UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

DISSERTAÇÃO DE MESTRADO

CRISTINA CARRA FORTE

AVALIAÇÃO DOS FATORES ASSOCIADOS AO GANHO DE PESO EM PACIENTES SUBMETIDOS AO TRANSPLANTE RENAL

PORTO ALEGRE, RS

2018

CRISTINA CARRA FORTE

AVALIAÇÃO DOS FATORES ASSOCIADOS AO GANHO DE PESO EM PACIENTES SUBMETIDOS AO TRANSPLANTE RENAL

Dissertação de Mestrado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS), como requisito para obtenção do título de Mestre em Endocrinologia.

Orientadora: Cristiane Bauermann Leitão

Co-orientadora: Gabriela Corrêa Souza

PORTO ALEGRE, RS

2018

CIP - Catalogação na Publicação

Forte, Cristina Carra
Avaliação dos fatores associados ao ganho de peso em pacientes submetidos ao transplante renal / Cristina Carra Forte. -- 2018.
54 f.
Orientadora: Cristiane Bauermann Leitão.

Coorientadora: Gabriela Corrêa Souza.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2018.

1. transplante renal. 2. ganho de peso. 3. microbiota. 4. desfechos. I. Leitão, Cristiane Bauermann, orient. II. Souza, Gabriela Corrêa, coorient. III. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

Esta dissertação de mestrado será apresentada no formato exigido pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. A dissertação é constituída de uma breve introdução em português e dois artigos em inglês, estes formatados conforme as exigências das respectivas revistas às quais foram ou serão submetidos para avaliação e publicação. Os artigos em inglês desta dissertação são um artigo de tipo Original e outro do tipo Revisão Sistemática.

DEDICATÓRIA

À minha família, com gratidão por seu amor, sua compreensão, presença e apoio incansável.

AGRADECIMENTOS

À Prof.ª Dra. Cristiane B. Leitão, pelos ensinamentos, orientação, dedicação e oportunidade para ingressar na vida acadêmica.

À Prof.ª Dra. Gabriela C. Souza, grande mestre e incentivadora da produção científica, pelo incentivo, dedicação, paciência e apoio ao longo deste trabalho.

À Nutr. Elis F. Pedrollo, por ter sido um anjo comigo, sempre disposta a me ajudar e ensinar. Agradeço imensamente por sua dedicação, ensinamentos e amizade.

A Deus, que sempre me acompanha e me ilumina, por ter colocado pessoas tão especiais no meu caminho, e tantas outras que direta ou indiretamente, colaboraram no desenvolvimento deste trabalho.

E à minha família, em especial à minha mãe e irmã que sempre estiveram ao meu lado, agradeço pelo incentivo, conselhos, dedicação e por me ensinarem os verdadeiros valores da vida. Obrigada por terem acreditado em mim e por todo amor e compreensão!

A todos, meus sinceros agradecimentos.

“Naquilo em que a vida depender só de
você, capriche!”

Lígia Guerra.

RESUMO

O transplante renal é considerado a melhor terapia de substituição renal para pacientes com doença renal crônica terminal, pois aumenta a qualidade de vida e sobrevida do paciente. O ganho de peso e suas consequências metabólicas são comuns no pós-transplante e podem estar associados a piores desfechos nestes pacientes. Além dos fatores classicamente associados ao ganho de peso, os pacientes submetidos ao transplante podem apresentar alguns outros, como uso de imunossupressores e perda de massa muscular. Aliados a estes, ainda existem outros potenciais indutores de ganho de peso que não foram adequadamente estudados, como por exemplo, as alterações na microbiota intestinal após o transplante. Pacientes obesos da população em geral apresentam modificações na microbiota intestinal quando comparados com indivíduos saudáveis. Poucos estudos avaliaram a microbiota intestinal em pacientes transplantados. O presente estudo teve os seguintes objetivos: identificar os fatores associados ao ganho de peso após o transplante renal (artigo original) e caracterizar a microbiota intestinal de pacientes submetidos a transplante de órgãos sólidos e sua possível relação com alterações no peso corporal (artigo de revisão sistemática). Para identificar os fatores associados ao ganho de peso, foi realizado um estudo de coorte retrospectivo com 374 pacientes submetidos ao transplante renal atendidos no Hospital de Clinicas de Porto Alegre (HCPA) entre Janeiro de 2006 e Julho de 2013. Os resultados obtidos indicaram que o sexo feminino, menor peso corporal pré-transplante, menor número de internações e rins provenientes de doadores vivos foram associados com o ganho de peso superior a 5% no primeiro ano pós-transplante renal. Na revisão sistemática, de 765 estudos inicialmente identificados, somente dois avaliaram a microbiota intestinal após o transplante renal. Foram descritas alterações na composição das bactérias intestinais após o transplante e estas foram associadas a maior incidência de rejeição aguda e infecções nos receptores. No entanto, nenhum estudo avaliou a relação da microbiota intestinal com alterações de peso corporal neste contexto. A identificação dos fatores relacionados ao ganho de peso após o transplante renal é importante para a seleção de pacientes em risco e que deveriam receber intervenções preventivas a fim de evitar o ganho de peso após o transplante. No que diz respeito à microbiota intestinal, são necessários mais estudos para avaliar se modificações na sua composição têm impacto no peso corporal após o transplante.

Palavras-chave: transplante renal, obesidade, ganho de peso, microbiota, desfechos.

LISTA DE FIGURAS

LISTA DE TABELAS

Artigo 1

Artigo 2

LISTA DE ABREVIATURAS E SIGLAS

ABTO - Associação Brasileira de Transplante de órgãos

ADA - American Diabetes Association

AR - Acute Rejection

ATG - Anti-thymocyte globulin

BMI - Body Mass Index

CMV - Citomegalovírus

CT - Colesterol Total

DCV - Doença Cardiovascular

DGF - Delayed Graft Function

DM - Diabetes Mellitus

DMPT - Diabetes mellitus pós-transplante

DRC - Doença Renal Crônica

GODT - Global Observatory on Donation and Transplantation

HCV - Hepatitis C

HDL - High Density Lipoprotein

LDL - Low Density Lipoprotein

MDRD - Modification of Diet in Renal Disease

MESH - Medical Subject Heading

MOOSE - Meta-analysis of Observational Studies in Epidemiology

MS - Metabolic Syndrome

NODAT - New Onset Diabetes After Transplantation

OMS - Organização Mundial da Saúde

PCR - Polymerase chain reaction

PTDM - Post-transplant Diabetes Mellitus

RBT - Registro Brasileiro de Transplante de Órgãos

TFG - Taxa de Filtração Glomerular

TG - Triglicerídeos

SUMÁRIO

1. INTRODUÇÃO

O transplante renal é reconhecido como o melhor tratamento de substituição renal, apresentando melhor custo-efetividade para pacientes com Doença Renal Crônica (DRC) em estágio cinco (1,2). Quando bem sucedido, proporciona aos pacientes melhora na qualidade de vida e diminuição da mortalidade, principalmente decorrente de eventos cardiovasculares (infarto agudo do miocárdio, acidente vascular cerebral e insuficiência cardíaca), em comparação com outros métodos de depuração artificial do sangue (hemodiálise e diálise peritoneal), contribuindo assim, para o aumento da expectativa de vida destes pacientes (3-6).

Esta terapia substitutiva apresenta números crescentes nas últimas décadas (3). Dados do *Global Observatory on Donation and Transplantation* (GODT), que engloba 102 países que realizam transplante renal, registraram que este é o tipo de transplante mais realizado em detrimento aos outros órgãos sólidos, seguido de fígado e coração, conforme observado na figura 1 (7).

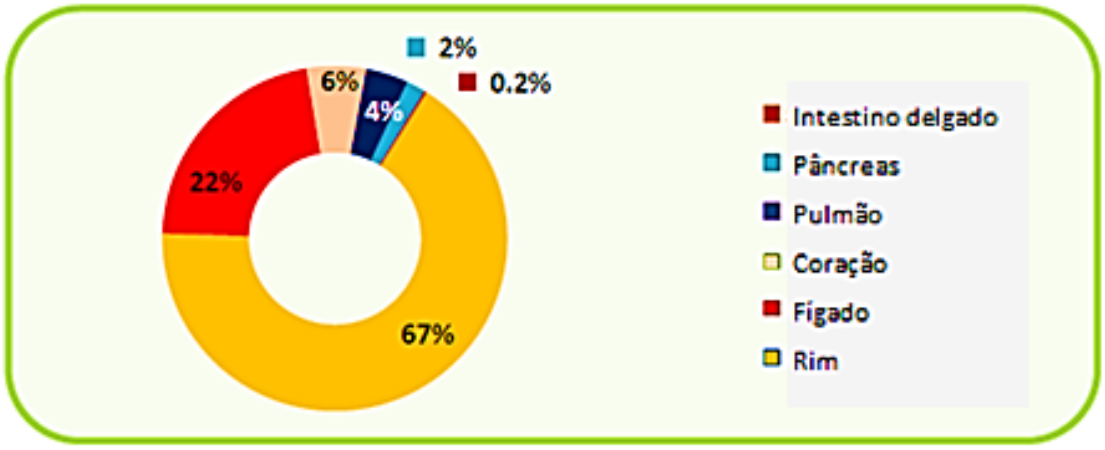


Figura 1. Porcentagem de órgãos transplantados em 2015. Adaptado da GODT, 2017.

Em relação à porcentagem de transplante renal de cada país, a Espanha é o país que mais realiza este procedimento (63%), seguido da Holanda (57%) e Estados Unidos (56,5%). O Brasil encontra-se na posição de número 37. Na figura 2, pode-se observar que a

Organização Mundial da Saúde (OMS) distribuiu a realização de transplantes renais por regiões, sendo a Europa a região que mais realiza este tipo de terapia substitutiva (7).

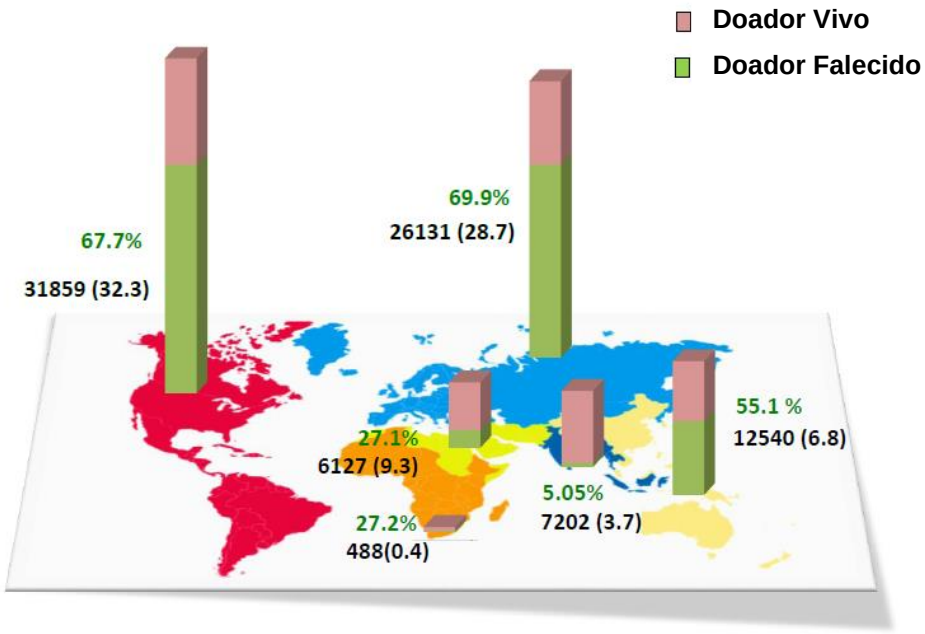


Figura 2. Distribuição de transplantes de rim entre as regiões da OMS em 2015. Adaptado da GODT, 2017.

Segundo a Associação Brasileira de Transplantes de Órgãos (ABTO), em 2016, foram registrados 7.955 transplantes, incluindo rim, fígado, coração, pâncreas e pulmão. Desses, 5.492 (69%) foram referentes ao transplante renal. Em números absolutos por doadores de rim, 1.200 transplantes foram realizados com rins de doadores vivos e 4.292, de doadores falecidos (8). De Janeiro a Setembro de 2017 foram realizados 4.429 transplantes renais no país (9).

Com a evolução da terapia imunossupressora antirrejeição, os desfechos pós-transplante renal melhoraram significativamente nos últimos anos, aumentando a sobrevida do paciente e do enxerto (10-12). No entanto, estes indivíduos tendem a sofrer alterações do estado nutricional, independentemente do estado nutricional pré-transplante (1).

Estudos demonstram que, aproximadamente, 50% dos pacientes apresentam ganho de peso após a realização de transplante renal (13-15). Esse ganho pode variar entre 5 e 10% do peso inicial, podendo atingir até 20% (13,16-19). Em relação a números absolutos, pode-se observar um ganho médio de seis a dez quilogramas durante o primeiro ano pós-transplante (20,21). Estas mudanças no peso corporal podem ocasionar desenvolvimento de diabetes melito pós-transplante, hipertensão arterial sistêmica, dislipidemia e síndrome metabólica, fatores esses associados a aumento do risco de doenças cardiovasculares (22-26). Além disso, a obesidade pode estar associada à comorbidades que pioram o estado geral do paciente, como por exemplo, a função tardia do enxerto e a perda do enxerto (22).

O ganho do peso corporal e as suas consequências metabólicas adversas estão associados a piores desfechos após o transplante renal. Uma revisão sistemática com metanálise demonstrou que a presença de obesidade, definida segundo a OMS como IMC ≥30 kg/m², antes do transplante renal está associada ao desenvolvimento de disfunção precoce do enxerto (DGF) (23). Por outro lado, a presença de síndrome metabólica (definida pela presença de pelo menos três dos seguintes critérios: circunferência abdominal >102 cm para homens e >88 cm para mulheres, glicemia >110 mg/dl ou DM prévio, triglicerídeos >150 mg/dl, Colesterol HDL <40 mg/dl para homens e >50 mg/dl para mulheres e, pressão arterial sistólica >130 mmHg ou pressão arterial diastólica >85 mmHg) após o transplante renal foi associada com maior risco de eventos cardiovasculares e mortalidade cardiovascular (25).

O aumento de peso em pacientes transplantados renais é comum tanto para pacientes obesos quanto para não obesos e, ocorre devido ao aumento de água e gordura corporal (27). Este aumento pode ser influenciado pela idade do paciente, pelo sexo e etnia, e pelo tipo de doador, ou seja, receptores de doadores vivos tendem a um aumento de peso mais significativo (21,28-31). Além disso, os fatores ambientais, como o excesso da ingestão

alimentar e o sedentarismo, além de fatores psicológicos, também podem estar envolvidos no ganho de peso corporal pós-transplante (21,32).

Além desses fatores classicamente associados a alterações de peso na população em geral, os pacientes submetidos ao transplante renal podem apresentar outros, como uso de imunossupressores/corticóides e perda de massa muscular durante o período de catabolismo que caracteriza o pós-transplante imediato (33,34). Aliados a estes, ainda existem outros potenciais indutores de ganho de peso nestes pacientes que não foram adequadamente estudados, sendo um exemplo as alterações na microbiota intestinal após o transplante.

A microbiota intestinal é composta predominantemente por bactérias, as quais encontram um meio favorável para a sua proliferação e diversificação das espécies (35,36). As comunidades microbianas intestinais podem exercer funções benéficas para seus hospedeiros que podem ser divididas em: biológica, exercendo função de barreira contra micro-organismos patogênicos; imunomoduladora, estimulando o sistema imune local e sistêmico; e, por fim, funções metabólicas e nutricionais, envolvendo a fermentação de alimentos e produção de nutrientes (36-38).

Pacientes obesos da população em geral apresentam modificações na microbiota intestinal quando comparados com indivíduos saudáveis e essas modificações vêm sendo implicadas na patogênese desta condição clínica (39). Poucos estudos avaliaram a microbiota intestinal em pacientes transplantados. Após o transplante renal ocorre uma diminuição na diversidade de bactérias intestinais e alguns filos, como os Fermicutes e Bacterioides, que usualmente são abundantes, e estes filos encontram-se diminuídos em casos de rejeição aguda e infecções urinárias e do trato respiratório (40-43). As alterações na microbiota intestinal que ocorrem após transplantes de órgãos sólidos podem ter um efeito no peso corporal após o procedimento.

Dessa forma, devido à importância da identificação de fatores associados ao ganho de peso nos pacientes submetidos ao transplante renal, esta dissertação tem os seguintes objetivos:

1. determinar quais fatores estão associados ao ganho de peso após o transplante renal em uma coorte de pacientes submetidos a este tipo de transplante em um centro transplantador do Sul do Brasil (artigo 1);

2. avaliar, por meio de uma revisão sistemática da literatura, se existem estudos que avaliaram alterações na microbiota intestinal após o transplante de órgãos sólidos e quais desfechos estão implicados com estas modificações, incluindo alterações no peso corporal dos pacientes transplantados (artigo 2).

2. REFERÊNCIAS

1. Martin C, Pecoits-Filho R, Riella MC. Nutrition for the post-renal transplant recipients. Transplant Proc, 2004;36:1650-54.

2. Jensen CE, Sorensen P, Petersen KD. In Denmark kidney transplantation is more cost-effective than dialysis. Dam Med J., 2014;61(3):A4796.

3. Hariharan S, Johson CP, Bresnahan BA, Taranto SE, Mclntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1088 to 1996. N Engl J Med, 2000;342(9):605-12.

4. 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.

5. 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.

6. Matas AJ, et al. OPTN/SRTR 2012 Annual Data Report: kidney. Am J Transplant, 2014;14(1):11-44.

7. Global Observatory on Donation and Transplantation (GODT): Organ Donation and Transplantation Activities. 2015 Reports. September 2017. Disponível em www.transplant-observatory/org, acessado em 06/01/2018.

8. Associação Brasileira de Transplante de Órgãos (ABTO). Registro Brasileiro de Transplantes. Ano XXII, n 4 Jan/Dez 2016.

9. Associação Brasileira de Transplante de Órgãos (ABTO). Registro Brasileiro de Transplantes. Ano XXIII, n 3 Jan/Set 2017.

10. Rosenberger J, GeckovaAM, 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.

11. Salas MAP, Serinivas TS. Update on the clinical utility of once-daily tacrolimus in the management of transplantation. Drug Desing, Development and Terapy, 2014;8:1183-1194.

12. Pestana JM. Desfechos clínicos de 11.436 transplantes renais realizados em centro único – Hospital do Rim. Journal Bras. Nefrol, 2017;39(3):287-295.

13. Johnson CP, Gallagher-Lepak S, Zhu Y-R, et al. Factors influencing weight gain after renal transplantation. Transplantation. 1993;56:822-826.

14. Baum CL. Weight gain and cardiovascular risk after organ transplanta- tion. J Parenter Enteral Nutr. 2001;25:114-119.

15. Chan W, Bosch JA, Jones D, McTernan PG, Phillips AC, Borrows R. Obesity in Kidney Transplantation. Journal of Renal Nutrition 2014; 24(1):1-12.

16. Souza GC, Costa C, Scalco R, Gonçalves of, Manfro RC. Serum Leptin, Insulin Resistance, and Body Fat After Renal Transplantation. Journal of Renal Nutrition 2008; 18(6):479-488.

17. Prisch JD. Weight Gain After Kidney Transplantation: Weigh Too Much! Transplantation, 2008;85(10):1387-88.

18. Vega J, Huidobro JPE, De La Barra S, Haro D. Influencia de la ganancia de peso derante el primer año del transplante renal en la sobrevida de injertos y pacientes. Rev Med Chile, 2015;143:961-970.

19. Chang SH, McDonald SP. Post-kidney Transplant Weight Change as Marker of Poor Survival Outcomes. Transplantation, 2008;85(10):1443-48.

20. Aksoy N. Weitght Gain After Kidney Transplanta. Experimental and Clinical Transplantation, 2016;(Suppl 3):138-140.

21. Cashion AK, Hathaway DK, Stanfill A, Thomas F, Ziebarth JD, Cui Y, Cowan PA, Eason J, Eason J. Pre-transplant predictors of one yr weight gain after kidney transplantation. Clin Transplant, 2014;28:1271-1278.

22. Lafranca JA, et al. Body mass index and outcome in renal transplant recipients: a systematic review and meta-analysis. BMC Med**,** 2015;13:111.

23. Nicoletto BB, Fonseca NK, Manfro RC, Goncalves LF, Leitao CB, Souza GC. Effects of obesity on kidney transplantation outcomes: a systematic review and meta-analysis. Transplantation 2014;98(2):167-76.

24. Hill CJ, et al. Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis. Nephrol Dial Transplant, 2015;30(8):1403-11

25. Pedrollo EF, Corrêa C, Nicoletto BB, Manfro RC, Leitão CB, Souza GC, Gonçalves LF. Efects of metabolic syndrome on kidney tranpslantation outcomes: a systematic review and meta-analysis. Transplantation International, 2016:1-8.

26. Mucha K, Foroncewicz B, Ryter M, Florczak M, Krajewska M, Mulka-Gierek M, Jabiry-Zieniewicz Z, Chmura A, Lisik W, Nazarewski S, Paczek L. Weight Gain in Renal Transplant Recipients in a Polish Single Centre. Ann Transplant 2015;20:16-20.

27. De Oliveira CM, Moura AE, Goncalves L, Pinheiro LS, Pinheiro FMJr, Esmeraldo RM. Post-transplantation weight gain: prevalence and the impact of steroid-free therapy. Transplant Proc, 2014;46(6):1735-1740.

28. Heng AE, Montaurier C, Cano N, et al. Energy expenditure, spontaneous physical activity and with weight gain in kidney transplant recipients. Clin Nutr, 2015;34(3):457-464.

29. Stanfill A, Bloodworth R, Cashion A. Lessons learned: experiences of gaining weight by kidney transplant recipients. Prog Transplant, 2012;22(1):71-78.

30. Bloodworth R, Ward K, Relyea G, Cashion AK. Food availability as a determinant of weight gain among renal transplant recipients. Res Nurs Health, 2014;37(3):253-259.

31. Baum CL, Thielke K, Westin E, Kogan E, Cicalese L, Benedetti E. Predictors of Weight Gain and Cardiovascular Risk in a Cohort of Racially Diverse Kidney Transplant Recipents. Nutrition, 2002;18(2):139-146.

32. Zelle DM, Kok T, Dontje ML, Danchell EI, Navis G, van Son WJ, Bakker SJ, Corpeleijn E. The role of diet and physical activity in post-transplant weight gain after renal transplatantion. Clin Transpalnt, 2013;27(4):484-90.

33. Pelletier SJ, Marasschio MA, Schaubel DE, et al. Suvival benefit of kidney and liver tranpalantation for obese patients on the waiting list. ClinTransplant, 2003;77-88.

34. Kugler C, Einhorn I, Gottlieb J, Warnecke G, Schwarz A, Barg-Hock H, Bara C, Haller H, Havarich A. Postopertative weight gaind during the first year after kidney, liver, heart, and lung transplant: a prospective study. Progress in Transplantation, 2015;25(1):49-55.

35. Perez HJ, Menezes ME, Acâmpara AJ. Microbiota intestinal: Estado da arte. Acta Gastroenterol Latino americana 2014;44(3)265-272.

36. Fiochi C, Souza HSP. Microbiota intestinal: sua importância e função. Jornalbrasileiromedicina 2012;100(3):30-38.

37. Mafra D, Fouque D. Gut microbiota and inflammation in chronic kidney disease patients. Clin Kidney J 2015;8:332–334.

38. Brandit KG, Sampaio MMSC, Miuki CJ. Importância da microflora intestinal. Pediatria 2006;28(2):117-2.

39. López-Cepero AA, Palacios C. Association of the Intestinal Microbiota and Obesity. P. R. Health Sci J. 2015;34(2):60-4.

40. Lee JR, Muthukumar T, Dadhania D, Toussaint NC, Ling L, Pamer E, Suthanthiran M. Gut Microbial Community Structure and Complications After Kidney Transplantation: A Pilot Study. Revista Transplantation 2014;98(7):697-705.

41. Sidaway P. Post-transplant complications associated with gut flora. Nature Reviews Nephrology, 2014;11:614.

42. Frickel WF, Maddox C, Song Y, Bromberg JS. Human Microbiota Characterization in the Course of Renal Transplantation. American Journal of Transplantation 2014;14:416–427.

43. Wang W, Xu S, Ren Z, Jiang J, Zheng S. Gut microbiota and allogeneic transplantation. JournalofTranslational Medicine 2015;13:275.

3. ARTIGO 1 – ORIGINAL

Factors associated with weight gain after kidney transplantation: a cohort study

Author names, affiliations and Email addresses

Cristina Carra Forte[a] **MD**. Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos Street, 2400, Porto Alegre, Brazil; e-mail: criscarraforte@yahoo.com.br

Elis Forcellini Pedrollo[b] **MD**. Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos Street, 2400 Porto Alegre, Brazil; e-mail: elispedrollo@gmail.com

Bruna Bellincanta Nicoletto[c] **PhD.** Área do Conhecimento de Ciências da Vida, Universidade de Caxias do Sul, Francisco Getúlio Vargas Street, 1130 – Building 57, Caxias do Sul, Brazil; e-mail: brunanicoletto@gmail.com

Jéssica Blatt[d]. **RD**. Nutrition Graduate Course, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;

Roberto Ceratti Manfro[f] **PhD**. Programa de Pós-Graduação em Medicina: Ciências Médicas, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
Division of Nephrology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. Ramiro Barcelos Street, 2350, Building 12, 2º floor, Porto Alegre, Brazil; e-mail: manfrorc@gmail.com

Gabriela Corrêa Souzae Ph.D. Programa de Pós-Graduação em Alimentação, Nutrição e Saúde, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
Division of Nutrition, Hospital de Clinicas de Porto Alegre, Ramiro Barcelos Street, 2350, Building 12, 2º floor, Room 2201F, Porto Alegre, Brazil; e-mail: gcsouza@hcpa.edu.br

Cristiane Bauermann Leitão[g] Ph.D. Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil;
Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Ramiro Barcelos Street, 2350, Building 12, 4º floor, Porto Alegre, Brazil; e-mail: cleitao@hcpa.edu.br

Corresponding author and contact information

Cristina Carra Forte; Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos Street, 2400, Porto Alegre, Brazil; e-mail: criscarraforte@yahoo.com.br; +55 (51) 99290-5581.

Abstract

Introduction: increased body weight, commonly observed after kidney transplantation, may be associated with worse outcomes in recipients. It is important to identify factors associated with weight gain after transplant in order to implement preventive interventions.

Objective: to identify predictors of one-year weight gain after renal transplantation.

Methods: a retrospective cohort study was conducted with 374 patients submitted to kidney transplantation in Hospital de Clínicas de Porto Alegre between January, 2006 and July, 2013. Clinical and laboratory variables were collected from electronic records and the outcome of interest was weight gain during the first year after renal transplantation. For statistical analysis we used SPPS software and a p-value <0.05 was considered statistically significant.

Results: There were 181 (48.4%) female patients, 334 (89.3%) with white ethnicity and the mean age was 44.4 ± 12.8 years. The mean BMI pre-transplant was 24.7 ± 4.1 kg/m², and 35 (9.9%) patients were classified as obese; 119 (33.6%) as overweight; 187 (52.8%) as normal weight; and 13 (3.7%) as malnutrition. After one year of follow-up, the mean BMI was 26.2 ± 5.0 kg/m², 61 (17.3%) patients were classified as obese; 133 (37.8%) as overweight; 148 (42.0%) as normal weight; and 10 (2.8%) as malnutrition. Weight gain was observed in 272 (72.7%) patients, and the average increase was 7.12 ± 5.9 kg. Patients who gained more than 5% of body weight during the first year post-transplant were more frequently females, and had lower body weight at baseline. In addition, they received a kidney from a living donor more frequently, and had a lower need for hospitalizations.

Conclusion: The female gender, lower pre-transplant body weight, lower number of hospitalizations and a kidney received from a living donor were associated with weight gain more than 5% in the first year post-transplant. The identification of risk factors for post-transplant weight gain is an important element when planning effective interventions to prevent weight gain and its consequences.

Keyword: kidney transplantation, weight gain, outcomes

Introduction

Renal transplantation is considered the best renal replacement therapy for patients with end-stage renal disease, since it enhances quality of life and patient survival when compared to other therapies, such as hemodialysis and peritoneal dialysis[1-5]. The number of solid organ transplants is increasing over the decades, mainly due to a rise in the amount of kidney transplants performed[6].

Faced with increased graft and patient survival after renal transplantation in recent decades, concerns about the quality of life of renal transplant recipients have been raised. Several factors have been associated with increased cardiovascular risk in renal transplant post operatory period, such as the development of post-transplant diabetes mellitus (PTDM), hypertension, dyslipidemia and obesity[7-9]. Approximately 50% of these patients gain weight after renal transplantation, regardless of pre-transplant nutritional status[10-12]. In our center, patients submitted to renal transplantation gain a mean of 2.9 kg within in one year of follow-up and 6.5 kg after five years, which represents 5.1% and 10.6% of body weight, respectively[13,14]. Factors such as ethnicity, correction of uremia, use of corticosteroids, increased food intake and sedentary lifestyle may be involved in the increase in body mass index (BMI) after renal transplantation[15-20].

Increased body weight and its negative metabolic consequences may be associated with worse outcomes after renal transplantation[21]. In a systematic review and meta-analysis conducted by our group, the diagnosis of metabolic syndrome after renal transplantation was associated with increased risk for graft loss, cardiovascular mortality and all-cause mortality[21].

Therefore, the identification of factors associated with weight gain in renal transplant patients may contribute to the implementation of preventive and therapeutic measures to avoid weight increase and its consequences. Thus, the aim of this study was to identify predictors of one-year weight gain after renal transplantation.

Patients and Methods

This retrospective cohort study assessed renal transplant patients, attending the Nephrology Division of the Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil, from January, 2006 to July, 2013. The study was approved by the Hospital Ethics Committee (protocol nº. 130051), in accordance with the ethical standards for human research set forth in

the Declaration of Helsinki[22]. All the researchers involved signed the Term of Commitment for the use of Data for research purposes, maintaining confidential information from patient registry.

The exclusion criteria were the following: age less than 18 years old, incomplete weight data pre-transplant and at 12 months post-transplantation, transplantation of multiple organs, less than one year of follow-up after transplantation, pre-transplantation diabetes mellitus - DM (diagnosed by the American Diabetes Association criteria)[23] and re-transplantation in the first year after transplantation.

Data were retrospective collected, and a structured questionnaire evaluated the following variables: age at transplant, gender, ethnicity, pre-transplant dry weight, etiology of renal disease, dialysis type (hemodialysis or peritoneal dialysis) and duration, donor type (living or deceased) and gender, presence of HCV or cytomegalovirus (CMV) antibodies, diagnosis of delayed graft function (DGF), and PTDM. The types of immunosuppressant medications in the first year post-transplantation were collected, as well as the cumulative doses of the prednisone. The estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula [24].

Anthropometric evaluation consisted of body weight (in kg) and height (in meters) measurements with patients wearing light clothes and without shoes, and BMI [calculated with the weight (kg)/height^2 (m) ratio][25]. Weight was assessed pre-transplant (dry weight), at three, six and 12 months after transplant. The BMI classification was based on cut-off points proposed by the World Health Organization[25]: low weight (BMI <18.5 kg/m²); normal weight (BMI 18.5-24.9 kg/m²); overweight (BMI 25.0-29.9 kg/m²); obesity grade I (BMI 30.0-34.9 kg/m²); obesity grade II (BMI 35.0-39.9 kg/m²) and obesity grade III (BMI ≥ 40.0 kg/m²).

Lipid profile (total cholesterol, HDL-cholesterol and triglycerides) and fasting glucose available at dialysis centers from the pre-transplant period were collected by medical charts review. Post-transplant information was collected by review of electronic charts.

The sample size calculation was performed with WinPepi software, based on the study by Cashion et al (2014)[17], which evaluated demographic, clinical and environmental factors associated with weight gain in the post-transplant period . A sample size of 258 subjects was needed considering a power of 90%, level of significance of 5%, an increase in body weight of at least 4 kg in one year of follow-up .

Data were analyzed using the statistical software package *Statistical Package for the Social Sciences* (SPSS Inc., version 22.0 for Windows, Chicago, IL, EUA) and were reported as mean ± standard deviation, median (interquartile range) or number of subjects (%) with the

specified variable. The association between categorical variables was assessed by chi-square and the differences between continuous variables were evaluated by ANOVA. To analyze the contribution of the factors related to the outcomes of interest, multiple logistic regression models were used, the independent variables were chosen according to the univariate analysis or their biological relevance in relation to the outcome. Statistical significance was set at a P value of less than 0.05 for all the analysis.

Results

Were initially evaluated 445 patients submitted to kidney transplantation between January 2006 and July 2013. Of these, 71 were excluded (<18 years old, n = 1; pre-transplant DM, n = 4; and incomplete weight data, n = 66). A total of 374 kidney transplant recipients were evaluated. There were 181 (48.4%) female patients, 334 (89.3%) with white ethnicity and the mean age was 44.4 ± 12.8 years. In relation to the etiology of renal disease, 128 (34.2%) patients had undetermined etiology, 106 (28.3%) hypertension, 61 (16.3%) glomerulonephritis, 53 (14.2%) polycystic kidney disease and 26 (7%) other causes. The dialysis type was hemodialysis in 351 (93.9%) patients, with a median duration of 2.66 (1.33-5.16) years. The mean BMI pre-transplant was 24.7 ± 4.1 kg/m², and 35 (9.9%) patients were classified as obese; 119 (33.6%) as overweight; 187 (52.8%) as normal weight; and 13 (3.7%) as malnutrition. After one year of follow-up, the mean BMI was 26.2 ± 5.0 kg/m², 61 (17.3%) patients were classified as obese; 133 (37.8%) as overweight; 148 (42.0%) as normal weight; and 10 (2.8%) as malnutrition.

Weight gain was observed in 272 (72.7%) patients, and the average amount gained was 7.12 ± 5.9 kg. Among patients with weight gain, 195 (71.6%) subjects had an increase of at least 5% in body weight, and 117 (43.0%) increased at least 10% from baseline.

Patients were separated into different groups based on its respective weight variation at one year of follow-up. One-hundred ninety five (52.1%) of total sample gained more than 5% of weight, 131 (35%) presented minor weight change (between 5% gain or 5% lost), and 48 (12.8%) patients lost more than 5% of body weight. Table 1 shows demographic, nutritional, clinical, and biochemical measures according to these three groups. Patients who gained more than 5% of body weight were younger, more frequently females, had a lower body weight at baseline, and were more commonly CMV positive. In addition, the >5% gain weight group received more frequently a kidney from a living donor, had a lower need for

hospitalization, lower rate of DGF and PTDM, and higher eGFR at all times than the other groups.

A multivariate model was built with >5% gain of body weight as the dependent variable and age at transplant, sex, pre-transplant weight, PTDM and rate of hospitalization as the independent ones (Table 2, Model 1). Female gender remained as a risk factor for weight gain; while increased age at transplant, higher pre-transplant weight and number of hospitalizations were protect factors against weight gain. In this model, PTDM was not associated with weight gain post-transplant. As receiving a kidney from a living donor, DGF and hospitalization rate are closely related, these three variables were not included in the same model. Separate models were constructed changing hospitalization rate for the other two variables. The model including DGF showed similar results, however DGF was not associate with weight gain and PTDM diagnosis was associated with protection against weight gain (Model 2). When living donor was included in the model (Model 3), female gender and pre-transplant body weight remain with similar associations. Living donor was associated with increased risk for weight gain, and PTDM was a protector factor. In this model, transplant age lost the association.

Discussion

In this retrospective cohort study conducted in a large tertiary care, university-affiliated hospital in southern Brazil, a high prevalence (52.1%) was observed in patients who gained more than 5% in the first year after renal transplantation. There was a significant association between greater weight gain and youngest age, female gender, lower BMI pre-transplant, CMV positive sorology, donor type (living), and lower number of hospitalizations. In addition, DGF, and PTDM were observed in a lower frequency in this group, as well as eGFR was higher 3, 6 and 12 months post-transplant. Most importantly, female gender, and lower pre-transplant body weight were independently associated with 5% weight gain after adjustments in different multivariate models. Receiving a kidney from a living donor and lower need for hospitalization were also associated with higher weight gain, probably reflecting a patient with a lower rate of post-transplant complications.

Weight gain is very often observed in kidney transplant recipients, especially during the first 12 months after transplant. In our study, 31.2% and 20.9% of the total sample gained at least 10% and 5% of body weight, respectively, after the first year of transplantation. The results found herein are consistent with previous studies[17,26].

We identified two factors as independently predictors for weight gain ≥5% from baseline to 12 months post-transplant in all multivariate models: female gender and lower pre-transplant weight. Other studies corroborated our findings. Female gender is a known risk factor for weight gain after renal transplant[27,28]. In a cohort study, weight gain one year post-transplant was significantly higher in women (13.6 kg) than in men (11.0kg, $p < 0.005$)[29]. Pre-transplant weight is an important factor to be considered when dealing with kidney transplant patients, since a systematic review and meta-analysis performed by our group demonstrated that the presence of obesity before renal transplantation is associated with a higher chance of early graft dysfunction[20].

So, the pattern of weight gain post-transplant would be even more relevant in previous overweight or obese subjects. Two recent studies reported that 29% and 38% of patient on the waitlist for renal transplantation were diagnosed as overweight or obese[30,31]. In our study, the prevalence of overweight or obesity pre-transplantation was even higher, about 43.5%, reaching a prevalence of 55.1% at 12 months post-transplantation. However, the weight gain was lower in this subset of patients, as the group of patients that gained more than 5% of body weight had a lower pre-transplant BMI. Similar results are reported by Baum et al. Initial BMI above 25 kg/m² predicted less weight gain 12 months post-transplant in a non-African American population[29]. The lower weight gain in overweight and obese transplant recipients may result from nutritional counseling that these patients could have received due to their increased BMI pre-transplant. However, this statement is merely speculative, since data on nutrition interventions were not reported in previous studies and was not collect in our cohort. A possible nutritional intervention may be an explanation also for the opposite association between PTDM and post-transplant weight gain.

Age at transplant was a protector factor for weight gain in some of our study multivariate models. Renal recipients younger than 30 years old had greater weight increase after kidney transplant than patients who are older than 50 years old in previous studies[32,10]. According to data from National Health and Nutritional Examination Survey III (NHANES III), the impact of age and sex is consistent with patterns of obesity in general population[33], as both factors are associated with higher prevalence of obesity.

Regarding the association of body weight gain and modifications in glomerular filtration rate, the literature results are still controversial. An observational cohort study of 84 patients observed a negative correlation between changes in BMI and eGFR[34]. The increase in BMI during the first year after kidney transplantation caused a significant decline in renal function, especially in the first three months post-transplant. On the other hand, a

retrospective study with 165 renal transplant patients observed that that patients who gained weight had increased eGFR (71.8±20.3 vs. 77.4±23.3 ml/min/1.73m^2, p<0.01) and patients who lost weight had a decrease in renal function (66.4±23.1 vs. 61.5±24.5 ml/min/1.73m^2, p<0.01) six months post-transplantation[35]. A third trial, including 1094 patients, lead to discrepant results and authors concluded that the association between changes in body weight and renal function varies according to the method used to estimate GFR and future studies must be conducted to investigate this association[36]. In our cohort, DGF was not independently associated with post-transplant body weight changes.

To date, no other study have reported an association between the number of hospitalizations and weight variations after kidney transplant. However, it is suggested that fewer hospitalizations are associated with less postoperative complications and better graft and patient survival[37]. Lower hospitalization rate may be a marker of better overall good heath, so patients with less transplant related complications would be hospitalized less frequently and have a better eGFR. In this sense, the association among number of hospitalization and eGFR with higher post-transplant weight gain probably is not of cause and effect. The same rationally may be the explanation why recipients from living donors, which are less prone to complications and with a better overall health status, gain more weight. Improvements in well-being might lead to greater appetite and consequently increased body weight.

This study has some limitations, mainly related to the retrospective design. We did not evaluate variables such as body composition, dietary intake, physical activity, schooling and family income which might be important factors associated with body weight post-transplant. However, despite these limitations, the study reaches its goal to show predictors of weight gain after renal transplant.

In conclusion, female gender and lower pre-transplant body weight were independently associated with weight gain more than 5% in the first year post kidney transplant. Lower rate of hospitalization and donation from a living donor were also risk factors for this outcome. Patients with the described characteristics should be closely followed to avoid excessive weight gain after kidney transplant. included in randomized clinical trials to receive nutritional counseling Randomized clinical trials should be conducted to evaluate if nutritional preventive interventions are capable to minimized body weight gain in these populations.

Table 1: Patients characteristics at baseline according to body weight change one year after kidney transplantation.

Variables	Weight loss >5% (n=48)	Weight change between <5% and >5% (n=131)	Weight gain >5% (n=195)	P
Patient related				
Age (mean/SD)*	47.6 ± 13.8[a]	46.2 ± 12.4[a]	42.4 ± 12.5[b]	0.006
Female gender, n (%)†	24 (50.0) [ab]	47 (35.9) [a]	110 (56.4) [b]	<0.001
Caucasian, n (%)†	44 (91.7)	117 (89.3)	173 (88.7)	0.747
Pre-transplant weight, kg (mean/SD)*	69.2 ± 10.9[a]	70.4 ± 13.2[a]	64.2 ± 12.2[b]	<0.001
BMI pre-transplant, kg/m²*	25.9 ± 3.4[a]	25.1 ± 3.9[ab]	24.2 ± 4.3[b]	0.016
BMI post-transplant, kg/m²*	23.2 ± 3.4[a]	25.3 ± 4.1[b]	27.7 ± 5.5[c]	<0.001
HCV, n (%)†	42 (87.5)	121 (92.4)	178 (91.3)	0.595
CMV, n (%)†	38 (79.2) [a]	95 (72.5) [a]	166 (85.6) [b]	0.015
Biochemical tests, mg/dL				
Total Cholesterol pre-transplant (mean/SD)*	176.3 ± 46.5	174.0 ± 43.4	165.2 ± 40.6	0.287
HDL-cholesterol pre-transplant (mean/SD)*	40.8 ± 14.7	38.9 ± 12.9	41.7 ± 12.4	0.383
LDL-cholesterol pre-transplant (mean/SD)*	100.7 ± 32.8	99.9 ± 33.9	98.9 ± 34.4	0.970
Triglycerides pre-transplant (median/percentiles)**	146.5 (107.0-230.0)	172 (106.0-242.0)	141 (104.0-189.5)	0.107
Glucose pre-transplant (mean/SD)*	95.7 ± 10.5	100.1 ± 49.5	92.6 ± 20.5	0.308
Glucose post-transplant	94.6 ± 17.3	90.3 ± 20.77	92.1 ± 20.3	0.663

Transplant related				
Donor type, living, n (%)†	9.0 (18.8) [a]	27.0 (20.6) [a]	71.0 (36.4) [b]	0.002
Number of hospitalizations (median/percentiles)**	1.0 (0.0-3.0)[a]	1.0 (0.0-2.0)[a]	1.0 (0.0-2.0)[b]	0.002
DGF, n (%)†	30 (63.8) [a]	74 (56.5) [ab]	87 (44.8) [b]	0.022
PTDM, n (%)†	13 (27.1) [ab]	45 (34.4) [a]	34 (17.4) [b]	0.002
Acute Rejection, n (%)†	25 (52.1)	87 (66.4)	129 (66.2)	0.160
MDRD 3 months (median/percentiles)**	33.5 (20.2-48.0)[a]	37.0 (24.0-50.0)[a]	48.0 (35.5-60.0)[b]	<0.001
MDRD 6 months (median/percentiles)**	39.5 (27.2-56.7)[a]	42.0 (32.5-52.2)[a]	49.0 (30.8-60.0)[b]	<0.001
MDRD 12 months (median/percentiles)**	39.0 (23.0-60.0)[a]	46.0 (35.0-59.0)[b]	52.0 (40.0-60.0)[c]	<0.001
Prednisone, n (%)†	48 (100)	126 (96.2)	189 (96.9)	0.176
Cumulative Prednisone dose (mg) (median/percentiles)**	21.300 (14.600-25.000)	21.600 (16.500-24.600)	22.100 (15.500-25.800)	0.739
Daily dose of prednisone (mg)	58.35	59.17	60.54	
Tacrolimus, n (%)†	40.0 (83.3)	96 (73.3)	156.0 (80.0)	0.129
Cyclosporine, n (%)†	4.0 (8.3)	28.0 (21.4)	31.0 (15.9)	0.156

DGF = Delayed Graft Function, PTDM = Diabetes Mellitus post-transplant, HCV = Hepatitis C, CMV = cytomegalovirus, MDRD = Modification of Diet in Renal Disease.

*ANOVA **ANOVAlog †Chi-Squared

Table 2: Multiple logistic regression analysis for weight gain > 5% (dependent variable) in first year post-transplant.

	Multiple regression	β (95% IC)	P value
Model 1	Gender (female)	1.681 (1.06 – 2.66)	0.027
	Pre-transplant weight	0.971 (0.95 – 0.99)	0.003
	Transplant age	0.982 (0.96 – 0.99)	0.042
	PTDM	0.617 (0.36 – 1.04)	0.72
	Number of hospitalizations	0.790 (0.66 – 0.93)	0.007
Model 2	Gender (female)	1.712 (1.08 – 2.71)	0.022
	Pre-transplant weight	0.977 (0.95 – 0.99)	0.015
	Transplant age	0.983 (0.96 – 1.00)	0.049
	PTDM	0.538 (0.31 – 0.90)	0.020
	DGF	0.664 (0.43 – 1.02)	0.065
Model 3	Gender (female)	1.733 (1.09 – 2.75)	0.020
	Pre-transplant weight	0.974 (0.95 – 0.99)	0.006
	Transplant age	0.989 (0.97 – 1.01)	0.266
	PTDM	0.540 (0.32 – 0.91)	0.021
	Living donor	2.122 (1.26 – 3.57)	0.005

PTDM = Diabetes Mellitus post-transplant; DGF = Delayed Graft Function

References

1. Wolfe RA, Ashby VB, Milford EL, 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;341:1725.

2. Martin C, Pecoits-Filho R, Riella MC. Nutrition for the post-renal transplant recipients. Transplant Proc, 2004;36:1650-54.

3. Sue Kent P, MS, RD, CSR, LD. Issues of Obesity in Kidney Transplantation. J Ren Nutr, 2007;17(2):107-13.

4. Moreso F, Hernandez D. Has the survival of the graft improved after renal transplantation in an era of modern immunosuppression? Nefrologia, 2013;33:14.

5. Tonelli M, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. Am Journal Transplant, 2011;11(10):2093-109.

6. Global Observatory on Donation and Transplantation (GODT): Organ Donation and Transplantation Activities. 2015 Reports. September 2017.

7. Amstrong KA, Campbell SB, Hawley CM, Johnson DW, Isbel NM. Impact of obesity on renal transplant outcomes. Nephrol, 2005; 10:405-13.

8. Wissing KM, Pipeleers L. Obesity, metabolic syndrome and diabetes mellitus after renal transplantation: Preventio and treatment. Transplantation Reviews, 2014;28(2):37-46.

9. Palepu S, Prasad GVR. New-onset diabetes mellitus after kidney transplantation: Current status and future directions. World J Diabetes, 2015;6(3):445-455.

10. Johnson CP, Gallagher-Lepak S, Zhu Y-R, et al. Factors influencing weight gain after renal transplantation. Transplantation, 1993;56:822-827.

11. Baum CL. Weight gain and cardiovascular risk after organ transplanta- tion. J Parenter Enteral Nutr, 2001;25:114-119.

12. Chan W, Bosch JA, Jones D, McTernan PG, Phillips AC, Borrows R. Obesity in Kidney Transplantation. Journal of Renal Nutrition, 2014; 24(1):1-12.

13. Souza GC, Costa C, Scalco R, Gonçalves of, Manfro RC. Serum Leptin, Insulin Resistance, and Body Fat After Renal Transplantation. Journal of Renal Nutrition, 2008; 18(6):479-488.

14. Nicoletto BB, Souza GC, Gonçalves LF, Costa C, Perry IS, Manfro RC. Leptin, Insulin Resistance, and Metabolic Changes 5 Years After Renal Transplantation. Journal of Renal Nutrition, 2012; 22(4):440-449.

15. Hricik DE. Weight gain after kidney transplantation. Am J Kidney Dis, 2001;38(2):409-410.

16. Dimeny EM. Cardiovascular disease after renal transplantation. Kidney Int, 2002;61(80):S78-S84.

17. Cashion AK, Hathaway DK, Stanfill A, Thomas F, Ziebarth JD, Cui Y, Cowan PA, Eason J. Pre-transplant predictores of on yr weight after kidney transplantation. Clín. Transplant, 2014; 28(11):1271-8.

18. de Oliveira CM, Moura ÁE, Gonçalves L, Pinheiro LS, Pinheiro FM Jr, Esmeraldo RM. Post-transplantation weight gain: prevalence and the impact of steroid-free therapy. Transplant Proc, 2014;46(6):1735-40.

19. Bloodworth RF. Food Availability as a Determinant of weight gain among Renal Transplant Recipients. Res Nurs Health, 2014;37(3):253–259.

20. Heng AE, Montaurier C, Cano N, Caillot N, Blot A, Meunier N, Pereira B, Marceau G, Sapin V, Jouve C, Boirie Y, Deteix P, Morio B. Energy expenditure, spontaneous physical activity and with weight gain in kidney transplant recipients. Clin Nutr, 2015;34(3):457-64.

21. Pedrollo EF, Corrêa C, Nicoletto BB, Manfro RC, Leitão CB, Souza GC, Gonçalves LFS. Effects of metabolic syndrome on kidney transplantation outcomes: a systematic review and meta-analysis. Transplantation International, 2016; 1-8.

22. Declaração de Helsinque da Associação Médica Mundial (WMA). Princípios Éticos para Pesquisa Médica envolvendo Seres Humanos, 2013.

23. American Diabetes Association. Standards of Medical Care In Diabetes.. Diabetes Care, 2017;40(suppl1):s11-24.

24. Brito TNS, Oliveira ARA, Silva AKC. Taxa de filtração glomeurlar estimada em adultos: características e limitações das equações utilizadas. Revista Brasileria de Análises Clínicas, 2016.

25. Organization WH. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation on Obesity. WHO Press Geneva, 2000;June 3-5.

26. Pirsh John D. Weight gain after Kidney Transplantation: weight too much! Transplantation, 2008;85(10):1387-1388.

27. Diaz JM, Sainz Z, Oliver A et al. Post-Renal Transplantation Weight Gain: Its Causes and Its Consequences. Transplant Proc, 2005;37:3839–41.

28. Pantik C, Cho YE, Hathaway D, Tolley E, Cashion A. Characterization of Body Composition and Fat Massa Distribuition 1 Year After Kidney Transplantation. Prog Transplant, 2017;27(1):10-15.

29. Baum CL, Thielke K, Westin E, Kogan E, Cicalese L, Benedetti E. Predictors of Weight Gain and Cardiovascular Risk in a Cohort of Racially Diverse Kidney Transplant Recipients. Nutrition, 2002;18(2):139-146.

30. Costa B, Moratelli L, Silva LB, Paiva ACM, Silva AN, Carminatti M, Bastos MG, Sanders-Pinheiro H. Body Mass Index y the First Year After Kidney Transplantatio. Transplantation Proceedings, 2014;46:1750-1752.

31. Mucha K, Foroncewicz B, Ryter M, Florczak M, Krajewska M, Mulka-Gierek M, Jabiry-Zieniewicz Z, Chmura A, Lisik W, Nazarewski S, Paczek L. Weight Gain in Renal Transplant Recipients in a Polish Single Centre. Ann Transplant, 2015;20:16-20.

32. Pischon T, Sharma AM. Obesity as a risk factor in renal transplant patients. Nephrol Dial Transplant, 2001;16:14-17.

33. National Institutes of Health. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults – the evidence report. Obes Res, 1998;6(suppl2):51S.

34. Kim IK, Choi SH, Son S, Ju MK. Early weight gains after transplantation can cause adverse effect on Transplant Kidney Function. Transplantation Proceedings, 2916;48(3):893-896.

35. Thoma B, Grover VK, Shorker A. Prevalence of weight gains in patients with better renal transplant function. Clin Nephrol, 2006;65(6):408-14.

36. Chang A, Greene TH, Wang X, Kendrick C, Kramer H, Wright J, Astor B, Shafi T, Toto R, Lewis J, Appel LJ, Grams M. The effects of weight change on glomerular filtration rate. Nephrol Dial Transplant, 2015;30:1870-1877.

37. Mehrabi A, Fonouni H, Wente M, Sadeghi M, Einsenbach C, Encke J, Schimied BM, Libicher M, Zeier M, Weitz J, Buchler MW, Schmidt J. Wound complications following kidney and liver transplantation. Clin Transplant, 2006;20(17):97:110.

4. ARTIGO 2 – REVISÃO SISTEMÁTICA

Intestinal microbiota changes after solid organ transplant: a systematic review.

Cristina Carra Forte[1], Elis Forcellini Pedrollo[1], Gabriela Corrêa Souza[2,3], Cristiane Bauermann Leitão[1,4]

[1] Programa Pós-graduação em Ciências Médicas: Endocrinologia, Universidade Federal do Rio Grande do Sul (UFRGS). Porto Alegre, RS, Brazil.

[2] Departamento de Nutrição, Escola de Medicina, Universidade Federal do Rio Grande do Sul (UFRGS). Porto Alegre, RS, Brazil.

[3] Divisão de Nutrição, Hospital de Clínicas de Porto Alegre (HCPA). Porto Alegre, RS, Brazil.

[4] Division of Endocrinology, Hospital de Clínicas de Porto Alegre (HCPA). Porto Alegre, RS, Brazil.

Corresponding author:

Cristina Carra Forte criscarraforte@yahoo.com.br Programa Pós-graduação em Ciências Médicas: Endocrinologia, Universidade Federal do Rio Grande do Sul (UFRGS). Rua Ramiro Barcelos, 2400 90040-341, Porto Alegre, RS, Brazil.

Artigo aceito para publicação na Revista *Clinical & Biomedical Research*.

Abstract

Introduction: The intestinal microbiota may undergo changes after solid organ transplantation. The purpose of this systematic review was to characterize the intestinal microbiota of patients undergoing solid organ transplantation.

Methods: MEDLINE, EMBASE and Cochrane Library databases were searched from inception to July 21, 2017. Studies of patients undergoing solid organ transplantation that evaluated changes in intestinal microbiota composition and one of the following outcomes were included: post-transplant weight, new onset diabetes after transplantation, delayed graft function, acute rejection, graft and patient survival, and post-transplant infections.

Results: Out of 765 studies found in this search, two studies (86 patients) fulfilled inclusion criteria. Both studies assessed kidney transplantation recipients, and a reduction in bacterial species diversity after transplantation was observed. Changes in intestinal microbiota were associated with acute rejection in both studies. One study reported diarrhea and urinary infections, while the other one reported urinary and respiratory infections. None of them reported other outcomes of interest.

Conclusion: Changes in intestinal microbiota were observed after kidney transplantation, and they were associated with higher incidence of acute rejection and infections in transplant recipients. However, data are still scarce and more studies are needed to evaluate if microbiota changes have an impact on post-transplant outcomes.

Key words: transplantation, intestinal microbiota, outcomes.

Introduction

The intestinal microbiota is composed mainly by bacteria, which find a favorable environment for proliferation. Deregulation of intestinal mucosal homeostasis leads to the development of diseases and detrimental conditions to the host[1,2]. These intestinal microbial communities perform some beneficial functions to their hosts, which are divided into three levels: (1) biological, as barriers against pathogenic microorganisms; (2) immunomodulatory, as a stimulus to the local and systemic immune system; and, finally, (3) nutritional and metabolic, involving the fermentation of food products and production of nutrients[3-6].

Changes in the intestinal microbiota have been reported in individuals with obesity and/or metabolic syndrome (MS)[7-9]. Obesity development is associated with specific phylum of bacteria inhabiting the human gut[8,10,11]. Thus, obese individuals may have a higher proportion of Firmicutes and a lower proportion of Bacteroides compared with individuals with healthy weight[8]. Furthermore, some authors have suggested that treatments with emphasis on balancing gut microbiota may be an alternative for obesity treatment[7-9]. Regarding MS, the intestinal microbiota has an important role in metabolic balance, affecting the absorption of glucose and lipids and intestinal motility[7].

Conversely, the intestinal microbiota may influence solid organ transplant outcomes. The gut microbiota of organ transplant recipients is expected to undergo changes in its composition, as the majority of patients use antibiotics as prophylaxis or treatment of infections during initial hospitalization[12-16]. Since changes in the gut microbiota are associated with metabolic disarrangements in both the obese and the MS population, as described above[7-9], similar effects might be observed in organ transplant recipients. Advances in immunosuppressive therapy have improved post-transplant outcomes in recent decades, increasing both graft and patient survival[17-19]. However, organ transplant recipients continue to show higher mortality than the general population, and this fact is directly related to the increased incidence of cardiovascular disease in the post-transplant period[17,20-26]. Several factors have been associated with increased cardiovascular risk after transplantation, especially the development of MS[27-31]. It is known that weight gain is significant in transplanted patients, affecting 30-50% of these individuals[32-34]. In addition, both obesity and MS are associated with worse outcomes after transplant[34-36].

Few studies have evaluated the composition of the intestinal microbiota in organ transplant recipients. Thus, the objective of this systematic review was to characterize the

intestinal microbiota in patients undergoing solid organ transplantation and its possible associations with post-transplant outcomes.

Methods

Data sources and searches

All studies were found using Medical Subject Headings (MeSH) and entry terms (Supplemental file) while searching MEDLINE (via PubMed), EMBASE and Cochrane Library databases, as well as gray literature (conference abstracts), from inception to July 21, 2017. All relevant articles were considered for review regardless of language.

Study Selection

Studies assessing changes in the gut microbiota of transplanted patients (kidney, liver, lung, pancreas or heart transplantation) were included. Bacterial species diversity was defined according to the Shannon index, which analyzes the diversity of categorical data considering heterogeneity, variety, complexity and abundance of bacterial species in the microbiota[37].

Studies with replicated data or pediatric patients were excluded, as well as studies that assessed database populations. Two independent investigators performed study selection, initially by titles and abstracts, and subsequently by full-text assessment. Disagreements were resolved by consensus or a third investigator.

Data Extraction and Quality Assessment

Data extraction was performed by two investigators according to the following data: author's name, year of publication, number of patients included, length of follow-up, demographic characteristics, number of fecal samples, microbiota features and the following post-transplant outcomes: post-transplant weight gain, new-onset diabetes after transplantation (NODAT), delayed graft function (DGF), acute rejection, graft and patient survival, and post-transplant infections (urinary tract, respiratory and intestinal infections). Both reviewers were not blinded to authors, institutions or article journals. The quality of studies was assessed using the Newcastle Quality Assessment Scale[38]. An overall score of 5 or less was considered low quality; 6 to 7 was considered moderate quality; and 8 to 9 was

considered high quality. This systematic review is described according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[39].

Results

Database search identified 765 studies. Of these, 48 studies were duplicated and 680 studies were excluded after an analysis of titles and abstracts. The remaining 37 studies were selected for full-text assessment, and only two of them fulfilled eligibility criteria (Figure 1). Both studies have evaluated the gut microbiota and kidney transplant. Table 1 shows demographic characteristics of the patients included in these studies and Table 2 shows the quality of the studies. Main results are described below.

Lee et al.[40] have assessed 85 fecal samples of 26 kidney transplant recipients. Samples were collected during the first 3 months after transplantation and accounted at least two per patient. The fecal microbial composition was identified by polymerase chain reaction (PCR). Reduced bacterial species diversity, according to the Shannon index, and increased amounts of Proteobacteria were found in post-transplant fecal samples compared with pre-transplant samples ($p = 0.04$). Three patients with acute rejection showed increased number of bacteria from the order Lactobacillales ($p = 0.04$) and a significant decrease in phylum Bacteroidetes ($p = 0.03$) compared with patients without acute rejection. Six patients developed diarrhea in the post-transplant period. These patients had decreased amounts of Bacteroidales, Bacteroidetes, Ruminococcus and Coprococcus compared with those without diarrhea ($p = 0.007$). Finally, patients with urinary tract infection ($n = 3$) showed increased frequency of the genus Enterococcus ($p = 0.005$).

Fricke et al.[41] have evaluated 60 patients during the first 6 months after kidney transplant and the composition of fecal microbiota was evaluated by rectal swab. Bacterial species diversity, according to the Shannon index, decreased significantly in the first month after kidney transplant ($p = 0.01$), and this change was maintained until the assessment of the last sample at 6 months. Fermicutes phylum accounted for most bacteria observed in the microbiota of post-transplant patients. Individuals with acute rejection ($n = 4$) had a significant decrease in four bacterial groups, including Anaerotruncus, Coprobacillus, Coprococcus and an unknown member of the Peptostreptococcaceae ($p < 0.005$), compared with the 14 patients without acute rejection. Four patients had an episode of respiratory or urinary tract infection and a decrease in the amount of Fermicutes phylum, mainly from the genus Anaerotruncus ($p < 0.001$).

Discussion

This systematic review has revealed that the diversity of bacterial species decreases in the intestinal microbiota of kidney transplant recipients. These alterations in the number of bacteria from were associated with acute rejection, diarrhea and respiratory and urinary infections.

The human microbiota tends to change rapidly during childhood, when food is introduced, and more slowly in adult age[3]. The components of the human intestinal microbiota are constantly being modified by modern lifestyle. It is well known that factors such as host diet, age range, hygiene and use of antibiotics play a relevant role in shaping the intestinal microbiota[5,42,43].

Some key contributing factors are associated with intestinal microbiota changing patterns[44], and the use of antibiotics and immunosuppressive therapy are among the most relevant. These interventions are associated with decreased intestinal bacteria diversity and dysregulation of the immune system, and patients undergoing solid organ transplantation commonly use both. Antibiotic effects depend on composition, dosage, spectrum, route of administration and duration of treatment[45,46]. These medications are not always harmless to the transplant patient and, in most cases, their frequent use is associated with intestinal dysbiosis and production of resistant pathogens[12].

A retrospective cohort study has reported a 50% incidence of infectious episodes in kidney transplant recipients during the first months after transplantation and concluded that the most frequent infection involved the urinary tract, followed by cytomegalovirus, surgical incision and lung infections[47]. Lee et al.[48] have demonstrated that the most commonly used antibiotics for urinary infections are cefazolin and vancomycin. Kidney transplant recipients with infections tend to be older, to use more potent immunosuppression, to have received the graft from a deceased donor and to have had a longer time on dialysis[47]. In addition, female gender, prolonged use of urinary catheter, retransplantation, cold ischemia time and DGF may be risk factors for urinary tract infections[47,48]. Infections remain a recurring problem in transplanted patients, resulting in deaths with functioning graft and triggering complications that affect the quality of life of patients[49]. Based on this information, the use of antibiotics is commonly required post-transplantation, and this may be the most important factor leading to microbiota changes in these patients.

The intestinal microbiota represents a stimulus for the development of the immune system, especially the establishment of lymphoid tissues, activation of neutrophils, induction

of IgA and regulation of homeostasis of intestinal T cells (regulatory T cell and T helper), which may interfere in the human susceptibility to infections and immune-mediated diseases[50,51]. When altered, the microbiota shows a reduction in the number of bacteria that favor regulatory cells or an increase in the number of cells that help the induction of immune systems in response to pathogens, leading to infections and diseases in individuals[52]. This deviation from a more tolerant immune system to the activation of effector cells may be the link between post-transplant microbiota changes and acute rejection observed in one of the studies[40,51]. However, further studies should be performed to evaluate the association of the intestinal microbiota with the mechanisms of infection development and acute rejection in transplant patients.

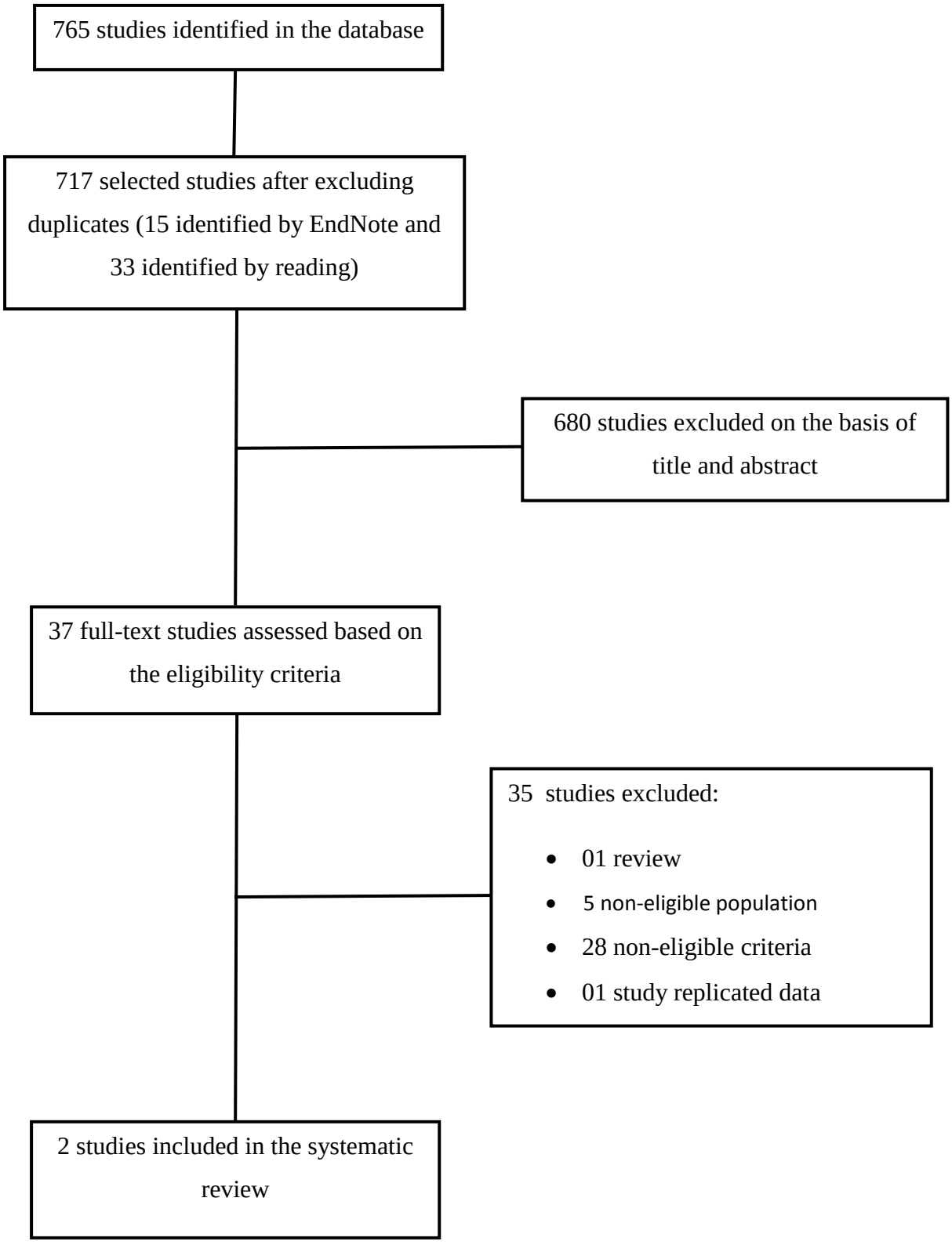
This systematic review has some limitations, including the scant number of studies assessing intestinal microbiota in patients after solid organ transplantation and their small sample size and clinical heterogeneity. Also, another clear limitation was the difference in the methods used in the studies for collecting microbiota samples.

Conclusion

Changes in the intestinal microbiota were observed after kidney transplantation, and they were associated with higher incidence of acute rejection and infections in recipients. However, data are still scarce and more studies are needed to evaluate if microbiota changes have an impact on other metabolic and graft-related post-transplant outcomes.

Supplemental file, Text 1. 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” OR “Transplantation, Liver” OR “Liver Transplantations” OR “Transplantations, Liver” OR “Transplantation, Hepatic” OR “Grafting, Liver” OR “Graftings, Liver” OR “Liver Grafting” OR “Liver Graftings” OR “Hepatic Transplantation” OR “Hepatic Transplantations” OR “Transplantations, Hepatic” OR “Grafting, Lung” OR “Graftings, Lung” OR “Lung Grafting” OR “Lung Graftings” OR “Transplantation, Lung” OR “Lung Transplantations” OR “Transplantations, Lung” OR “Grafting, Heart” OR “Graftings, Heart” OR “Heart Grafting” OR “Heart Graftings” OR “Transplantation, Heart” OR “Heart Transplantations” OR “Transplantations, Heart” OR “Cardiac Transplantation” OR “Cardiac Transplantations” OR “Transplantations, Cardiac” OR “Transplantation, Cardiac” OR “Grafting, Pancreas” OR “Graftings, Pancreas” OR “Pancreas Grafting” OR “Pancreas Graftings” OR “Transplantation, Pancreas” OR “Pancreas Transplantations” OR “Transplantations, Pancreas” AND "Microbiotas" OR "Microbiome" OR "Microbiomes" OR "Human Microbiome" OR "Human Microbiomes" OR "Microbiomes, Human" OR "Microbiome, Human".



Supplemental file, Figure 1. Flowchart: identification and selection of articles included in the systematic review.

Supplemental file, Table 1. Patients characteristics of included studies**.**

	Study	
General characteristics	**Lee JR et al[40]**	**Fricke WF et al[41]**
Transplant recipients, n (%)	26 (100)	60 (100)
Men, n (%)	13 (50)	38 (63)
Womem, n (%)	13 (50)	22 (37)
Age (years)	56 (46-63)	58 (30-79)
Etinicity		
White, n (%)	16 (61)	36 (60)
Hispanic, n (%)	6 (23)	0
African American, n (%)	4 (15)	24 (40)
Type of transplantation		
Living-donor, N (%)	14 (54)	N/A
Deceased donor, N (%)	12 (46)	N/A
Organ type		
Kidney, N (%)	24 (92)	N/A
Simultaneous pancreas and kidney, N (%)	2 (8)	N/A
Imunossupression with Tacrolimus	26 (100)	N/A
Perioperative antibiotics		
Cefazolin, n (%)	21 (81)	N/A
Vancomycin, n (%)	3 (11)	N/A
Ampicilin and Sulbactan, n (%)	2 (8)	N/A

N/A: Not available

Supplemental file, Table 2. Quality scoring based on the Newcastle-Ottawa Quality Assessment Scale

Study, Year (Ref)	Selection	Comparability	Outcome
Lee JR et al, 2014[40]	***	-	****
Fricke WF et al, 2014[41]	****	-	****

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

References

1. Perez HJ, Menezes ME, d'Acâmpora AJ. Microbiota intestinal: estado da arte. Acta Gastroenterol Latinoam. 2014;44:265-72.

2. Sekirov I, Russell SL, Antunes LC, Finlay BB. Gut microbiota in health and disease. Physiol Rev. 2010;90:859-904.

3. Fiochi C, Souza HS. Microbiota intestinal: sua importância e função. J Bras Med. 2012;100:30-8.

4. Mafra D, Fouque D. Gut microbiota and inflammation in chronic kidney disease patients. Clin Kidney J. 2015;8:332-4.

5. Brandt KG, Sampaio MM, Miuki CJ. Importância da microflora intestinal. Pediatria. 2006;28:117-27.

6. Schippa S, Conte MP. Dysbiotic events in gut microbiota: impact on human health. Nutrients. 2014;6:5786- 805.

7. Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. World J Gastroenterol. 2014;20:16079-94.

8. López-Cepero AA, Palacios C. Association of the intestinal microbiota and obesity. P R Health Sci J. 2015;34:60-4.

9. Escobedo G, López-Ortiz E, TorresCastro I. Gut microbiota as a key player in triggering obesity, systemic inflammation and insulin resistance. Rev Invest Clin. 2014;66:450-9.

10. Kobyliak N, Virchenko O, Falalyeyeva T. Pathophysiological role of host microbiota in the development of obesity. Nutr J. 2016;15:43.

11. Sanz Y, Santacruz A, Gauffin P. Gut microbiota in obesity and metabolic disorders. Proc Nutr Soc. 2010;69:434-41.

12. Lange K, Buerger M, Stallmach A, Bruns T. Effects of antibiotics on gut microbiota. Dig Dis. 2016;34:260-8.

13. Alkatheri AM. Urinary tract infections in Saudi renal transplant recipients. J Infect Dis Immun. 2013;5:18-23.

14. Parapiboon W, Ingsathit A, Jirasiritham S, Sumethkul V. High incidence of bacteriuria in early post-kidney transplantation; results from a randomized controlled study. Transplant Proc. 2012;44:734-6.

15. Di Cocco P, Orlando G, Mazzota C, Rizza V, D'Angelo M, Clemente K, et al. Incidence of urinary tract infections caused by germs resistant to antibiotics commonly used after renal transplantation. Transplant Proc. 2008;40:1881-4.

16. Säemann M, Hörl WH. Urinary tract infection in renal transplant recipients. Eur J Clin Invest. 2008;38:58-65.

17. Manfro RC, Carvalhal GF. Transplante renal. Rev AMRIGS. 2003;47:14-9.

18. Posadas Salas MA, Srinivas TR. Update on the clinical utility of oncedaily tacrolimus in the management of transplantation. Drug Des Devel Ther. 2014;8:1183-94.

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

20. Gillis KA, Patel RK, Jardine AG. Cardiovascular complications after transplantation: treatment options in solid organ recipients. Transplant Rev. 2014;28:47-55.

21. Alencastro MG, Lemos JR, Bastos NM, Vicari AR, Gonçalves LF, Manfro RC. Avaliação da síndrome metabólica e suas associações com inflamação e função do enxerto em pacientes receptores de transplante renal. J Bras Nefrol. 2013;35:299-307.

22. Gonçalves MA, Lunardelli A, Lecke SB, Ghem C, Oliveira JR. Perfil lipídico de transplantados renais em uso de terapia imunossupressora. Rev Bras Anal Clin. 2014;46:68-73.

23. 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:A7.

24. 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;123:55-80.

25. 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;27:262- 70.

26. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet. 2011;378:1419-27.

27. Armstrong KA, Campbell SB, Hawley CM, Johnson DW, Isbel NM. Impact of obesity on renal transplant outcomes. Nephrol. 2005;10:405-13.

28. Ye X, Kuo HT, Sampaio MS, Jiang Y, Bunnapradist S. Risk factors for development of new-onset diabetes mellitus after transplant in adult lung transplant recipients. Clin Transplant. 2011;25:885-91.

29. Hackman KL, Bailey MJ, Snell GI, Bach LA. Diabetes is a major risk factor for mortality after lung transplantation. Am J Transplant. 2014;14:438-45.

30. Beckmann S, Ivanovic N, Drent G, Ruppar T, De Geest S. Weight gain, overweight and obesity in solid organ transplantation--a study protocol for a systematic literature review. Syst Rev. 2015;4:2.

31. Milaniak I, Przybylowski P, Wierzbicki K, Sadowski J. Post-transplantation body mass index in heart transplant recipients: determinants and consequences. Transplant Proc. 2014;46:2844-7.

32. Chan W, Bosch JA, Jones D, McTernan PG, Phillips AC, Borrows R. Obesity in kidney transplantation. J Ren Nutr. 2014;24:1-12.

33. Baum CL. Weight gain and cardiovascular risk after organ transplantation. JPEN J Parenter Enteral Nutr. 2001;25:114-9.

34. Kugler C, Einhorn I, Gottlieb J, Warnecke G, Schwarz A, Barg-Hock H, et al. Postoperative weight gain during the first year after kidney, liver, heart, and lung transplant: a prospective study. Prog Transplant. 2015;25:49-55.

35. Nicoletto BB, Fonseca NK, Manfro RC, Gonçalves LF, Leitão CB, Souza GC. Effects of obesity on kidney transplantation outcomes: a systematic review and meta-analysis. Transplantation. 2014;98:167-76.

36. Pedrollo EF, Corrêa C, Nicoletto BB, Manfro RC, Leitão CB, Souza CG, et al. Effects of metabolic syndrome on kidney transplantation outcomes: a systematic review and meta-analysis. Transpl Int. 2016;29:1059-66.

37. Haegeman B, Hamelin J, Moriarty J, Neal P, Dushoff J, Weitz JS. Robust estimation of microbial diversity in theory and in practice. ISME J. 2013;7:1092-101.

38. Wells GA, Shea B, O'Connel D, Peterson J, Welch V, Losos M, , et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in metaanalysis. In: Proceedings of the Third Symposium on Systematic Reviews: Beyond the Basics: Improving Quality and Impact; 2010; Oxford. Oxford; 2010. p. 13-5.

39. 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. Metaanalysis of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283:2008-12.

40. Lee JR, Muthukumar T, Dadhania D, Toussaint NC, Ling L, Pamer E, et al. Gut microbial community structure and complications after kidney transplantation: a pilot study. Transplantation. 2014;98:697-705.

41. Fricke WF, Maddox C, Song Y, Bromberg JS. Human microbiota characterization in the course of renal transplantation. Am J Transplant. 2014;14:416-27.

42. Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. Gut. 2008;57:1185-91.

43. Sommer F, Bäckhed F. The gut microbiota: masters of host development and physiology. Nat Rev Microbiol. 2013;11:227-38.

44. Boerner PB, Sarvetnick NE. Type 1 diabetes: role of intestinal microbiome in humans and mice. Ann N Y Acad Sci. 2011;1243:103-18.

45. Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology. 2010;156:3216-23.

46. Willing BP, Russell SL, Finlay BB. Shifting the balance: antibiotic effects on host-microbiota mutualism. Nat Rev Microbiol. 2011;9:233-43.

47. Sousa SR, Galante NZ, Barbosa DA, Pestana JO. Incidência e fatores de risco para complicações infecciosas no primeiro ano após o transplante renal. J Bras Nefrol. 2010;32:77-84.

48. Lee JR, Bang H, Dadhania D, Hartono C, Aull MJ, Satlin M, et al. Independent risk factors for urinary tract infection and for subsequent bacteremia or acute cellular rejection: a single-center report of 1166 kidney allograft recipients. Transplantation. 2013;96:732-8.

49. Jha V. Post-transplant infections: an ounce of prevention. Indian J Nephrol. 2010;20:171-8.

50. Kverka M, Tlaskalová-Hogenová H. Intestinal microbiota: facts and fiction. Dig Dis. 2017;35:139-47.

51. Hopper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. Science. 2012;336:1268-73.

52. Kosiewicz MM, Zirnheld AL, Alard P. Gut microbiota, immunity, and disease: a complex relationship. Front Microbiol. 2011;2:180.

5. CONSIDERAÇÕES FINAIS

Os dados do artigo original (artigo 1) desta dissertação sugerem que o ganho de peso em pacientes submetidos ao transplante renal é crescente e significativo. Estas alterações no peso corporal podem ser influenciadas pelo sexo e peso pré-transplante. Além disso, fatores relacionados ao transplante como o tipo de doador (vivo *versus* falecido), número de hospitalizações, taxa de filtração glomerular e ausência de diabetes melito também podem contribuir para o ganho de peso nestes indivíduos.

Em relação ao artigo de revisão sistemática (artigo 2), observou-se que ocorrem alterações na microbiota intestinal dos pacientes submetidos ao transplante renal, porém a influência da microbiota no peso corporal de pacientes transplantados não foi avaliada na literatura disponível.

Os nossos resultados têm uma aplicação prática. As pacientes femininas e com IMC pré-transplante mais baixo devem ter o peso monitorado mais frequentemente e medidas preventivas para evitar ganho de peso excessivo devem ser implementadas. Mais estudos são necessários para determinar se estas medidas serão efetivas na prevenção do ganho de peso pós-transplante e que intervenções irão resultar em melhores desfechos para o paciente e para o enxerto renal. Ainda, são necessários estudos que avaliem a microbiota intestinal e sua possível relação com alterações de peso corporal após o transplante de órgãos sólidos.