis is available in Fig. S2.

Trial sequential analyses

Trial sequential analysis software was utilized to evaluate sample size and its relationship with outcomes. The sample size obtained in this meta-analysis has a power higher than 99% for the evaluation of graft loss. A power of 60% was reached for the outcome death by CVD, and the sample was clearly underpowered for the analysis of all-cause mortality, in which a power of 30% was obtained, considering an incidence of 4% in the control group, heterogeneity = 58%, and assuming α = 0.05.

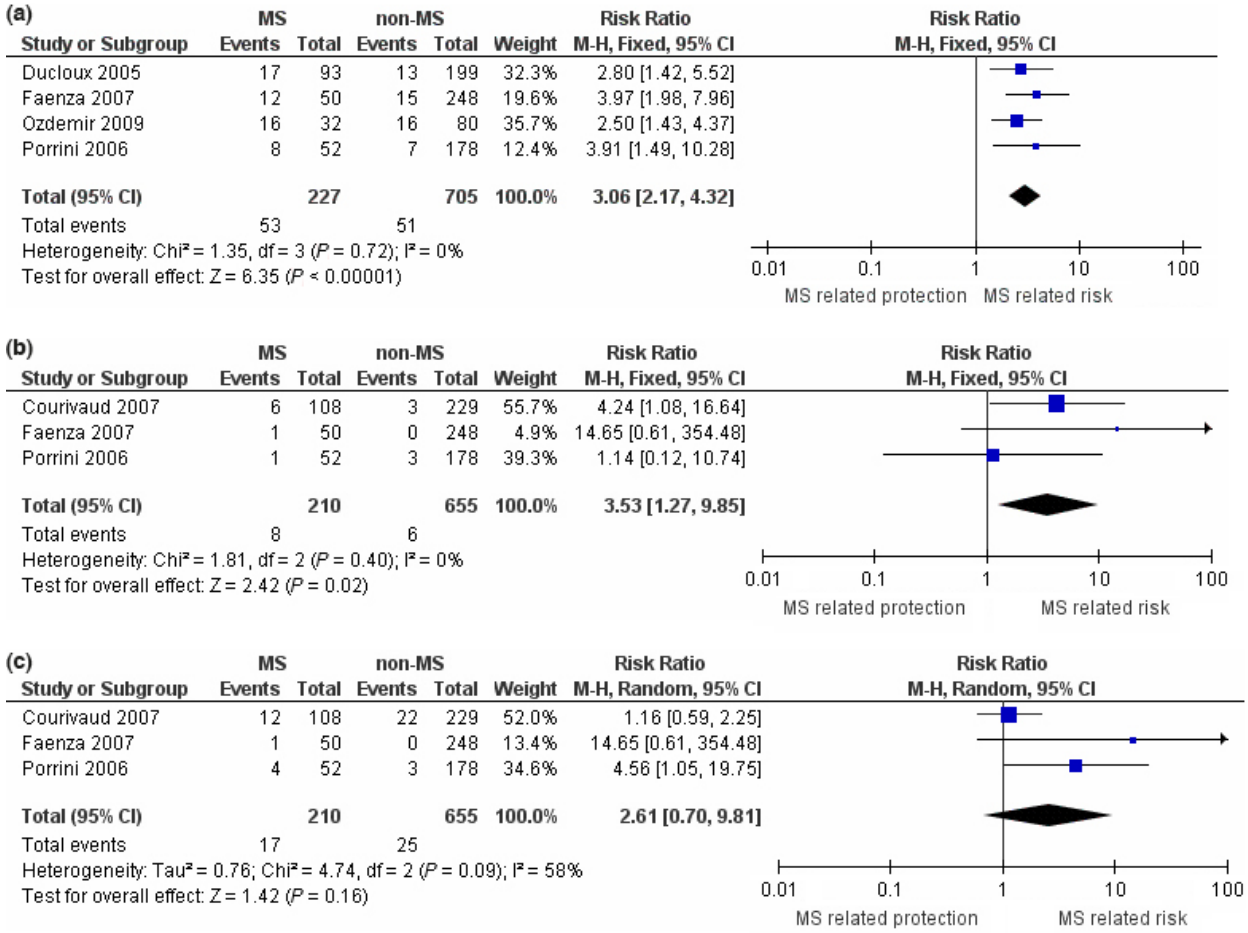

Figure 1 Forest plot graphic showing the associations between metabolic syndrome and graft loss (a), death from cardiovascular causes (b), and all-cause mortality (c).

Discussion

In the present systematic review and meta-analysis, we demonstrated in kidney transplant recipients that the presence of MS is associated with graft loss and death by CVD. However, data regarding the association between all-cause mortality after kidney transplantation and MS were inconclusive due to the small number of studies and patients included in this analysis.

The mechanisms involved in loss of renal graft function in patients with MS remain to be elucidated [25,38]. Different hypothesis have been proposed in addition to immunologic factors leading to long-term renal function impairment. Nonimmunologic factors such as hypertension, dyslipidemia, diabetes, and obesity, all components of MS, have being described as playing a role in graft function deterioration [39,42]. The better understanding of this situations physiopathology will most probably rely on developing appropriate experimental models that can reproduce this clinical situation.

Appetite increases after kidney transplantation as a consequence of uremia correction and corticosteroids use, which frequently promotes weight gain, and may at times lead to obesity [16]. Importantly, this weight gain seems to be related to decreased patient and graft survival [43,44]. Also, obesity promotes a pro-inflammatory state that may be detrimental to the renal graft function [45]. It has being found that the plasmatic concentrations of proinflammatory adipokines, such as tumor necrosis factor alpha (TNF-α), are elevated in patients with MS [46,47]. TNF-α has been shown to be involved in inflammation and scaring in a crescentic glomerulonephritis experimental model [48]. Macrophage infiltration and upregulation of inflammatory cytokines that may be toxic to renal epithelial, mesangial, and endothelial cells have been shown in this model [48,49]. Nevertheless, a specific

role of TNF-α in MS-induced renal injury has not been well demonstrated [38]. Besides, it is conceivable that inflammation in association with other obesity-related factors such as excess excretory load, renal sodium retention, hyperinsulinemia, and insulin resistance may contribute to renal dysfunction and deterioration [46–48].

According to our results, death from CVD is associated with MS diagnosed after transplantation, with no heterogeneity observed. Traditional risk factors for CVD, namely DM, hypertension, and dyslipidemia, are more frequently found in the kidney transplant population than in the general population and are all components of MS [50]. Other risk factors may apply particularly to this population such as systemic inflammation, use of immunosuppressive agents, graft function, frequent infections, and perhaps graft rejection [51,52].

Interestingly, one of the studies included in this meta-analysis [25] observed that in kidney transplant recipients the aggregation of MS features was associated with increased incidence of cardiovascular events. In such study, the presence of only 1 MS factor leads to a 2% incidence of cardiovascular events, while in patients with two factors, the percentage increased to 17.1%; with three factors, to 25%; and finally with four factors, 33.3% of incidence. Moreover, another study [28] demonstrated that MS could be considered a better predictor to estimate measured glomerular filtration rate decline in kidney transplant recipients than its individual components.

In the general population, controversy remains over the concept of MS, and the question about whether the syndrome is more than the simple aggregation of cardiovascular risk factors has been discussed in several studies. A meta-analysis that assessed 37 studies (including 43 cohorts and 172 573 patients) concludes that subjects with MS are at increased risk for cardiovascular events, even after adjustments for cardiovascular risk factors [53], which reinforces the idea that MS confers a higher risk than the summation of individual risk factors.

The strength of this analysis relies on the utilization of TSA to estimate sample power for each of the evaluated outcomes. TSA is an accepted tool to verify whether the available information derived from individual studies is enough to support firm conclusions regarding the association between two variables [52,53], in our case, the MS and post-transplant outcomes. Therefore, it is possible to minimize β-error when handling with negative results. In this context, TSA found a power higher than 99% when evaluating kidney graft loss, which guaranties the accuracy of this association, and further studies are no longer required for this particular outcome. The power for death from CVD was of 60%, but TSA harm boundary was reached, meaning that the association is strong enough to assure that the inclusion of more studies/patients would not alter the results.

However, the association between MS after kidney transplantation and all-cause mortality was inconclusive. Notably, this outcome showed both heterogeneity and the possibility of small study bias. We also verified that the data extracted for all-cause mortality do not have enough power (30% according TSA) to draw firm conclusions. Further analyses will be required to clarify this possible association as more data became available.

This systematic review and meta-analysis have some limitations. All the studies evaluated MS through BMI and not abdominal circumference, which is a better variable to characterize central obesity. Furthermore, several studies did not report relevant data regarding population characteristics that could perhaps better explain some findings. Small study bias was only suggested by Egger's test for all-cause mortality, but the trim-and-fill analysis showed no interference in the results. However, funnel plot evaluations must be interpreted with caution when few studies are available [54], so we may not securely exclude the possibility of publication bias in this aspect of the meta-analysis.

In conclusion, our results have shown that graft loss and death by CVD are associated with MS diagnoses after kidney transplantation. Larger studies should be designed to elucidate its association with all-cause mortality, as the combined sample size from the available studies still lacks power to the analysis of this outcome. Lastly, prospective randomized clinical trials should be conducted to define whether interventions on each MS component would result in better outcomes after kidney transplant.

Authorship

EFP and BBN: Participated in the conception, design, and interpretation of data; drafting and revising the article; providing intellectual content of critical importance to the work; final approval of the version to be published. CC: Participated in the design and interpretation of data; providing intellectual content of critical importance to the work; final approval of the version to be published. RCM: Participated in the conception and interpretation of data; drafting and revising the article; providing intellectual content of critical importance to the work; final approval of the version to be published.

CBL: Participated in the design and interpretation of data; drafting and revising the article; providing intellectual content of critical importance to the work; final approval of the version to be published. GCS: Participated in the interpretation of data; drafting and revising the article; providing intellectual content of critical importance to the work; final approval of the version to be published. LFSG: Participated in the interpretation of data; providing intellectual content of critical importance to the work; final approval of the version to be published.

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Conflict of interest

The authors have no conflict of interests to declare. The results presented in this study have not been published previously in whole or part, except in abstract form.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Medline search strategy.

Figure S1. Flowchart: identification and selection of articles included in the meta-analysis.

Figure S2. Meta-analyses funnel plots.

Table S1. Quality scoring based on the Newcastle-Ottawa Quality Assessment Scale.

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