UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

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ELIS FORCELLINI PEDROLLO

Impacto da Síndrome Metabólica em Desfechos do Transplante Renal

Revisão Sistemática e Metanálise

Porto Alegre

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Dissertação apresentada ao Programa de Pós-Graduação em Medicina, Ciências Médicas, UFRGS, como requisito para a obtenção do título de Mestre.

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DEDICATÓRIA

Aos meus pais, pelo amor incondicional e apoio incansável.

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“Protect your kidneys, save your heart”

World Kidney Day 2011

RESUMO

Introdução: A Síndrome Metabólica (SM) tem sido associada à proteinúria a redução da taxa de filtração glomerular. Em transplantados renais a imunossupressão aumenta a incidência de fatores de risco cardiovasculares, predispondo à síndrome. O objetivo dessa revisão sistemática e metanálise é buscar informações precisas, visando esclarecer qual o impacto da SM no pós- transplante. **Métodos:** Estratégias de buscas foram utilizadas no MEDLINE, no EMBASE e na Cochrane Library até o dia 4 de Outubro de 2014. Foram selecionados estudos que compararam indivíduos com e sem SM, submetidos a transplante renal e que avaliaram os seguintes desfechos: perda de enxerto, eventos cardiovasculares (ECV), morte por doença cardiovascular (DCV) e morte por todas as causas. Dois revisores independentes extraíram os dados e avaliaram a qualidade dos estudos. **Resultados:** Dos 585 estudos inicialmente identificados, 5 foram selecionados, incluindo um total de 1269 pacientes. A SM mostrou-se associada à perda de enxerto (risco relativo, 3,02; intervalo de confiança (IC) 95%,2,17-4.32; I^2=0%; P heterogeneidade= 1,35), ECV (risco relativo, 3,53; IC95%, 1,27-9.85; I^2= 0%; P heterogeneidade= 1,81) e morte por DCV (risco relativo, 2,61; IC 95%, 0,70-9,81; I^2=58%; P heterogeneidade= 0.76). Não foi encontrada associação entre a SM e morte por todas as causas. **Conclusão:** Encontrou-se associação entre perda de enxerto, ECV e morte por DCV com o diagnostico de SM após transplante renal. Estudos com maior tamanho amostral e poder devem ser realizados para que se possa avaliar a possível associação entre mortalidade por todas as causas e SM após o transplante renal. Há necessidade de estudos clínicos randomizados a fim de verificar se intervenções em cada componente da síndrome resultariam em melhores desfechos após o transplante renal.

Palavras chave: Síndrome metabólica, transplante renal, revisão sistemática e metanálise.

ABSTRACT

Background: Metabolic syndrome (MS) has been associated with proteinuria and reduced glomerular filtration rate. Immunosuppressive agents increase the incidence of traditional cardiovascular risk factors and thus have expected effects on components of MS after transplantation. The purpose of this systematic review and meta-analysis is provide valid information regarding the syndrome and clarify this question. **Methods:** MEDLINE, EMBASE and Cochrane Library were searched up to October 4, 2014. Papers that compared MS and non-MS patients who underwent renal transplantation and assessed one of the following outcomes: graft loss, cardiovascular events (CVE), death by cardiovascular disease (CVD) and all-cause-mortality were included. Two independent reviewers summarized the data and evaluated the quality of the articles. **Results:** From 585 studies identified, 5 were included (1269 patients). MS was related to graft loss (relative risk, 3.02; 95% confidence interval, 2.17-4.32; I^2= 0%; P heterogeneity= 1.35), CVE (relative risk, 3.53; 95% confidence interval, 1.27-9.85; I^2= 0%; P heterogeneity= 1.81) and death by CVD (relative risk, 2.61; 95% CI, 0,70-9,81; I^2=58%; P heterogeneity= 0.76). No association was found between MS and all cause-mortality. **Conclusion:** Graft loss, CVE and death by CVD were associated with the MS diagnoses after kidney transplantation. Larger studies should be design to elucidate its association with mortality by all-causes, since the combined sample size from the available studies still lack power. Lastly, prospective randomized clinical trials should be conducted in order to define if interventions on each MS component would result in better outcomes after kidney transplantation.

Keywords: Metabolic syndrome, kidney transplantation, systematic review and meta-analysis.

LISTA DE FIGURAS

LISTA DE TABELAS

LISTA DE ABREVIATURAS

ABTO	Associação Brasileira de Transplante de Órgãos
ADA	Associação Americana de Diabetes
CA	Circunferência Abdominal
DCV	Doenças Cardiovasculares
DM	Diabetes Melito
DMPT	Diabetes Melito Pós-Transplante Renal
DM 2	Diabetes Melito tipo 2
DP	Diálise Peritoneal
EASD	Associação Europeia para o Estudo do Diabetes
ECV	Eventos Cardiovasculares
ECR	Ensaios Clínicos Randomizados
HAS	Hipertensão Arterial Sistêmica
HD	Hemodiálise
HDL	High Density Lipoprotein
HLA	Antígenos leucocitários humanos
IDF	Federação Internacional de Diabetes
IL-6	Interleucina 6
IMC	Índice de Massa Corporal
JNC VIII	Joint National Committee on Prevention, Detection and Evaluation of High Blood Pressure
NCEP/ATPIII	National Cholesterol Education Program (Adult Treatment Panel III)
OMS	Organização Mundial da Saúde
PA	Pressão Arterial
PAD	Pressão Arterial Diastólica

PAS	Pressão Arterial Sistólica
RA	Rejeição Aguda
RCQ	Relação Cintura Quadril
RI	Resistência à insulina
SM	Síndrome Metabólica
SNS	Sistema Nervoso Simpático
SRA	Sistema Renina-Angiotensina
TFG	Taxa de Filtração Glomerular
TGL	Triglicerídeos
TNF-α	Fator de Necrose Tumoral Alfa

SUMÁRIO

1 Introdução

O transplante renal é o tratamento com melhor custo-eficácia para pacientes com doença renal em estágio terminal (1). Além disso, é considerado o tratamento de substituição renal que proporciona melhor qualidade de vida para esses pacientes em comparação com outros métodos de substituição renal, como a hemodiálise (HD) e a diálise peritoneal (DP) (2).

Nas últimas décadas tem sido evidenciada a melhora na sobrevida do enxerto e do paciente entre os receptores de transplante renal (3, 4). A terapia imunossupressora, principalmente os inibidores da calcineurina (ciclosporina e tacrolimus) são os responsáveis - parcialmente - pela sobrevida desses pacientes e pela redução do uso de corticosteroides. Contudo, essa mesma imunossupressão, tão necessária para a manutenção do enxerto renal, desencadeia uma série de efeitos colaterais que devem ser considerados (5). Muito frequentemente se observa no paciente transplantado episódios de rejeição, perda precoce, nefropatia crônica do enxerto, hipertensão arterial sistêmica (HAS), dislipidemias, desenvolvimento de Diabetes Melito (DM) e eventos cardiovasculares (ECV), os quais estão relacionados com a redução da sobrevida do enxerto e do próprio paciente (6-8).

A Síndrome Metabólica (SM), que é um agrupamento de anormalidades bioquímicas e clínicas, tais como a obesidade abdominal, dislipidemia, HAS e o metabolismo da glicose comprometido, tem sua causa - em parte - relacionada ao uso da terapia imunossupressora no pós-transplante (9-11). Sua prevalência na população geral tem aumentado de maneira significativa e mais recentemente, tem sido observado que a SM é comum, também, no pós-transplante renal, apresentando uma alta prevalência (12-14). Muito embora a definição e a

patogênese dessa síndrome ainda estejam sob questionamentos, a SM tornou-se um problema de saúde pública relevante, tendo em vista o seu impacto sobre as doenças cardiovasculares (DCV) (15, 16). A SM aumenta o risco de disfunção crônica do enxerto e o desenvolvimento de DCV, que é a principal causa de óbitos em transplantados renais (15-17).

Com base nas atuais evidências acerca da relevância da SM na sobrevida do paciente e do enxerto, faz-se importante verificar a associação da SM como fator de risco para desfechos negativos no pós-transplante renal.

2 Revisão da Literatura

2.1 Transplante Renal

Dados da Associação Brasileira de Transplante de Órgãos (ABTO) registraram que no ano de 2013, dos 7.649 transplantes realizados no país, 71% foram de rim (18), sendo que o Brasil é o segundo país que mais realiza transplantes renais no mundo (em número absoluto de transplantes), ficando apenas atrás dos Estados Unidos. De janeiro a setembro de 2014, dos 5.900 transplantes realizados no Brasil, 4.221 foram transplantes renais (19).

A taxa de mortalidade em longo prazo é menor em receptores de transplante do que para aqueles que permanecem na lista de espera ou mesmo em diálise (20). Um estudo com 46.164 pacientes na lista de espera para transplante nos EUA relatou que pacientes transplantados na faixa etária de 20 a 39 anos, de ambos os sexos, tinham uma sobrevida de 17 anos a mais do que aqueles que permaneciam na lista (21).

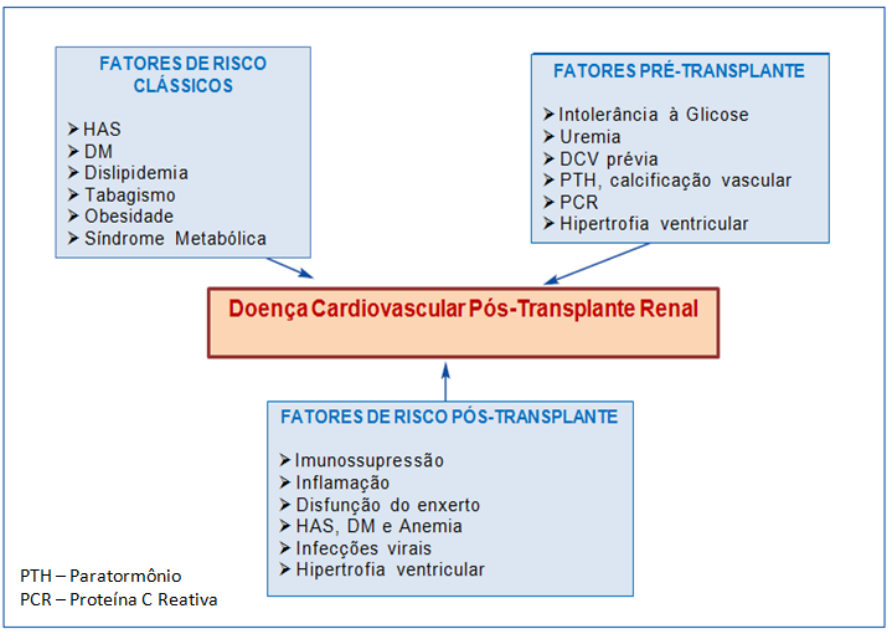
A terapia imunossupressora, especialmente os glicocorticóides e os inibidores de calcineurina, como ciclosporina e tacrolimus, são utilizados na prevenção e tratamento da rejeição aguda (RA) e de outros desfechos clínicos desfavoráveis (22). Essa imunossupressão, no entanto, pode ser responsável por reações adversas, que podem impactar na morbidade e mortalidade dos pacientes transplantados (23). Nos últimos 20 anos, a melhor compreensão acerca da terapia combinada de drogas imunossupressoras, aliada à melhora na preservação dos órgãos e compatibilidade imunológica, bem como a profilaxia para infecções oportunistas tem contribuído para os melhores resultados obtidos no transplante

renal (24). Em consequência, houve um aumento significativo nas taxas de sobrevida de pacientes e de enxertos. A sobrevida após o transplante varia de 82% em cinco anos para receptores de rim de doadores falecidos a 91,6% para pacientes transplantados com rins de doadores vivos com antígenos leucocitários humanos (HLA) idênticos (3, 4).

Muito embora tenha sido a partir do uso da terapia imunossupressora mais seletiva e efetiva, que se obteve uma melhora considerável no que diz respeito à sobrevida dos pacientes e dos enxertos renais, sabe-se que em longo prazo, os resultados podem levar à consequências insatisfatórias e a maioria é ocasionada por doença crônica do enxerto (nefrotoxidade e rejeição crônica) e óbito com enxerto funcionante (25, 26).

A mortalidade por DCV está fortemente relacionada à doença renal em seus diferentes estágios, envolvendo uma série de fatores de risco (figura 1). Sabe-se que durante o período em que o paciente está sob o tratamento de HD, o risco para o desenvolvimento de DCV é de 10 a 20 vezes superior ao da população em geral (27). Já para o paciente transplantado, o risco passa a ser inferior ao que se tinha no tratamento dialítico. Apesar disso, o risco de DCV é significativamente maior quando comparado ao da população em geral (28), principalmente em pacientes com idade entre 25 – 55 anos. Dados recentes registram que complicações cardíacas são causas prevalentes (18 a 30%) de óbitos em pacientes transplantados (29, 30). Conforme registros atualizados do Reino Unido, ECV combinados com doenças cerebrovasculares representam 22,9% das causas de morte dos pacientes transplantados, se sobrepondo aos 21,6% de mortes causadas por infecções (31).

Figura 1. Transplante Renal e DCV

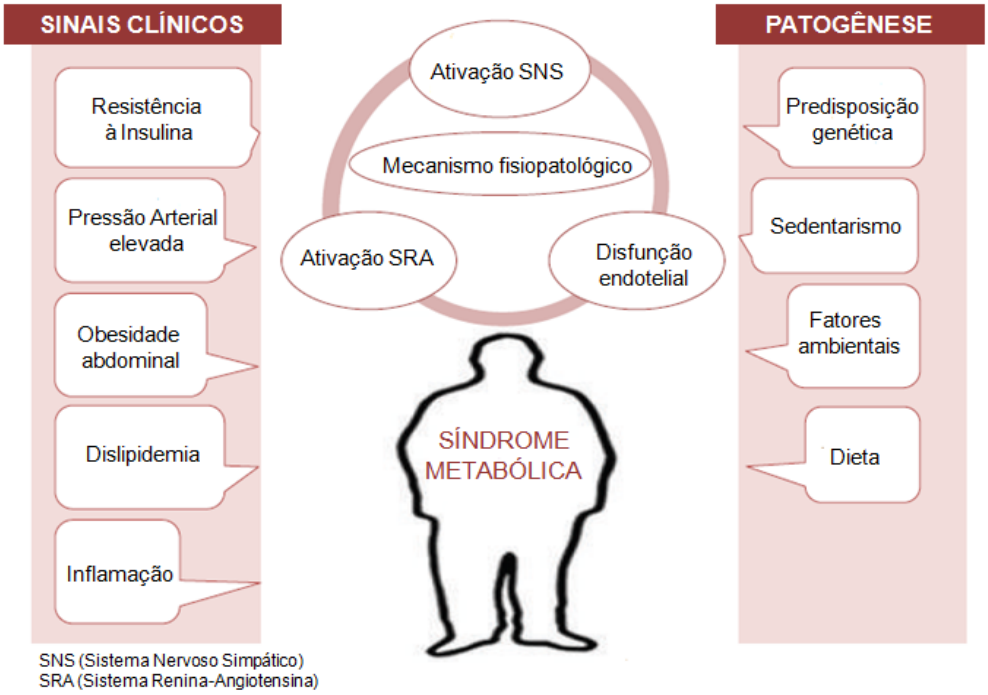


Fonte: Adaptado de Moreso *et al*. 2013 (25).

2.2 Síndrome Metabólica

A SM, também denominada Síndrome X, como inicialmente foi proposta por Gerald M. Reaven, em 1988 (32), é um agrupamento de fatores de risco cardiovasculares já bem estabelecidos, tais como a obesidade, a HAS, a dislipidemia e o comprometimento do metabolismo da glicose (33). Essa síndrome representa uma complexa interação entre fatores genéticos e ambientais que estão intrinsecamente relacionados através das vias de homeostase energética (Figura 2). Dentre esse aglomerado de anormalidades bioquímicas que a compõe, a obesidade é considerada a principal característica do fenótipo de um indivíduo que apresenta SM, pois contribui para o desenvolvimento da RI, hiperinsulinemia e dislipidemia (13, 34).

Figura 2. Sinais clínicos e patogênese da SM



Fonte: Adaptado de Canale *et al*, 2014 (35).

No passado, a SM foi descrita como um instrumento útil na prevenção de DCV e DM no pós-operatório (36). Em 10 anos, mais de 1.000 estudos sobre o tema surgiram na literatura, apesar da discussão provocada por uma publicação da Associação Americana de Diabetes (ADA) e pela Associação Europeia para o estudo de Diabetes (AEED), na qual sugeriam que a SM havia sido amplamente impulsionada pela indústria, sendo assim embasada em interesses meramente comerciais (37). Em contrapartida, a Federação Internacional de Diabetes (IDF) afirmou que a síndrome em questão atende a um propósito útil, que se atém aos interesses do indivíduo, da comunidade e do âmbito clínico daqueles que apresentam risco aumentado para o desenvolvimento de DCV e Diabete Melito tipo 2 (DM 2) (38). O fato de não se ter uma padronização na sua definição, acarreta dificuldades na comparabilidade de diferentes estudos (39).

2.2.1 Critérios diagnósticos da Síndrome Metabólica

A IDF considera que a SM deve ser diagnosticada quando o indivíduo apresentar obesidade central associada a dois fatores adicionais. Já para a Organização Mundial da Saúde (OMS), o comprometimento do metabolismo da glicose com a RI aumentada, somado a outros dois fatores define a síndrome (40).

Dentre as diferentes definições, a mais utilizada é a proposta pela *National Cholesterol Education Program (Adult Treatment Panel III)* – (NCEP/ ATP III). Esse critério diagnóstico simplesmente define SM como a presença de três ou mais fatores de risco, evitando, dessa maneira, que um dos fatores da síndrome passe a assumir uma posição central e se sobreponha aos demais (9) (Tabela 1).

Tabela 1. Diferentes Classifiações da síndrome metabólica

	OMS	IDF	NCEP/ ATPIII
Obesidade	Relação cintura/quadril > 0,9 (homens) > 0,85 (mulheres) ou IMC > 30kg/m²	Circunferência abdominal > 94cm (homens europeus) > 90 cm (homens asiáticos) > 80 (mulheres) ***	Circunferência abdominal >102cm (homens) > 88cm (mulheres)
Glicemia	Diabetes Mellitus, Intolerância glicídica ou Resistência à Insulina comprovada pelo *camp**	>110mg/dl ou DM prévia	>110mg/dl ou DM prévia
TGL	>150mg/dL**	>150mg/dL**	>150mg/dL**
HDL	< 35mg/dL (homens) < 39mg/dL (mulheres)	< 40mg/dL (homens) < 50mg/dL (mulheres) ou tratamento para dislipidemia	< 40mg/dL (homens) < 50mg/dL (mulheres)
Pressão Arterial	Pressão Sistólica > 140mmHg	Pressão Sistólica > 130mmHg ou Pressão Diastólica > 85mmHg ou tratamento para HAS	Pressão Sistólica > 130mmHg ou Pressão Diastólica > 85mmHg
Outros	Excreção urinária de Albumina > 20 mcg ou relação albumina/creatinina > 30mg/g		

*Dois fatores e obrigatoriamente o componente assinalado ** TGL elevados ou HDL baixo constituem um fator pela OMS;
*** Componente obrigatório; ****Presença de três ou mais dos componentes citados.
IDF: International Diabetes Federation; NCEP:National Cholesterol Edication Program; OMS: Organização Mundial da Saúde

2.2.2 Fisiopatologia da Síndrome Metabólica

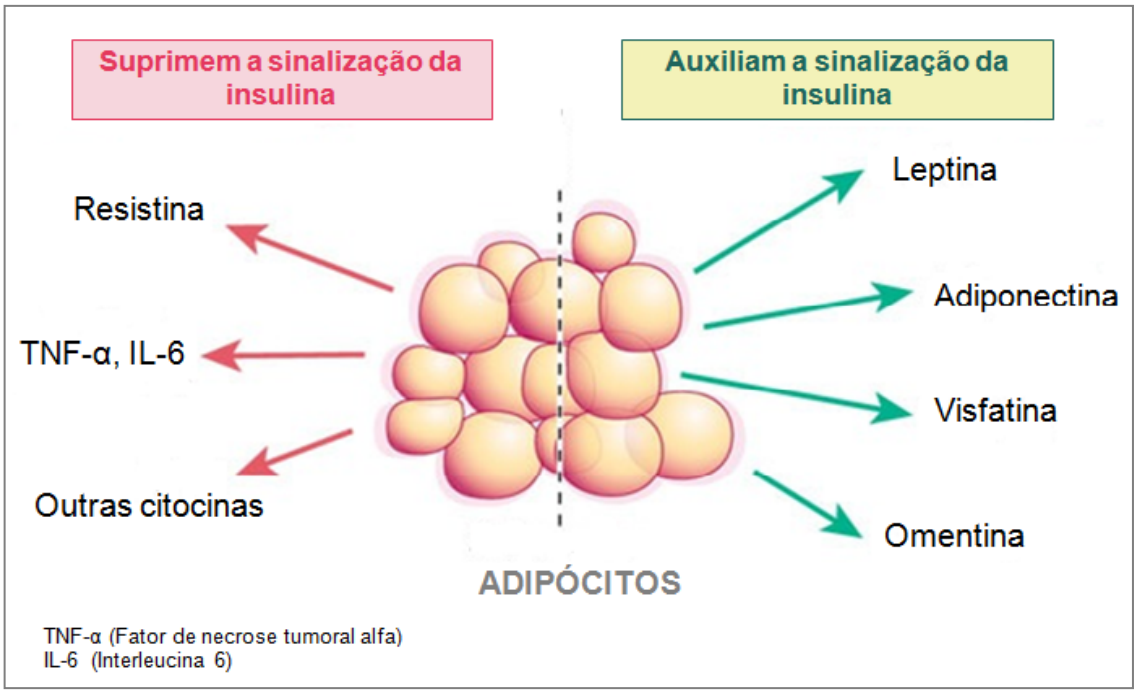
Os mecanismos fisiopatológicos essencialmente vinculados ao desenvolvimento da síndrome são a RI, a atividade aumentada do sistema nervoso simpático (SNS) aliada ao comprometimento da medula adrenal e das funções hormonais do tecido adiposo. A RI é ocasionada tanto pela predisposição genética, quanto pelos fatores ambientais, e na grande maioria dos casos, está relacionada à obesidade (41). Nas últimas décadas, repetidamente tem sido constatado que o processo inflamatório desempenha um papel importante na patogênese da RI (42-44).

Até 1993 supunha-se que o tecido adiposo era mero componente metabólico do organismo, o qual desempenhava um papel de isolante térmico para os órgãos internos e armazenamento de energia em excesso. Sua concepção foi somente remodelada, quando se descobriu que os adipócitos eram responsáveis pela produção do fator de necrose tumoral alfa (TNF-α) (45). Outrossim, desde a descoberta da leptina, o tecido adiposo passa a ser estudado como um órgão dinâmico e maleável, desempenhando funções metabólicas e fundamentalmente secretoras, produzindo uma variedade de mediadores, então designados adipocinas, os quais modulam os processos fisiológicos que caracterizam a SM (46).

Atualmente uma série de adipocinas tem sido identificadas (Figura 3), as quais desempenham uma função complexa no metabolismo e principalmente nos processos fisiopatológicos associados à obesidade (47). A expansão do tecido adiposo e especialmente dos depósitos de gordura visceral, ocasionam a desregulação da secreção dessas adipocinas, que combinadas às citocinas liberadas pelos macrófagos, afetam a sensibilidade da insulina na musculatura

esquelética, no fígado e no próprio tecido adiposo. Dessa forma, embasando-se na hipótese inflamatória da SM, entende-se que esses fatores se responsabilizam pela inflamação de todo o corpo, sendo, por conseguinte, um fator de risco para aterosclerose e DM 2 (48).

Figura 3. Adipocinas e citocinas envolvidas na fisiopatologia da SM

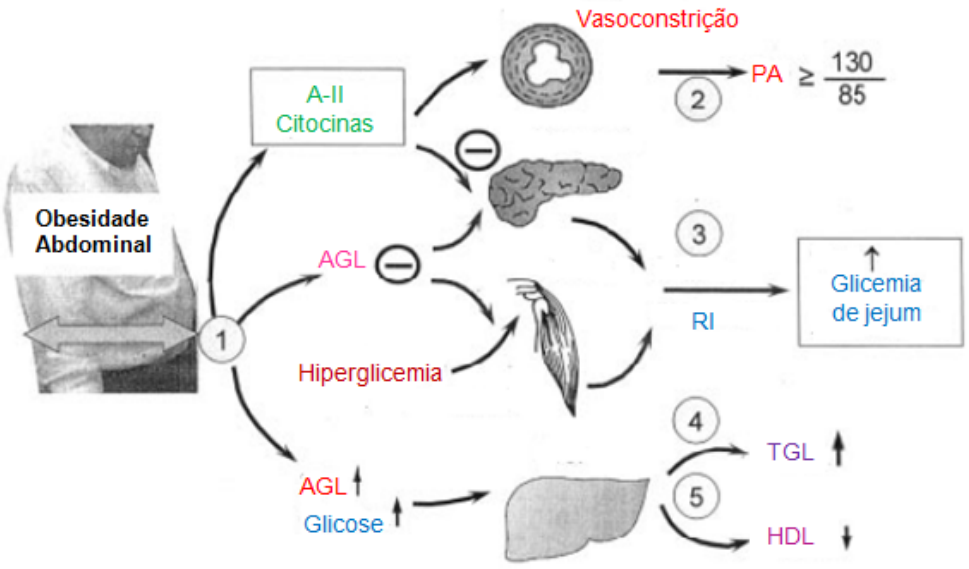


Algumas hipóteses têm sido sugeridas para explicar o porquê da SM poder ser considerada um estado pró-hipertensivo (49). Apesar de ainda ser necessário um maior número de estudos que avaliem a sua fisiopatologia e o papel da interação ambiental e genética, se tem um consenso, quase geral, de que a RI e a obesidade abdominal sejam as principais envolvidas na patogênese da síndrome (9, 33, 50). No entanto, especula-se que o mecanismo inicial da SM seja a promoção da HAS e uma série de processos aterogênicos. Apenas quando o pâncreas está incapacitado de satisfazer a demanda necessária de insulina que ocorre o comprometimento glicêmico. Dessa forma, a hiperglicemia deve ser vista como um estágio mais avançado da perda do controle da homeostase glicídica (33). Além disso, a insulina

é um importante mediador de funções vasodilatadoras. Em pacientes obesos com RI, tais funções são comprometidas ou mesmo revertidas, o que também pode levar ao desenvolvimento de HAS (51, 52).

O excesso de tecido adiposo abdominal, característico da síndrome, está associado a uma maior liberação de ácidos graxos livres, angiotensina II e adipocinas (Figura 4) (53, 54). O aumento da circulação desses ácidos graxos e de angiotensina II pode causar danos ao pâncreas e levar à vasoconstrição (53). Outro fator que também está relacionado ao aumento da PA é a condição inflamatória causada pelo TNF-α e algumas interleucinas, que minimizam a eficácia da insulina.

Figura 4. Hipertensão e Dislipidemia na SM



A-II (Angiotensina II); AGL (Ácidos graxos livres); PA (Pressão arterial); RI (Resistência à insulina) TGL (Triglicerídeos); HDL (High-density lipoprotein-colesterol).

Fonte: Adaptado de Opie *et al*., 2007 (55).

Além do comprometimento da PA, a hiperglicemia e o aumento da circulação de ácidos graxos livres fornecem os substratos necessários para o incremento da produção hepática de triglicerídeos (TGL). A partir desse aumento de TGL

circulantes, as lipoproteínas transportam mais TGL e menos APO (principalmente Apo 1), (Figura 4), o que caracteriza o perfil lipídico de portadores da SM (56).

2.3 Síndrome Metabólica e Transplante Renal

A SM tem sido associada à proteinúria e à redução da taxa de filtração glomerular (TFG), sugerindo uma possível associação com a doença renal crônica (57, 58). Assim sendo, uma vez que o diabetes melito pós-transplante (DMPT) renal, as DCV e a proteinúria são frequentemente observados como complicações no pós-transplante, o estudo da SM em indivíduos transplantados tem despertado considerável interesse (59). Há, portanto, alguns fatores de risco para o desenvolvimento de SM nestes pacientes, os quais devem ser considerados: a terapia imunossupressora, a obesidade, a HAS, e a hiperlipidemia (59).

A imunossupressão aumenta não apenas a incidência, mas também a gravidade de fatores de risco cardiovascular já bem estabelecidos, desempenhando, portanto, um papel fundamental no desenvolvimento da SM nesses pacientes. Os corticosteróides afetam negativamente parâmetros como a PA, o metabolismo lipídico e glicídico, podendo ainda atuar no aumento do apetite, promovendo assim o ganho de peso, que pode levar à obesidade (59). Ensaios clínicos randomizados (ECR) demonstraram melhoras em todos esses parâmetros a partir da retirada de esteróides ou através da imunossupressão isenta dos mesmos (60). Uma metanálise publicada em 2010 com 34 ECR que avaliaram imunossupressão isenta de esteróides foi associada à melhoras na incidência de DMPT, PA e perfil lipídico dos receptores transplante renal (61).

Os inibidores da calcineurina apresentam uma série de efeitos adversos que também devem ser considerados, incluindo a nefrotoxicidade, que pode

indiretamente promover a DCV. A ciclosporina quando comparada ao tacrolimus é mais comumente associada com HAS e dislipidemia. Contudo, o tacrolimus é mais frequentemente relacionado à intolerância à glicose e ao desenvolvimento de DMPT (6). Todavia, já é sabido que com a eliminação completa dos mesmos, o risco da RA se sobrepõe a quaisquer outros benefícios (59). O mesmo ocorre quando se faz a eliminação completa do uso de inibidores da calcineurina, objetivando a melhora de parâmetros metabólicos: observa-se um aumento do risco de rejeição (62-64).

A obesidade, por sua vez, está relacionada a uma série de desfechos negativos no pós-transplante. Dentre os quais, a maior incidência de função tardia do enxerto e a RA. A menor sobrevida do enxerto e do paciente também tem sido descritos (65-68). Além disso, sabe-se que a obesidade pode estar associada à maior incidência de infecções cirúrgicas, contribuindo para um pior prognóstico dos receptores de transplante renal (69). Outra complicação comum no pós-transplante renal é a HAS, que está fortemente relacionada à perda da função renal, à menor sobrevida do enxerto e à morbidade cardiovascular (70). Sua definição é embasada nos critérios do oitavo relatório da Joint National Committee on Prevention, Detection and Evaluationof High Blood Pressure (JNC VIII), a qual determina pressão arterial sistólica (PAS) > 140 mmHg ou pressão arterial diastólica (PAD) > 90mmHg (71). A cada 10 mmHg adicionais na PAS, ocorre um aumentode morte por todas as causas e morte por perda de enxerto, em 18 e 17%, respectivamente (72). Também é considerado fator de risco para o desenvolvimento da SM, a hiperlipidemia. Sabe-se que a hipercolesterolemia e a hipertrigliceridemia apresentam prevalências de 40 a 60%, respectivamente. Além de aumentar o risco para DCV, a hiperlipidemia tem sido associada a uma menor sobrevida do enxerto (73).

Alguns estudos já avaliaram a prevalência e o impacto da síndrome em pacientes transplantados renais. Há registros de que a SM teria uma prevalência de 63% em até 6 anos após o transplante (13). Em contrapartida, outro estudo que incluiu 337 receptores de transplante renal observou uma prevalência de 32% em um ano pós-transplante, concluindo que indivíduos do sexo masculino, com idade avançada e aumento de índice de massa corporal (IMC) mostraram-se como fatores preditivos para o desenvolvimento da SM no ano que sucede o transplante renal (74).

Estudo que avaliou SM pós-transplante renal relatou uma associação positiva entre o número de fatores que compõe a SM e a prevalência de ECV. Em pacientes que apresentavam um único fator, houve 2% de incidência de ECV; já com dois fatores, esse percentual passou para 17,1%; com três, a incidência chegou a 25 %. Por fim, naqueles pacientes que tinham os quatro componentes que designam a síndrome, foi observada a mais alta das incidências, chegando a 33% (39).

O fato dos componentes individuais da SM, especialmente a obesidade e a HAS desempenharem um efeito deletério sobre os desfechos do transplante renal já é bem definido. No entanto, não se sabe ao certo se a síndrome, avaliada como uma entidade, e não a partir dos componentes individuais que a definem, pode mais eficientemente predizer esses desfechos (13, 75, 76). Em um estudo recentemente publicado, sugere-se a validade e superioridade dos modelos que usam a SM comparados aos componentes individuais da síndrome para a avaliação da perda de enxerto (77).

Dessa maneira, torna-se importante o estudo da SM no âmbito do transplante renal. Uma vez bem elucidado o impacto da síndrome sobre desfechos negativos no

pós-transplante, será possível aprimorar o manejo terapêutico nesse sentido, atuando de maneira preventiva a fim de evitar a disfunção crônica do enxerto, melhorando assim a sobrevida do próprio paciente.

3. Objetivos

3.1 Objetivo principal

Realizar uma revisão sistemática e metanálise a fim de identificar o impacto da SM no pós-transplante renal.

3.2 Objetivos secundários

- ✓ Avaliar o impacto da SM com relação à perda de enxerto;
- ✓ Avaliar o impacto da SM com relação a ECV;
- ✓ Avaliar o impacto da SM com relação à morte por DCV;
- ✓ Avaliar o impacto da SM com relação à morte por todas as causas.

4 Referências Bibliográficas da Revisão

1. Jensen CE, Sorensen P, Petersen KD. In Denmark kidney transplantation is more cost-effective than dialysis. Dan Med J. 2014;61(3):A4796.
2. Ogutmen B, Yildirim A, Sever MS, Bozfakioglu S, Ataman R, Erek E, et al. Health-related quality of life after kidney transplantation in comparison intermittent hemodialysis, peritoneal dialysis, and normal controls. Transplant Proc. 2006;38(2):419-21.
3. Serur D, Saal S, Wang J, Sullivan J, Bologa R, Hartono C, et al. Deceased-donor kidney transplantation: improvement in long-term survival. Nephrol Dial Transplant. 2011;26(1):317-24.
4. Narayanan R, Cardella CJ, Cattran DC, Cole EH, Tinckam KJ, Schiff J, et al. Delayed graft function and the risk of death with graft function in living donor kidney transplant recipients. Am J Kidney Dis. 2010;56(5):961-70.
5. Yabu JM, Vincenti F. Kidney transplantation: the ideal immunosuppression regimen. Adv Chronic Kidney Dis. 2009;16(4):226-33.
6. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003;3(2):178-85.
7. Israni AK, Snyder JJ, Skeans MA, Peng Y, Maclean JR, Weinhandl ED, et al. Predicting coronary heart disease after kidney transplantation: Patient Outcomes in Renal Transplantation (PORT) Study. Am J Transplant. 2010;10(2):338-53.
8. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM. Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. Kidney Int. 2002;62(4):1440-6.
9. National Cholesterol Education Program (NCEP) Expert Panel on Detection Ea, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.

10. Oda E. Metabolic syndrome: its history, mechanisms, and limitations. Acta Diabetol. 2012;49(2):89-95.
11. Nedbálková M, Svojanovský J, Trnavský K, Kuman M, Jarkovský J, Karpíšek M, et al. [Metabolic syndrome after kidney transplantation]. Vnitr Lek. 2014;60(3):196-204.
12. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among u.s. Adults. Diabetes Care. 2004;27(10):2444-9.
13. De Vries APJ, Bakker SJL, Van Son WJ, Van Der Heide JJH, Ploeg RJ, The HT, et al. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. American Journal of Transplantation. 2004;4(10):1675-83.
14. Oruc M, Koseoglu K, Seyahi N, Alagoz S, Trabulus S, Altiparmak MR. Progression of metabolic syndrome in renal transplant recipients. Transplantation Proceedings. 2013;45(9):3273-8.
15. Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49(4):403-14.
16. Salminen M, Kuoppamäki M, Vahlberg T, Räihä I, Irjala K, Kivelä SL. Metabolic syndrome and vascular risk: a 9-year follow-up among the aged in Finland. Acta Diabetol. 2011;48(2):157-65.

17. Porrini E, Delgado P, Torres A. Metabolic syndrome, insulin resistance, and chronic allograft dysfunction. Kidney Int Suppl. 2010(119):S42-6.

18. Associação Brasileira de Transplante de Órgãos (ABTO). Registro Brasileiro de Transplantes. Ano XIX, n 4 Jan/Dez 2013

19. Associação Brasileira de Transplante de Órgãos (ABTO). Registro Brasileiro de Transplantes. Ano XX, n 3 Jan/Set 2014

20. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant. 2011;11(10):2093-109.

21. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725-30.

22. Opelz G. Effect of the maintenance immunosuppressive drug regimen on kidney transplant outcome. Transplantation. 1994;58(4):443-6.

23. Rosenberger J, Geckova AM, Dijk JP, Roland R, Heuvel WJ, Groothof F JW. Factors modifying stress from adverse effects of immunosuppressive medication in kidney transplant recipients. Clin Transplant. 2005;19(1):70-6.

24. Garcia GG, Harden P, Chapman J, 2012 WKDSC. The global role of kidney transplantation. Am J Nephrol. 2012;35(3):259-64.

25. Moreso F, Hernández D. Has the survival of the graft improved after renal transplantation in the era of modern immunosuppression? Nefrologia. 2013;33(1):14-26.

26. Weiner DE, Carpenter MA, Levey AS, Ivanova A, Cole EH, Hunsicker L, et al. Kidney function and risk of cardiovascular disease and mortality in kidney transplant recipients: the FAVORIT trial. Am J Transplant. 2012;12(9):2437-45.
27. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis. 1998;32(5):853-906.
28. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108(17):2154-69.
29. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Ishani A, et al. US Renal Data System 2013 Annual Data Report. Am J Kidney Dis. 2014;63(1 Suppl):A7.
30. Pruthi R, Casula A, MacPhee I. UK Renal Registry 15th annual report: Chapter 3 demographic and biochemistry profile of kidney transplant recipients in the UK in 2011: national and centre-specific analyses. Nephron Clin Pract. 2013;123 Suppl 1:55-80.
31. Farrugia D, Cheshire J, Begaj I, Khosla S, Ray D, Sharif A. Death within the first year after kidney transplantation--an observational cohort study. Transpl Int. 2014;27(3):262-70.
32. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607.

33. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: Executive Summary. Crit Pathw Cardiol. 2005;4(4):198-203.
34. Porrini E, Delgado P, Bigo C, Alvarez A, Cobo M, Checa MD, et al. Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. Am J Kidney Dis. 2006;48(1):134-42.
35. Canale MP, Manca di Villahermosa S, Martino G, Rovella V, Noce A, De Lorenzo A, et al. Obesity-related metabolic syndrome: mechanisms of sympathetic overactivity. Int J Endocrinol. 2013;2013:865965.
36. Khunti K, Davies M. Metabolic syndrome. BMJ. 2005;331(7526):1153-4.
37. Mitka M. Does the metabolic syndrome really exist? Diabetes and heart disease groups spar over issue. JAMA. 2005;294(16):2010-3.
38. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. Diabetes Care. 2005;28(11):2745-9.
39. Faenza A, Fuga G, Nardo B, Donati G, Cianciolo G, Scolari MP, et al. Metabolic syndrome after kidney transplantation. Transplant Proc. 2007;39(6):1843-6.
40. Procopiou M, Philippe J. The metabolic syndrome and type 2 diabetes: epidemiological figures and country specificities. Cerebrovasc Dis. 2005;20 Suppl 1:2-8.
41. Eckel RH. Mechanisms of the components of the metabolic syndrome that predispose to diabetes and atherosclerotic CVD. Proc Nutr Soc. 2007;66(1):82-95.

42. Alemany M. Relationship between energy dense diets and white adipose tissue inflammation in metabolic syndrome. Nutr Res. 2013;33(1):1-11.
43. Tracy RP. Inflammation, the metabolic syndrome and cardiovascular risk. Int J Clin Pract Suppl. 2003(134):10-7.
44. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest. 2003;112(12):1821-30.
45. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87-91.
46. Athyros VG, Tziomalos K, Karagiannis A, Anagnostis P, Mikhailidis DP. Should adipokines be considered in the choice of the treatment of obesity-related health problems? Curr Drug Targets. 2010;11(1):122-35.
47. Haas B, Schlinkert P, Mayer P, Eckstein N. Targeting adipose tissue. Diabetol Metab Syndr. 2012;4(1):43.
48. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol. 2010;316(2):129-39.
49. Gupta AK, Dahlof B, Sever PS, Poulter NR, Investigators A-SCOT-BPLA. Metabolic syndrome, independent of its components, is a risk factor for stroke and death but not for coronary heart disease among hypertensive patients in the ASCOT-BPLA. Diabetes Care. 2010;33(7):1647-51.
50. Mulé G, Cerasola G. The metabolic syndrome as a prohypertensive state. Am J Hypertens. 2008;21(1):8.

51. Deedwania P. Hypertension, dyslipidemia, and insulin resistance in patients with diabetes mellitus or the cardiometabolic syndrome: benefits of vasodilating β-blockers. J Clin Hypertens (Greenwich). 2011;13(1):52-9.
52. Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. Rev Endocr Metab Disord. 2013;14(1):5-12.
53. Jandeleit-Dahm KA, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. J Hypertens. 2005;23(3):463-73.
54. Belfort R, Mandarino L, Kashyap S, Wirfel K, Pratipanawatr T, Berria R, et al. Dose-response effect of elevated plasma free fatty acid on insulin signaling. Diabetes. 2005;54(6):1640-8.
55. Opie LH. Metabolic syndrome. Circulation. 2007;115(3):e32-5.
56. Ingelfinger JR, Solomon CG. Angiotensin-converting-enzyme inhibitors for impaired glucose tolerance--is there still hope? N Engl J Med. 2006;355(15):1608-10.
57. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. J Am Soc Nephrol. 2003;14(2):469-77.
58. Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE, et al. A central body fat distribution is related to renal function impairment, even in lean subjects. Am J Kidney Dis. 2003;41(4):733-41.
59. Hricik DE. Metabolic syndrome in kidney transplantation: management of risk factors. Clin J Am Soc Nephrol. 2011;6(7):1781-5.

60. Marcén R. Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. Drugs. 2009;69(16):2227-43.
61. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. Transplantation. 2010;89(1):1-14.
62. Ekberg H, Grinyó J, Nashan B, Vanrenterghem Y, Vincenti F, Voulgari A, et al. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. Am J Transplant. 2007;7(3):560-70.
63. Abramowicz D, Manas D, Lao M, Vanrenterghem Y, Del Castillo D, Wijngaard P, et al. Cyclosporine withdrawal from a mycophenolate mofetil-containing immunosuppressive regimen in stable kidney transplant recipients: a randomized, controlled study. Transplantation. 2002;74(12):1725-34.
64. Schnuelle P, van der Heide JH, Tegzess A, Verburgh CA, Paul LC, van der Woude FJ, et al. Open randomized trial comparing early withdrawal of either cyclosporine or mycophenolate mofetil in stable renal transplant recipients initially treated with a triple drug regimen. J Am Soc Nephrol. 2002;13(2):536-43.
65. Weissenbacher A, Jara M, Ulmer H, Biebl M, Bösmüller C, Schneeberger S, et al. Recipient and donor body mass index as important risk factors for delayed kidney graft function. Transplantation. 2012;93(5):524-9.
66. Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, et al. Obesity and outcome following renal transplantation. Am J Transplant. 2006;6(2):357-63.

67. Aalten J, Christiaans MH, de Fijter H, Hené R, van der Heijde JH, Roodnat J, et al. The influence of obesity on short- and long-term graft and patient survival after renal transplantation. Transpl Int. 2006;19(11):901-7.
68. Ghahramani N, Reeves WB, Hollenbeak C. Association between increased body mass index, calcineurin inhibitor use, and renal graft survival. Exp Clin Transplant. 2008;6(3):199-202.
69. Merion RM, Twork AM, Rosenberg L, Ham JM, Burtch GD, Turcotte JG, et al. Obesity and renal transplantation. Surg Gynecol Obstet. 1991;172(5):367-76.
70. Thomas B, Taber DJ, Srinivas TR. Hypertension after kidney transplantation: a pathophysiologic approach. Curr Hypertens Rep. 2013;15(5):458-69.
71. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20.
72. Kasiske BL, Anjum S, Shah R, Skogen J, Kandaswamy C, Danielson B, et al. Hypertension after kidney transplantation. Am J Kidney Dis. 2004;43(6):1071-81.
73. Kasiske B, Cosio FG, Beto J, Bolton K, Chavers BM, Grimm R, et al. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. Am J Transplant. 2004;4 Suppl 7:13-53.
74. Courivaud C, Kazory A, Simula-Faivre D, Chalopin JM, Ducloux D. Metabolic syndrome and atherosclerotic events in renal transplant recipients. Transplantation. 2007;83(12):1577-81.

75. Sharif A. Metabolic syndrome and solid-organ transplantation: Minireview. American Journal of Transplantation. 2010;10(1):12-7.

76. Vetromile F, Szwarc I, Garrigue V, Delmas S, Fesler P, Mimran A, et al. Early high pulse pressure is associated with graft dysfunction and predicts poor kidney allograft survival. Transplantation. 2009;88(9):1088-94.

77. Mohsin N, Mourad G, Faure M, Szawarc I, Bringer J. Metabolic syndrome performs better than the individual factors in predicting renal graft outcome. Transplant Proc. 2013;45(10):3517-9.

5 ARTIGO EM INGLÊS

“Effect of Metabolic Syndrome on Kidney Transplantation Outcomes:

A Systematic Review and Meta-analysis”

REVISTA DE ESCOLHA:

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EFFECTS OF METABOLIC SYNDROME ON KIDNEY TRANSPLANTATION OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABBREVETIONS

BMI: Body Mass Index

CKD: Chronic kidney Disease

CVD: Cardiovascular Disease

CVE: Cardiovascular Events

CRP: C - Reactive Protein

ERSD: End Stage Renal Disease

FPG: Fasting Plasma Glucose

GFR: Glomerular Filtration Rate

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HDL-c: High Density Lipoprotein Cholesterol

HLA: Human Leukocyte Antigen

IDF: International Diabetes Federation

LDL-C: Low Density Lipoprotein Cholesterol

MOOSE: Meta-analysis of Observational Studies in Epidemiology

MS: Metabolic Syndrome

NCEP/ATPIII: National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

NODAT: New Onset Diabetes After Kidney Transplantation

TNF-α: Tumor Necrosis Factor Alpha

TSA: Trial Sequential Analysis

WHO: World Health Organization

ABSTRACT

Background: Metabolic syndrome (MS) has been associated with proteinuria and reduced glomerular filtration rate. Immunosuppressive agents increase the incidence of traditional cardiovascular risk factors and thus have expected effects on components of MS after transplantation. The purpose of this systematic review and meta-analysis is provide valid information regarding the syndrome and clarify this question.

Methods: MEDLINE, EMBASE and Cochrane Library were searched up to October 4, 2014. Papers that compared MS and non-MS patients who underwent renal transplantation and assessed one of the following outcomes: graft loss, cardiovascular events (CVE), death by cardiovascular disease (CVD) and all-cause-mortality were included. Two independent reviewers summarized the data and evaluated the quality of the articles.

Results: From 585 studies identified, 5 were included (1269 patients). MS was related to graft loss (relative risk, 3.02; 95% confidence interval, 2.17-4.32; I^2=0%; P heterogeneity= 1.35), CVE (relative risk, 3.53; 95% confidence interval, 1.27-9.85; I^2= 0%; P heterogeneity= 1.81) and death by CVD (relative risk, 2.61; 95% CI, 0,70-9,81; I^2=58%; P heterogeneity= 0.76). No association was found between MS and all cause-mortality.

Conclusion: Graft loss, CVE and death by CVD were associated with the MS diagnoses after kidney transplantation. Larger studies should be designed to elucidate its association with mortality by all-causes, since the combined sample size from the available studies still lack power. Lastly, prospective randomized clinical

trials should be conducted in order to define if interventions on each MS component would result in better outcomes after kidney transplant.

Keywords: Metabolic syndrome, kidney transplantation, systematic review and meta-analysis.

INTRODUCTION

Kidney transplantation confers the greatest survival benefit among all the others renal replacement treatments (1) and provides the most cost-effective relation for the majority of patients with end-stage renal disease (ERSD) (2-5). Although long-term allograft and patient survival after kidney transplant have significantly improved over the past decades, cardiovascular disease (CVD) limits patient survival and death with a functioning graft remains the leading cause of late renal allograft loss (6-10).

Metabolic Syndrome (MS), also termed insulin resistance syndrome (11), is defined as an aggregation of clinical and biochemical dysfunctions, such as obesity, hypertension, dyslipidemia, and impaired glucose metabolism (12, 13). There are complex associations among different environmental, genetic and metabolic factors interconnected by energy homeostasis pathways that represent the MS (14, 15). MS is a well-defined risk factor for cardiovascular disease and mortality. Moreover, the syndrome has been associated with proteinuria and reduced glomerular filtration rate (GFR) (16-18) suggesting a link with chronic kidney disease (CKD). To extend that diabetes mellitus (DM), CVD and proteinuria are very often observed after renal transplantation, recently MS has attracted a great deal of interest in the kidney transplant setting (19).

The prevalence of MS after kidney transplantation varies largely from as low as 20% to as high as 65%, probably reflecting the difference in the studied samples (20-25). Even though the individual elements of MS, mainly hypertension and obesity also have a negative effect on kidney transplant outcomes (24-28) , it is not clear whether the MS as an entity predicts better than its individual elements those outcomes (29).

Immunosuppressive agents increase the incidence and severity of traditional cardiovascular risk factors and thus have potential effects on components of the MS after transplantation. In renal transplant recipients the syndrome is associated with CVD and new-onset diabetes after kidney transplantation (NODAT), deteriorating graft function and graft loss as well (19). For these reasons, we performed a systematic review and meta-analysis, considering that the assessment of overall prevalence and the impact of MS condition on relevant outcomes may provide valid information regarding the syndrome and the management of its risk factors in renal transplant recipients.

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. From that, 43 studies were chosen for full-text assessment, and 5 fulfilled all inclusion and exclusion criteria, supplying data on 1.269 kidney transplant recipients.

The main characteristics of the 5 articles included in the meta-analysis are exposed in Table 1. Several characteristics selected *a priori* to be extracted from original articles were not available, such as: primary kidney disease, panel-reactive antibodies, total-cholesterol, previous dyslipidemia, number of mismatched human leukocyte antigen (HLA), cold ischemia, hepatitis C virus status, abdominal circumference and weight. Triglycerides level was present in 3 studies (24, 30, 31), and high density lipoprotein cholesterol (HDL-c), pre-transplant DM diagnoses and

cytomegalovirus presence were found in only 2 studies (30, 31). C- reactive protein (CRP) levels were referred in two studies (24, 26), immunosuppressive therapy and glucose level in only one (24) and previous CVD was reported in only one article (30).

Information of abdominal circumference was not available in the majority of the trials, so all included papers adopted the body mass index (BMI) instead of abdominal circumference as one of the MS criterion. In addition, all studies used the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NCEP/ATP III) to define MS (12). Therefore, MS was defined as any combination of three or more of the following five factors: overweight or obesity (BMI >25 Kg/m²); fasting plasma glucose (FPG) >110 mmol/L, including pretransplant diabetes, or NODAT; hypertension (BP>135/85 mmHg); hypertriglyceridemia (triglycerides>150mg/dL), and low HDL-c (<40mmol/L for men and <50mmol/L for woman). MS diagnoses were assessed 12 months after kidney transplantation.

In agreement with the Newcastle Quality Assessment Scale for cohort studies, all the studies evaluated were classified as articles with a high quality level, considering that 2 studies (24, 32) scored 9 points and the other 3 (26, 30, 31) reached an score of 8, indicating a low risk of bias. Considering that this systematic review includes only observational studies, the overall GRADE (Grading of Recommendations Assessment, Development and Evaluation) quality rating was considered very low.

Metabolic Syndrome and kidney transplant outcomes

Graft loss

A total of 4 studies assessed graft loss, including 932 kidney transplant recipients. MS was associated with an increased risk of graft loss (relative risk [RR], 3.02; 95% confidence interval [CI], 2.17-4.32; I^2=0%; P_{for} heterogeneity =0.72) (Figure 1A).

Cardiovascular Events

This outcome was evaluated by 2 articles, including 635 patients. An association between MS after transplantation and the development of cardiovascular events was found (RR, 3.54; 95% CI, 2.31-5.40; I^2= 0%; P heterogeneity= 0.01), with no heterogeneity (Figure 1B).

Death by Cardiovascular Disease

Three studies appraised 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= 1.81.) as it is presented in the Figure 1C.

All-Cause Mortality

Three studies assessed all cause-mortality, with a total of 865 subjects included. No association between MS post transplantation and this outcome was observed (Figure 1D). (RR, 2.61; 95% CI, 0.70-9.81; I^2=58%; P heterogeneity= 0.76).

Publication Bias

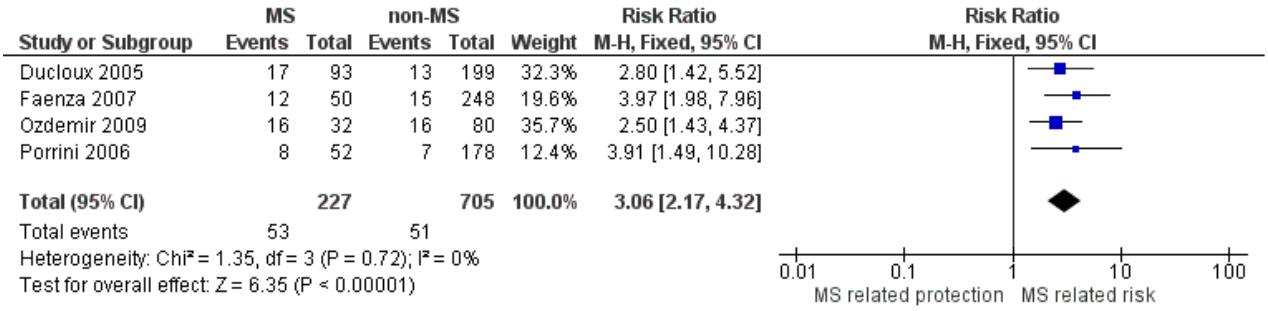
Contour-enhanced funnel plots and the Egger regression test revealed no publication bias for graft loss (P=0.268) and cardiovascular death (P=0.613). We were not able

to evaluate the risk of publication bias for the outcome of cardiovascular events, because only two trials were included in this meta-analysis. For all-cause mortality a possibility of publication bias was observed (P=0.067), but it did not influence the results based on trim-and-fill analysis. The funnel plot for each meta-analysis can be found in supplemental digital content.

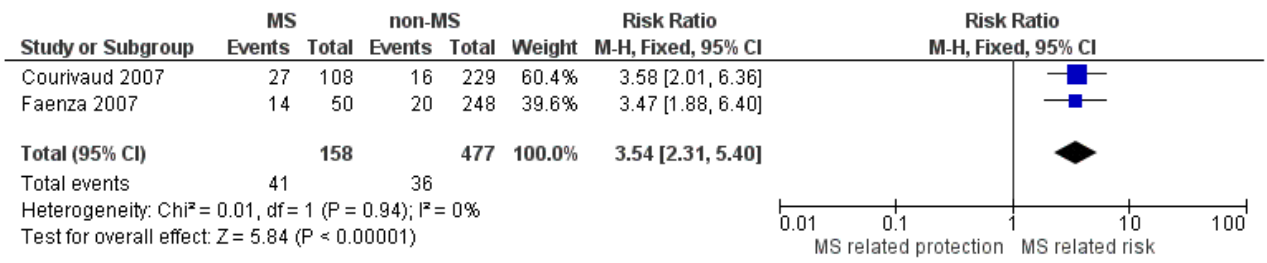
Trial Sequential Analyses

Considering the sample size obtained through these articles, our meta-analysis has a power >99% regarding graft loss and cardiovascular events. A power of 60% was found when death by CVD was analyzed. The assessment of all cause-mortality showed a power of 30%, considering an incidence of 4% in the control group, heterogeneity= 58% and assuming α=0.05.

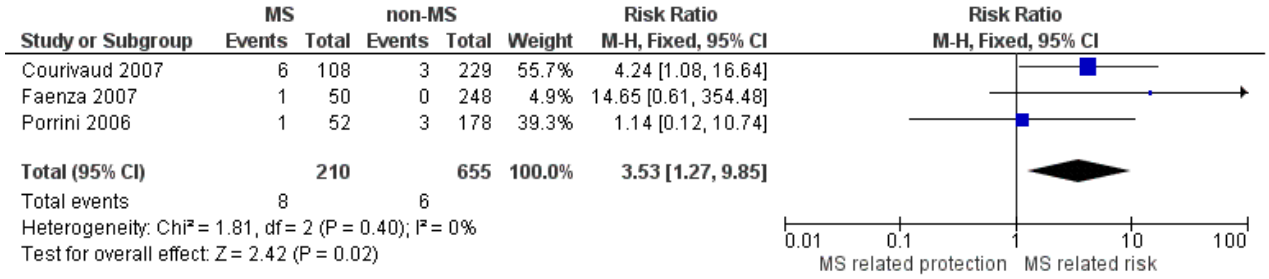
A **Graft Loss**



B **Cardiovascular Events**



C **Death by CVD**



D **All-cause mortality**

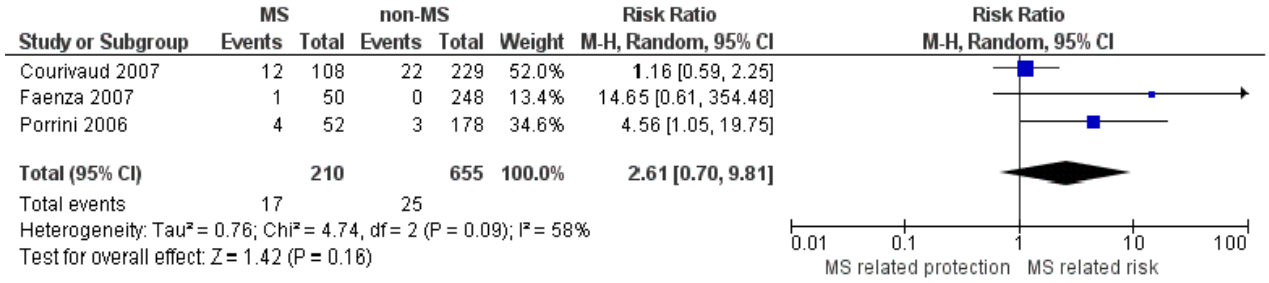


FIGURE 1. Forest plot graphic showing the association between metabolic syndrome and kidney transplant graft loss (A); cardiovascular events (B), death from cardiovascular causes (C) and all cause-mortality (D).

Figure 2. Characteristics of the studies included in the meta-analysis

Study, Year (Ref)	Posttransplant MS Prevalence (%)	Groups	Patients, n	Ethnicity, % Caucasian	Age, years Mean ± SD	Men %	Deceased Donor (%)	Re-tx (%)	Dialysis duration (months)	BMI, kg/m2 Mean ± SD	Smoking status %	Hypertension %
Courivaud *et al*., 2007 (30)	32	MS	12	NA	50±9	67	NA	NA	NA	24,6±4,6	23	99
		non-MS	229		43±11							76
Doucloux *et al*., 2005 (31)	32	MS	93	NA	45±13	67	NA	NA	NA	24,4±4,4	22,3	72
		non-MS	199									
Faenza *et al*., 2007 (26)	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±34,8			
Ozdemir *et al*., 2009 (32)	28.6	MS	32	NA	29,1±8,9	NA	NA	NA	32,90±8,87	22±3.0	69,75	NA
		non-MS	80		30,9±9,1	NA			30,91±9,14	22±3.5	20	
Porriniet al., 2006 (24)	22.6	MS	52	NA	52 ± 11	71.2	100	NA	22,5±20	32.0 ± 4.2	NA	NA
		non-MS	178		43 ± 13	70.0			24,5±24	26.1 ± 5.2		

Ref = reference; SD = standard deviation; BMI = body mass index; NA = not available.

DISCUSSION

This systematic review demonstrated that MS is associated with graft loss, cardiovascular events (CVE) and death by CVD in kidney transplant recipients. All cause mortality, however, was not related to MS after kidney transplantation.

The underlying mechanisms of graft loss in MS remain speculative (26, 33). However, different mechanisms have been proposed for the association between MS and impaired renal function.

In addition to immunologic factors leading to long-term renal function impairment, there are also some nonimmunologic factors such as hypertension, dyslipidemia, diabetes and obesity (all components of MS) that must be mentioned (34-37). To better understanding the reason why MS performs a relevant role on renal graft loss is necessary the comprehension of its physiopathology.

The type of immunosuppressive therapy can be associated with graft survival. A histophatological study suggested that chronic calcineurin-inhibitor nephrotoxicity is the prevalent cause of late chronic renal transplant dysfunction, which can accelerate the process of graft loss. Furthermore, corticosteroids at high dosages, may stimulate appetite and promote weight gain, predisposing obesity (19). There are evidences suggesting that renal transplant patients experience an average weight gain between 5 and 10 kilograms seems to be related with decreased patient and graft survival (38-40).

Obesity is related to proinflammatory conditions, affecting the renal function (41). In order that, plasma concentrations of some proinflammatory adipokines, such as tumor necrosis factor alpha (TNF-α) are elevated in patients with MS (42, 43). Apart from, TNF-α has been shown to mediate inflammation of renal injury (44), causing

macrophage infiltration and upper regulation of inflammatory cytokines that may be toxic to renal epithelial, mesangial and endothelial cells (44, 45). Nevertheless, the specific role of TNF-α in MS-induced renal injury has not been well elucidated (33). Anyhow, is plausible to suggest that inflammation presents an association with process of graft loss in renal transplant recipients. Others factors related to obesity such as excess excretory load, renal sodium retention, hyperinsulinaemia and insulin resistance may contribute to renal dysfunction.

According to our results, both outcomes: CVE and death from CVD also presented an association with MS diagnosed after transplantation, with no heterogeneity. The factors that contribute most to CVD risk in renal transplant recipients are the known traditional risk factors to the general population, such as diabetes, arterial hypertension and dyslipidemia, which are components of the syndrome. Long-term cohort studies of the European population have shown an increase in the incidence of CVE and mortality in relation to diabetes before and after transplantation, where diabetes is defined as an independent risk factor for the development of cardiovascular complications (46). Therefore, it its acceptable that this is due to dysfunctions associated with metabolic and vascular profile, reflected in higher cholesterol and triglycerides levels and increased blood pressure (47).

There are others causes that must be involved, mainly those that also can affect systematic inflammation, such as the immunosuppressive treatment, infections and also graft rejection (48). A formula for 7-year CVD and mortality risk calculation for prevalent renal transplant recipients was recently developed by Soveri *el at (49)*. There are some variables included in this formula, such as recipient age, coronary artery disease, LDL-c, creatinine, diabetes, number of transplants and time on renal replacement therapy and smoking. Besides, it is also conceivable remind that arterial

hypertension is highly prevalent in renal transplant recipients and may have a particular effect on CVE, consequently affecting the death by CVD. Curiously, both studies that evaluated CVE in this systematic review presented high prevalence of hypertension as well (Table 1).

Interestingly, the study by Faenza *et al* reported a higher CVE among patients affected by MS in comparison with those without: in patients whit 1 factor of the syndrome, was observed 2% of incidence of CVE; with 2 factors, this value increased to 17,1%; with 3 factors, 25% and finally with 4 factors, 33,3% (26). There are two studies that must be considered about cardiovascular complications after kidney transplantation and MS: Assessment of Lescol in Renal Transplantation (ALERT) trial (50) and Patient Outcomes in Renal Tranplantation (PORT) study (51). An association between the MS and graft loss was found in PORT but not in ALERT. Both were not included on this systematic review, because we could not analyze papers with known population databases, considering that these studies possibly could share patients that already have been assessed. However, the PORT study (51) differs from our studies in the aspect that the population represents long-term renal transplant recipients survivors, and the ALERT trial (50) also included different types of transplant recipients, not only renal transplantation.

The only endpoint that did not presented any association with MS after kidney transplantation was all-cause mortality. Interestingly, this outcome showed heterogeneity and publication bias as well. Through the TSA results, it was possible to verify that all-cause mortality does not have enough power (30%) to conclude this association. Unfortunately, these articles are the only studies available at the medical literature until now.

The relevance of MS in renal transplant recipients is embarrassed by the fact that the incidence of CVD actually decreases after transplant when compared with the incidence of dialysis period on the transplant waiting list (52). However, considering that the prevalence of the syndrome increases in concert with postransplantation weigh gain and there are an association with these negative outcomes, it becomes even more clear that this clustering of clinical and biochemical dysfunctions, termed MS, deserves a special attention. Finally, glucose intolerance, hypertension and dyslipidemia directly could damage the kidneys through renal or systemic atherosclerosis.

This systematic review and meta-analysis presents some limitations. All the studies evaluated MS through BMI and not abdominal circumference, which is the variable usually employed to characterize central obesity. Furthermore, several studies did not report important data regarding population characteristics, limiting some speculations that possibly could better explain our finds.

In conclusion, our results shown with plainness that graft loss, CVE and death by CVD are associated with the MS diagnoses after kidney transplantation. Larger studies should be design to elucidate its association with mortality by all-causes, since the combined sample size from the available studies still lack power. Lastly, prospective randomized clinical trials should be conducted in order to define if interventions on each MS component would result in better outcomes after kidney transplant.

MATERIALS AND METHODS

Search Strategy and Study Selection

Papers were identified using Medical Subject Heading (MeSH) terms by searching MEDLINE (accessed by Pubmed), EMBASE and Cochrane Library, gray literature and hand searching (through reference lists of obtained articles) up to October 4, 2014. The Medline strategy is presented on supplemental digital content. 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.

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, CVE, cardiovascular death and death by all causes. MS was defined based on National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPII) (12), International Diabetes Federation (IDF) (53) or World Health Organization (WHO) criteria (54).

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

Data Extraction

Titles and abstracts of retrieved studies were separately assessed by two researchers (E.F.P. and C.C). Both of them were not blinded to article journals, institutions and authors. Abstract with scantly information concerning the eligibility criteria were retrieved for full-text evaluation. The two reviewers managed apart all the data extraction. In the 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 length from kidney transplantation to MS diagnoses and to outcomes evaluation. There were some demographic and transplant related attributes extracted as well: age, gender, ethnicity, primary kidney disease, weight, abdominal circumference, BMI, blood pressure, time on dialysis, smoking status, retransplantation, donor type (living or deceased),immunosuppressive therapy, cold ischemia, panel reactive antibodies, HLA mismatches, glucose level, total cholesterol, HDL-c, triglycerides, GFR, CRP and prevalence of pre-transplant DM, hypertension and CVD.

Quality Assessment

The Newcastle Quality Assessment Scale for cohort studies was used to identify risk of bias. A total score of 5 or less was deemed as low; 6 and 7, moderate; and 8 and 9 high level of quality. GRADE guidelines (55) 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 RR of postransplantation 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% 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). For meta-analysis with significant risk for publication bias, we used trim-and-fill method to evaluate if it could influence the results(56). 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.

References

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725-30.
2. Moreso F, Hernández D. Has the survival of the graft improved after renal transplantation in the era of modern immunosuppression? Nefrologia. 2013;33(1):14-26.
3. Garcia GG, Harden P, Chapman J, 2012 WKDSC. The global role of kidney transplantation. Nephrol Dial Transplant. 2013;28(8):e1-5.
4. Haller M, Gutjahr G, Kramar R, Harnoncourt F, Oberbauer R. Cost-effectiveness analysis of renal replacement therapy in Austria. Nephrol Dial Transplant. 2011;26(9):2988-95.
5. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am J Transplant. 2011;11(10):2093-109.
6. Pascual M, Theruvath T, Kawai T, Tolkoff-Rubin N, Cosimi AB. Strategies to improve long-term outcomes after renal transplantation. N Engl J Med. 2002;346(8):580-90.
7. Collins AJ, Foley RN, Chavers B, Gilbertson D, Herzog C, Ishani A, et al. US Renal Data System 2013 Annual Data Report. Am J Kidney Dis. 2014;63(1 Suppl):A7.
8. Pruthi R, Casula A, MacPhee I. UK Renal Registry 15th annual report: Chapter 3 demographic and biochemistry profile of kidney transplant recipients in the UK in

2011: national and centre-specific analyses. Nephron Clin Pract. 2013;123 Suppl 1:55-80.

9. Farrugia D, Cheshire J, Begaj I, Khosla S, Ray D, Sharif A. Death within the first year after kidney transplantation--an observational cohort study. Transpl Int. 2014;27(3):262-70.
10. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet. 2011;378(9800):1419-27.
11. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-607.
12. National Cholesterol Education Program (NCEP) Expert Panel on Detection Ea, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.
13. Oda E. Metabolic syndrome: its history, mechanisms, and limitations. Acta Diabetol. 2012;49(2):89-95.
14. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol. 2002;156(11):1070-7.
15. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA. 2002;288(21):2709-16.

16. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, et al. Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. J Am Soc Nephrol. 2003;14(2):469-77.
17. Pinto-Sietsma SJ, Navis G, Janssen WM, de Zeeuw D, Gans RO, de Jong PE, et al. A central body fat distribution is related to renal function impairment, even in lean subjects. Am J Kidney Dis. 2003;41(4):733-41.
18. Moehlecke M, Leitão CB, Kramer CK, Rodrigues TC, Nickel C, Silveiro SP, et al. Effect of metabolic syndrome and of its individual components on renal function of patients with type 2 diabetes mellitus. Braz J Med Biol Res. 2010;43(7):687-93.
19. Hricik DE. Metabolic syndrome in kidney transplantation: management of risk factors. Clin J Am Soc Nephrol. 2011;6(7):1781-5.
20. Bellinghieri G, Bernardi A, Piva M, Pati T, Stoppa F, Scaramuzzo P, et al. Metabolic syndrome after kidney transplantation. J Ren Nutr. 2009;19(1):105-10.
21. Luan FL, Langewisch E, Ojo A. Metabolic syndrome and new onset diabetes after transplantation in kidney transplant recipients. Clin Transplant. 2010;24(6):778-83.
22. Salerno MP, Piselli P, Rossi E, Favi E, Gargiulo A, Spagnoletti G, et al. Metabolic syndrome and cardiovascular disease in kidney transplantation. Transplant Proc. 2011;43(4):1067-8.
23. Adeseun GA, Rivera ME, Thota S, Joffe M, Rosas SE. Metabolic syndrome and coronary artery calcification in renal transplant recipients. Transplantation. 2008;86(5):728-32.

24. Porrini E, Delgado P, Bigo C, Alvarez A, Cobo M, Checa MD, et al. Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. Am J Kidney Dis. 2006;48(1):134-42.
25. De Vries APJ, Bakker SJL, Van Son WJ, Van Der Heide JJH, Ploeg RJ, The HT, et al. Metabolic syndrome is associated with impaired long-term renal allograft function; not all component criteria contribute equally. American Journal of Transplantation. 2004;4(10):1675-83.
26. Faenza A, Fuga G, Nardo B, Donati G, Cianciolo G, Scolari MP, et al. Metabolic syndrome after kidney transplantation. Transplant Proc. 2007;39(6):1843-6.
27. Sui W, Zou H, Zou G, Yan Q, Chen H, Che W, et al. Clinical study of the risk factors of insulin resistance and metabolic syndrome after kidney transplantation. Transpl Immunol. 2008;20(1-2):95-8.
28. Sharif A, Ravindran V, Dunseath G, Luzio S, Owens DR, Baboolal K. Comparison of rival metabolic syndrome classifications against pathophysiological markers in renal transplant recipients. Transplantation. 2010;89(3):347-52.
29. Mohsin N, Faure M, Szwarc I, Pernin V, Mourad G. Different classifications yield variance in metabolic syndrome prevalence and dynamics in renal transplant recipients. Transplant Proc. 2013;45(10):3514-6.
30. Courivaud C, Kazory A, Simula-Faivre D, Chalopin JM, Ducloux D. Metabolic syndrome and atherosclerotic events in renal transplant recipients. Transplantation. 2007;83(12):1577-81.
31. Ducloux D, Kazory A, Simula-Faivre D, Chalopin JM. One-year post-transplant weight gain is a risk factor for graft loss. Am J Transplant. 2005;5(12):2922-8.

32. Ozdemir FN, Karakan S, Akgul A, Haberal M. Metabolic syndrome is related to long-term graft function in renal transplant recipients. Transplant Proc. 2009;41(7):2808-10.
33. Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. Clin J Am Soc Nephrol. 2007;2(3):550-62.
34. Roodnat JI, Mulder PG, Zietse R, Rischen-Vos J, van Riemsdijk IC, IJzermans JN, et al. Cholesterol as an independent predictor of outcome after renal transplantation. Transplantation. 2000;69(8):1704-10.
35. Tutone VK, Mark PB, Stewart GA, Tan CC, Rodger RS, Geddes CC, et al. Hypertension, antihypertensive agents and outcomes following renal transplantation. Clin Transplant. 2005;19(2):181-92.
36. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003;3(2):178-85.
37. Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, et al. Obesity and outcome following renal transplantation. Am J Transplant. 2006;6(2):357-63.
38. Cashion A, Hathaway D, Stanfill A, Thomas F, Ziebarth J, Cui Y, et al. Pre-transplant Predictors of One Year Weight Gain After Kidney Transplantation. Clin Transplant. 2014.
39. Cashion AK, Sánchez ZV, Cowan PA, Hathaway DK, Lo Costello A, Gaber AO. Changes in weight during the first year after kidney transplantation. Prog Transplant. 2007;17(1):40-7.

40. Elster EA, Leeser DB, Morrissette C, Pepek JM, Quiko A, Hale DA, et al. Obesity following kidney transplantation and steroid avoidance immunosuppression. Clin Transplant. 2008;22(3):354-9.
41. Cannon RM, Jones CM, Hughes MG, Eng M, Marvin MR. The impact of recipient obesity on outcomes after renal transplantation. Ann Surg. 2013;257(5):978-84.
42. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol. 2004;15(11):2792-800.
43. Dandona P, Aljada A, Chaudhuri A, Mohanty P, Garg R. Metabolic syndrome: a comprehensive perspective based on interactions between obesity, diabetes, and inflammation. Circulation. 2005;111(11):1448-54.
44. Khan SB, Cook HT, Bhangal G, Smith J, Tam FW, Pusey CD. Antibody blockade of TNF-alpha reduces inflammation and scarring in experimental crescentic glomerulonephritis. Kidney Int. 2005;67(5):1812-20.
45. Klahr S, Morrissey J. Progression of chronic renal disease. Am J Kidney Dis. 2003;41(3 Suppl 1):S3-7.
46. Hjelmesaeth J, Ueland T, Flyvbjerg A, Bollerslev J, Leivestad T, Jenssen T, et al. Early posttransplant serum osteoprotegerin levels predict long-term (8-year) patient survival and cardiovascular death in renal transplant patients. J Am Soc Nephrol. 2006;17(6):1746-54.
47. González-Posada JM, Hernández D, Genís BB, Tamajón LP, Pérez JG, Maceira B, et al. Increased cardiovascular risk profile and mortality in kidney allograft recipients with post-transplant diabetes mellitus in Spain. Clin Transplant. 2006;20(5):650-8.
48. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation. 2006;82(5):603-11.

49. Soveri I, Holme I, Holdaas H, Budde K, Jardine AG, Fellström B. A cardiovascular risk calculator for renal transplant recipients. Transplantation. 2012;94(1):57-62.
50. Soveri I, Abedini S, Holdaas H, Jardine A, Eriksson N, Fellstrom B. Graft loss risk in renal transplant recipients with metabolic syndrome: subgroup analyses of the ALERT trial. J Nephrol. 2012;25(2):245-54.
51. Israni AK, Snyder JJ, Skeans MA, Kasiske BL. Clinical diagnosis of metabolic syndrome: predicting new-onset diabetes, coronary heart disease, and allograft failure late after kidney transplant. Transpl Int. 2012;25(7):748-57.
52. Meier-Kriesche HU, Schold JD, Srinivas TR, Reed A, Kaplan B. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. Am J Transplant. 2004;4(10):1662-8.
53. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.
54. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998;15(7):539-53.
55. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

56. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Performance of the trim and fill method in the presence of publication bias and between-study heterogeneity. Stat Med. 2007;26(25):4544-62.

6 CONSIDERAÇÕES FINAIS

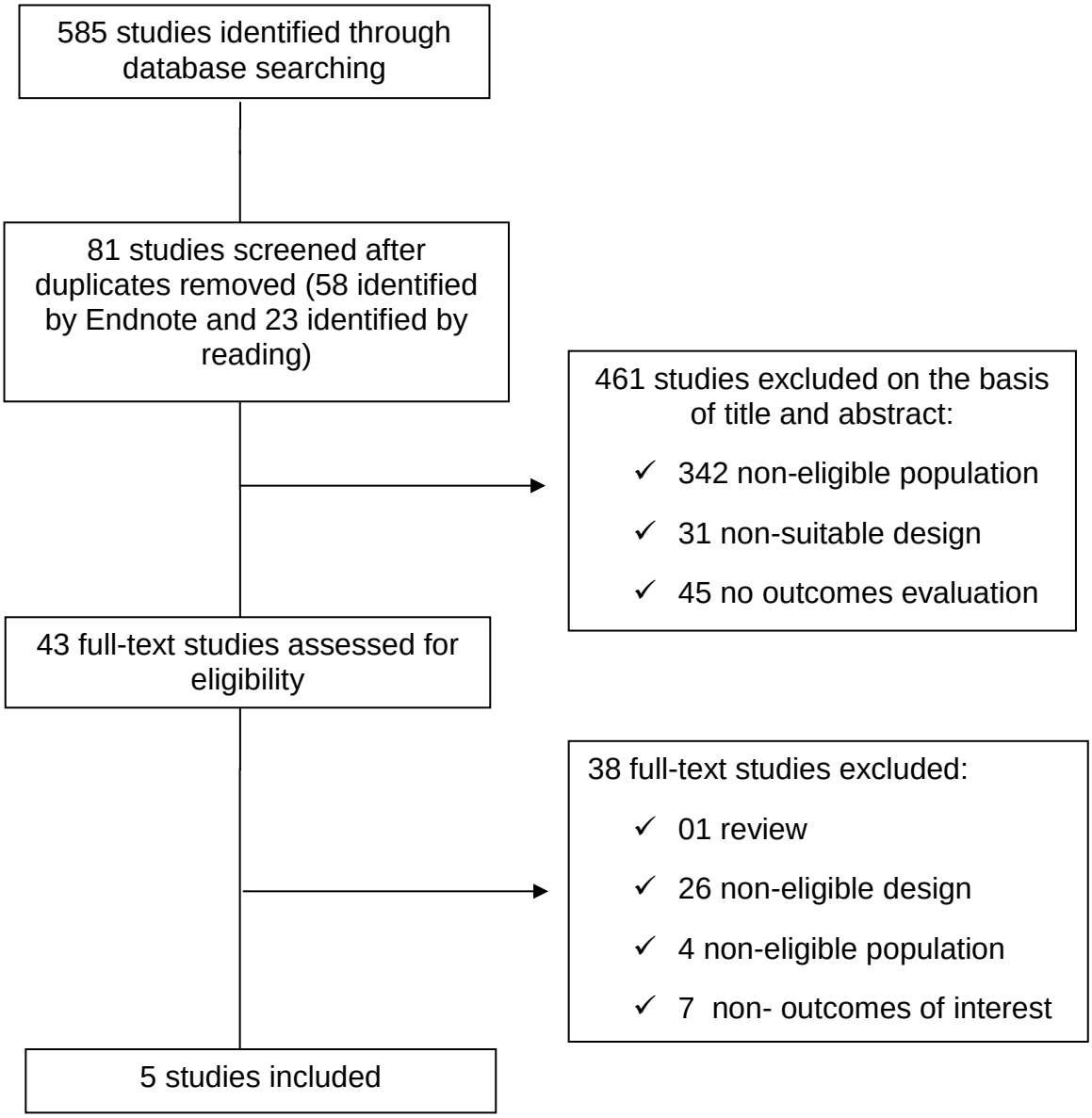
O presente estudo teve como objetivo identificar o impacto da SM no pós-transplante renal. Muito embora essa revisão sistemática seja embasada em estudos observacionais, seus resultados mostram de maneira muito clara a importância dessa condição no âmbito do paciente transplantado. Os desfechos de perda do enxerto, ECV e a morte por DCV apresentaram associação com o diagnóstico da síndrome após o transplante renal. No entanto, ainda há a necessidade de estudos maiores para que se possa elucidar também o efeito da SM sobre a mortalidade por todas as causas. Assim sendo, a realização de estudos clínicos randomizados que definissem possíveis intervenções em cada componente da síndrome, eventualmente resultariam em melhores desfechos após o transplante renal, principalmente na disfunção crônica do enxerto, melhorando assim a sobrevida do paciente.

7 APÊNDICE - SUPPLEMENTAL DIGITAL CONTENT

SDC, Medline Search Strategy

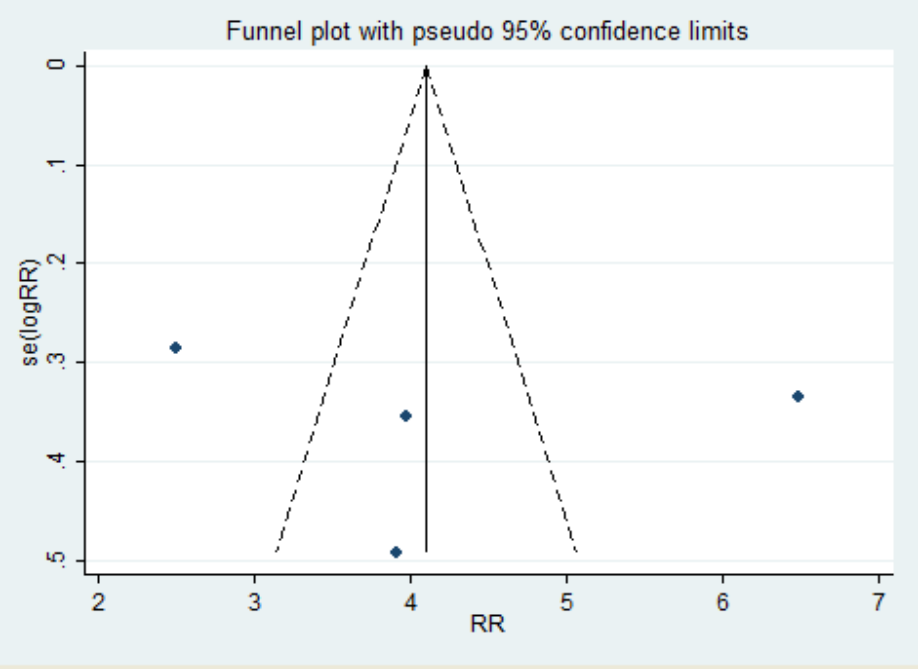
"Transplantation"[Mesh] OR" Transplantation" OR “Transplantations” OR “Recipient, Transplant” OR ”Transplant Recipient” OR “Transplant Recipients” OR ”Recipients, Transplant” OR "Organ Transplantation"[Mesh] OR “Transplantation, Organ” OR “Organ Transplantations” OR “Transplantations, Organ” OR “Grafting, Organ” OR “Graftings, Organ” OR “Organ Grafting” OR “Organ Graftings” OR "transplantation" [Subheading] OR “grafting” OR “grafts” OR "Transplantation, Heterotopic"[Mesh] OR “Heterotopic Transplantation” OR “Heterotopic Transplantations” OR “Transplantations, Heterotopic” OR "Kidney Transplantation"[Mesh] OR “Transplantation, Renal” OR “Renal Transplantation” OR “Renal Transplantations” OR “Transplantations, Renal” OR “Grafting, Kidney” OR “Kidney Grafting” OR “Transplantation, Kidney” OR “Kidney Transplantations” OR “Transplantations, Kidney” AND "Metabolic Syndrome X"[Mesh] OR "Metabolic Syndrome X" OR “Insulin Resistance Syndrome X” OR “Syndrome X, Metabolic” OR “Syndrome X, Insulin Resistance” OR ”Metabolic X Syndrome” OR “Syndrome, Metabolic X” OR “X Syndrome, Metabolic” OR “Dysmetabolic Syndrome X” OR “Syndrome X, Dysmetabolic” OR “Reaven Syndrome X” OR ”Syndrome X, Reaven” OR “Metabolic Cardiovascular Syndrome” OR “Cardiovascular Syndrome, Metabolic” OR “Cardiovascular Syndromes, Metabolic” OR “Syndrome, Metabolic Cardiovascular” OR "Abdominal obesity metabolic syndrome" [Supplementary Concept] OR “Abdominal Obesity-MetabolicSyndrome”

SDC, Figure 1. Identification and selection of articles included in the meta-analysis.

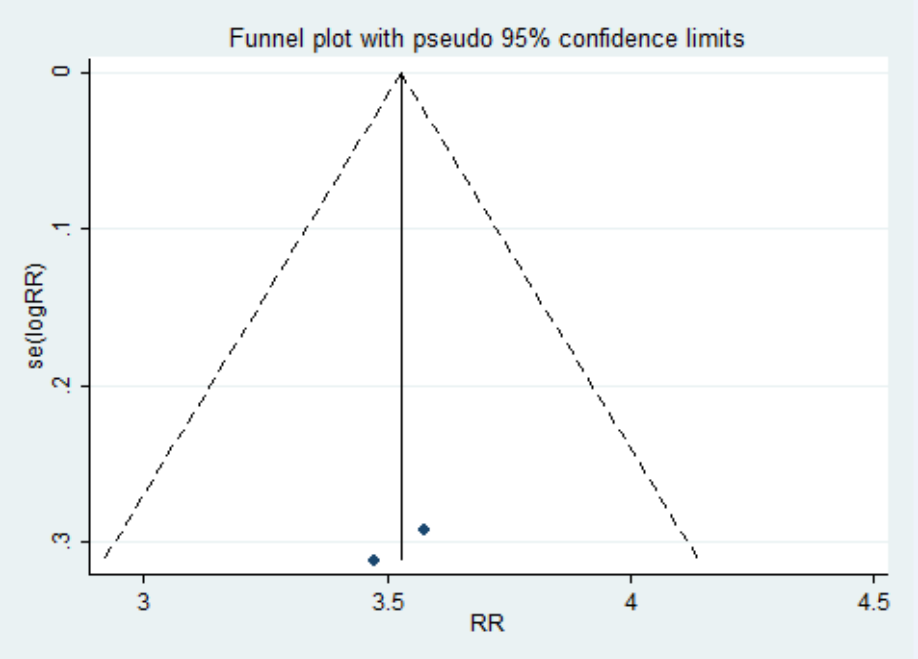


SDC, Figure 2. Meta-analyses funnel plots.

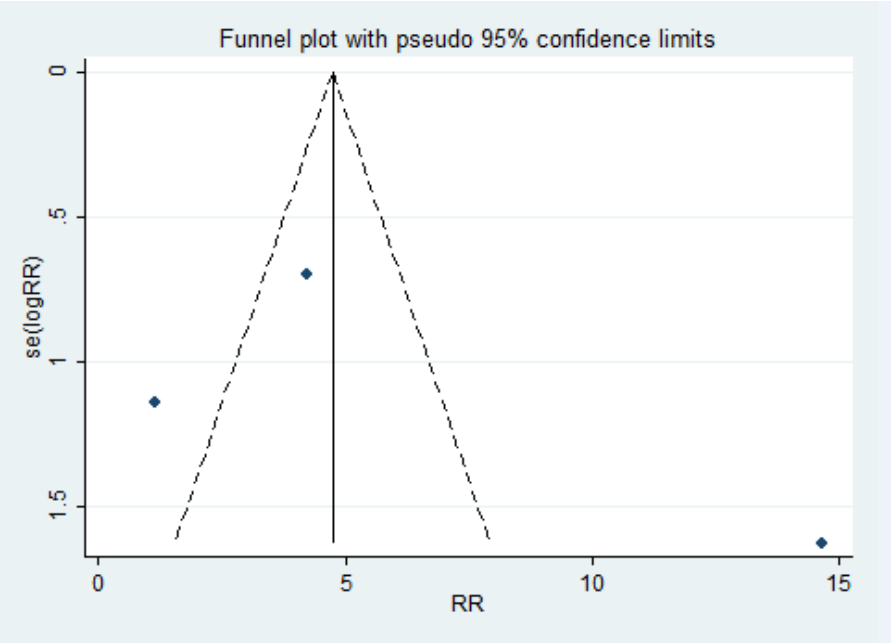
A. Graft Loss



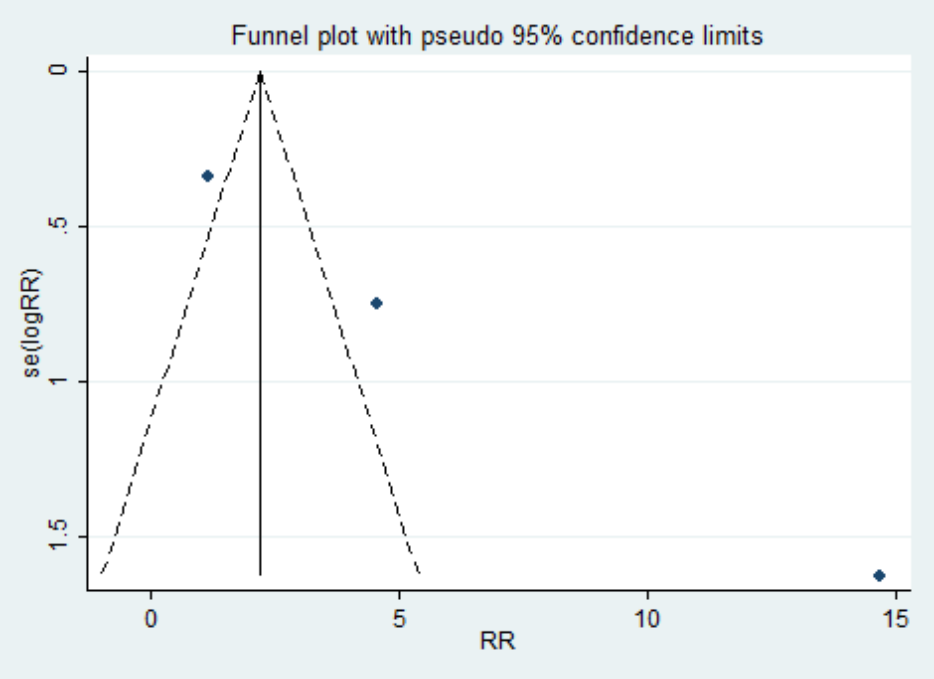
B. CVE



C. Death by CVD



D. All-cause mortality



SDC, Table 1. Quality scoring based on the Newcastle-Ottawa Quality Assessment Scale

Study, Year (Ref)	Selection	Comparability	Outcome
Courivaud *et al*., 2007[a] (30)	****	*	***
Ducloux *et al*., 2005[a] (31)	****	*	***
Faenza *et al*., 2007[a] (26)	****	*	***
Ozdemir *et al*., 2009 (32)	****	**	***
Porrini *et al*., 2006 (24)	****	**	***

Ref = reference; [a] Study groups were controlled for age, gender and donor type in assessment of comparability, except for ethnicity.

8 ANEXO – DIRETRIZES PARA META-ANÁLISE E REVISÃO SISTEMÁTICA DE ESTUDOS OBSERVACIONAIS

MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies*

Title	Identify the study as a meta-analysis (or systematic review)
Abstract	Use the journal's structured format
Introduction	**Present** • The clinical problem • The hypothesis • A statement of objectives that includes the study population, the condition of interest, the exposure or intervention, and the outcome(s) considered
Sources	**Describe** • Qualifications of searchers (eg, librarians and investigators) • Search strategy, including time period included in the synthesis and keywords • Effort to include all available studies, including contact with authors • Databases and registries searched • Search software used, name and version, including special features used (eg, explosion) • Use of hand searching (eg, reference lists of obtained articles) • List of citations located and those excluded, including justification • Method of addressing articles published in languages other than English • Method of handling abstracts and unpublished studies • Description of any contact with authors
Study Selection	**Describe** • Types of study designs considered • Relevance or appropriateness of studies gathered for assessing the hypothesis to be tested • Rationale for the selection and coding of data (eg, sound clinical principles or convenience) • Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) • Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) • Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results • Assessment of heterogeneity • Statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated
Results	**Present** • A graph summarizing individual study estimates and the overall estimate • A table giving descriptive information for each included study • Results of sensitivity testing (eg, subgroup analysis) • Indication of statistical uncertainty of findings
Discussion	**Discuss** • Strengths and weaknesses • Potential biases in the review process (eg, publication bias) • Justification for exclusion (eg, exclusion of non–English-language citations) • Assessment of quality of included studies • Consideration of alternative explanations for observed results • Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) • Guidelines for future research • Disclosure of funding source

*Modified from Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.