Universidade Federal de Juiz de Fora
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ANÁLISE COMPARATIVA DA PROGRESSÃO E TRATAMENTO MULTIDISCIPLINAR DA DOENCA RENAL CRÔNICA ENTRE PACIENTES EM TRATAMENTO CONSERVADOR E TRANSPLANTADOS RENAIS

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Tese de Doutorado no Programa de Pós-Graduação em Saúde, área de concentração em Saúde Brasileira, da Universidade Federal de Juiz de Fora.

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RESUMO

Introdução. As complicações e fatores de risco tradicionais para progressão da doença renal crônica (DRC), típicos dos pacientes pré dialíticos (PPD), também são observados nos pacientes transplantados renais (PTR), e seu estudo é relevante diante da estacionária sobrevida em longo prazo do enxerto renal. A abordagem multidisciplinar, reconhecidamente o melhor modelo de assistência a PPD, é pobremente descrita no tratamento da DRC em PTR. **Objetivo.** Comparar cobertura e performance do tratamento das complicações e fatores de risco relacionados à progressão da DRC, sobrevida renal e dos pacientes, e taxa de progressão da DRC, entre um grupo de PPD e um de PTR, ambos seguidos por equipe multidisciplinar. **Casuística e Métodos.** Estudo de coorte retrospectiva, com 101 PTR em acompanhamento em hospital universitário e 101 PPD selecionados por escore de propensão, utilizando dados semestrais de prontuário referentes a período de seguimento de 12 a 60 meses. Comparamos sobrevida dos pacientes e da função renal, decaimento da taxa de filtração glomerular (TFG), prevalência de complicações e fatores de risco relacionados à progressão da DRC, porcentagem de pacientes sem tratamento destas, porcentagem de consultas sem tratamento destas, e porcentagem de consultas dentro das metas de tratamento. A variação da TFG, estimada pela fórmula CKD-Epi, foi calculada pelo modelo linear generalizado misto; a sobrevida da função renal e dos pacientes pelo método Kaplan-Meier, e as diferenças foram comparadas por odds ratio ou risco relativo, conforme apropriado. **Resultados.** Ambas coortes foram comparáveis em termos de TFG e distribuição em categorias da DRC, porém PTR eram mais jovens (43,4±12,5 vs. 50,2±13,5 anos, $p<0,001$) e tiveram seguimento mais longo (55,7±12,1 vs. 31,6±11,5 meses, $p<0,001$). Pressão

arterial sistólica e diastólica, e prevalência de proteinúria >1g/dia, foram maiores nos PPD ao início do estudo, mas não se mantiveram durante o seguimento. Anemia foi mais comum (38,6% vs 15,8%, RR 2,43, IC 1,46-4,06, p<0,001) e recebeu tratamento mais frequentemente nos PTR (73,9% vs 11,3%, OR 0,15, IC 0,1-0,23, p<0,001), mas o número de pacientes sem tratamento de anemia durante o seguimento foi semelhante entre os grupos. Hipercolesterolemia sem tratamento foi menos comum nos PTR (15,7% vs 22,9%, OR 0,68, IC 0,52-0,89, p=0,005), mas hiperfosfatemia não tratada (56,1% vs 30,0%, RR 1,86, IC 1,01-3,44, p=0,044) e hiperuricemia não tratada (60,4% vs 35,4%, RR 1,7, IC 1,31-2,21, p<0,001) foram mais comuns nesta coorte. A porcentagem de consultas com pacientes nas metas de tratamento avaliadas foi semelhante entre os grupos, exceto pressão arterial diastólica (83,4% vs 77,3%, RR 0,92, IC 0,88-0,97, p=0,002) e hipertrigliceridemia (67,7% vs 58,2%, OR 0,85, IC 0,78-0,93, p<0,001), mais frequentemente controlados nos PPD, e proteinúria (92,7% vs. 83,5%, RR 1,1, IC 1,05-1,16, p<0,001) e LDL colesterol, mais frequentemente na meta nos PTR. A sobrevida dos pacientes e o decaimento da TFG (0,81 mL/min/ano nos PTR vs 1,07 mL/min/ano nos PPD, p=0,48, IC -0,04–0,08) foram semelhantes, mas os PPD evoluíram mais frequentemente para diálise (9,9% vs 6,9%, p<0,001). **Conclusão**. Diferentes prevalências de algumas complicações podem ser explicadas pelo maior número de pacientes incidentes no grupo PPD e pelos efeitos adversos dos imunossupressores nos PTR. Observamos boa performance do modelo multidisciplinar no tratamento das complicações da DRC em PTR, em comparação com PPD, sugerindo que este modelo de tratamento pode contribuir para melhor qualidade de acompanhamento clínico dos PTR.

Palavras-chave: Doença renal crônica. Transplante renal. Complicações. Relações Interprofissionais. Administração dos cuidados ao paciente. Progressão. Fatores de risco.

ABSTRACT

Introduction. Traditional complications and risk factors for chronic kidney disease (CKD) progression, typically present in predialysis patients (PDP), are also observed in kidney transplant recipients (KTR). Their study in KTR is relevant, due to the lack of improvement in long-term graft survival. Multidisciplinary approach, established as the best model of assistance for PDP, is poorly described regarding treatment of CKD among KTR. **Objective.** To compare coverage of treatment of complications and risk factors for CKD progression, kidney and patient survival, and progression rate of CKD, between a group of PDP and one of KTR, both followed by a multidisciplinary team. **Patients and Methods.** Retrospective cohort study, with 101 KTR followed at a universitary hospital and 101 PDP selected by propensity score method, using semestral data from medical records regarding a period of 12 to 60 months of follow-up. We compared patient and kidney function survival, glomerular filtration rate (GFR) decline, prevalence of complications and risk factors related to CKD progression, percentage of patients without treatment of those, percentage of medical visits without treatment of the same conditions throughout follow-up, and percentage of medical visits within treatment goals. Variation of GFR, estimated by the CKD-Epi formula, was determined using a mixed generalized linear model; survival of kidney function free of dialysis and patient survival were determined by Kaplan-Meier curves, and differences regarding treatment were compared through odds ratio or relative risk, as appropriate. **Results.** Both cohorts had comparable GFR and CKD category distribution, and comparable prevalence of diabetes and cardiovascular comorbidities, but KTR were younger (43.4±12.5 vs. 50.2±13.5 years, $p<0.001$) and had a longer follow-up (55.7±12.1 vs. 31.6±11.5 months, $p<0.001$). Differences in systolic and diastolic blood

pressure, and in proteinuria >1g/day at the beginning of the study, higher among PDP, did not persist throughout follow-up. Anemia was more common (38.6% vs 15.8%, RR 2.43, CI 1.46-4.06, p <0.001) and more often treated among KTR (73.9% vs 11.3%, OR 0.15, CI 0.1-0.23, p <0.001), but the number of patients without treatment of anemia during follow-up was similar between groups. Untreated hypercholesterolemia was less common in KTR (15.7% vs 22.9%, OR 0.68, CI 0.52-0.89, p=0.005), but untreated hyperphosphatemia (56.1% vs 30.0%, RR 1.86, CI 1.01-3.44, p=0.044) and untreated hyperuricemia (60.4% vs 35.4%, RR 1.7, CI 1.31-2.21, p<0.001) were more common in this cohort. Percentage of medical visits with patients within most treatment goals was similar between groups, with exception of diastolic blood pressure (83.4% vs 77.3%, RR 0.92, CI 0.88-0.97, p=0.002) and hypertrigliceridemia (67.7% vs 58.2%, OR 0.85, CI 0.78-0.93, p<0.001), more often controlled in PDP, and proteinuria (92.7% vs. 83.5%, RR 1.1, CI 1.05-1.16, p<0.001) and LDL cholesterol, more often controlled in KTR. Patient survival and GFR slope (0.81 mL/min/year in KTR vs 1.07 mL/min/year in PDP, p=0.48, CI -0.04–0.08) were similar between groups, but PDP progressed more often to dialysis (9.9% vs 6.9%, p<0.001). **Conclusion**. Differences in prevalence of some complications could be explained by a large number of incident patients in the PDP group and by adverse effects of immunosuppressive medication in KTR. We observed a good performance by the multidisciplinary model for treatment of CKD-related complications in KTR in comparison to PDP, suggesting that this model of assistance can contribute to improve the quality of clinical follow-up of KTR.

Keywords: Chronic kidney disease. Kidney transplant. Complications. Interprofessional relations. Patient care management. Progression. Risk factors.

LISTA DE ABREVIATURAS

AAS	Ácido acetilsalicílico
BRA	Bloqueadores do receptor AT_1 da angiotensina II
CKD-Epi	*Chronic Kidney Disease Epidemiology Collaboration*
DRC	Doença Renal Crônica
DRC-T	Doença Renal Crônica do Transplantado
HAS	Hipertensão arterial sistêmica
HLA	Antígeno leucocitário humano, ou “Human Leukocitary Antigen”
HU-UFJF	Hospital Universitário da Universidade Federal de Juiz de Fora
IECA	Inibidores da enzima conversora da angiotensina
IMC	Índice de massa corporal
IMEPEN	Instituto Mineiro de Estudos e Pesquisa em Nefrologia
JBN	Jornal Brasileiro de Nefrologia
K/DIGO	*Kidney Disease Improving Global Outcomes*
K/DOQI	*Kidney Disease Outcomes Quality Initiative*
LDL	Lipoproteínias de baixa densidade, ou “Low Density Lipoproteins”
NIEPEN	Núcleo Interdisciplinar de Estudos e Pesquisa em Nefrologia
PA	Pressão arterial
PPD	Pacientes em tratamento conservador, ou “pré dialíticos”
PTH	Paratormônio
PTR	Pacientes transplantados renais
SPSS	*Statistical Package for the Social Sciences*
TCLE	Termo de Consentimento Livre e Esclarecido
TFG	Taxa de filtração glomerular
UFJF	Universidade Federal de Juiz de Fora

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SUMÁRIO

1 INTRODUÇÃO

O transplante renal é reconhecidamente a melhor modalidade de terapia renal substitutiva, uma vez que, além de significativa recuperação da taxa de filtração glomerular (TFG), proporciona a retomada de funções fisiológicas cardinais, como, por exemplo, a eritropoiese, e o controle mais adequado da doença mineral óssea, da volemia e da pressão arterial, resultando em menor mortalidade em longo prazo, além de maior independência física e melhor qualidade de vida para o paciente, quando comparado à hemodiálise e à diálise peritoneal (WOLFE et al, 1999; REBOLLO et al, 2000; MEIER-KRIESCHE, 2004; DJAMALI et al, 2006; PESAVENTO, 2009; TONELLI et al, 2011; OVERBECK et al, 2015).

Nas últimas décadas, o domínio de melhores estratégias de imunossupressão possibilitou importante redução da incidência de rejeições agudas, resultando em maiores médias de sobrevida do enxerto renal em curto prazo (NANKIVELL e KUYPERS, 2011; GONDOS et al, 2013; CHAPMAN, 2014). Por sua vez, a sobrevida do enxerto renal em longo prazo é tema de importante discussão, sendo descrita como relativamente estável ou com modesta tendência de melhora em diversos trabalhos, especialmente norte-americanos, mas também sendo apresentada como progressivamente melhor nos últimos anos, de acordo com dados de outros estudos multicêntricos (HARIHARAN, 2000; MEIER-KRIESCHE et al, 2004; MEYERS e KIRK, 2005; LAMB et al, 2011; GONDOS et al, 2013).

Estes dados reforçaram, recentemente, o interesse pelos fenômenos implicados no decaimento da TFG em pacientes transplantados renais (PTR), notadamente após o final do primeiro ano pós transplante (DJAMALI et al, 2006; GOURISHANKAR et al, 2010). Em contraste com a importância destinada ao tratamento imunossupressor, os PTR muitas vezes deixam de receber uma

abordagem completa, multidisciplinar, direcionada às complicações relacionadas à doença renal crônica (DRC) e aos fatores clássicos relacionados à sua progressão (DJAMALI et al, 2003; KARTHIKEYAN et al, 2003; MARCÉN et al, 2005; AKBARI et al, 2007).

Dentre os poucos estudos acerca do tema, destacam-se dois trabalhos canadenses, do mesmo grupo de estudo, que evidenciam o benefício da adoção do modelo de cuidado multidisciplinar na obtenção de metas de controle clínico e na redução do número de internações hospitalares de PTR, ao compararem grupos de pacientes acompanhados com e sem equipe multidisciplinar em diferentes cenários (AKBARI et al, 2007; BISSONNETTE et al, 2013).

Além da elevada incidência de infecções e neoplasias, responsáveis por grande parte da morbimortalidade verificada entre os PTR, devemos considerar que esta coorte de pacientes já foi exposta a um processo de perda da função dos rins nativos, e a variáveis períodos em terapia dialítica, com resultante deterioração endotelial e elevado risco de eventos cardiovasculares (WOLFE et al, 1999; DJAMALI et al, 2003; LIEFELDT, 2010, NEALE E SMITH, 2015).

Diante da importância do reconhecimento e controle dos fatores de risco responsáveis pela elevada morbidade e mortalidade verificadas nos PTR, e do pequeno número de trabalhos disponíveis acerca do tema, o presente estudo objetiva analisar comparativamente dois grupos de pacientes, sendo o primeiro constituído por PTR, e o segundo por pacientes renais crônicos em tratamento conservador, ou pré dialíticos (PPD), ambos com ao menos 1 ano de seguimento multidisciplinar, quanto à taxa anual de progressão da DRC, sobrevida da função renal livre de diálise, mortalidade, prevalência de fatores de risco para progressão e complicações advindas

da DRC, disponibilidade do tratamento destas complicações, e cumprimento de metas de tratamento estabelecidas na literatura, em ambos grupos.

2. REVISÃO BIBLIOGRÁFICA

2.1 DRC em Transplantados Renais

2.1.1 Fisiopatologia

O transplante renal alogênico é capaz de propiciar aos pacientes renais crônicos em diálise, ou classificados na categoria 5 da DRC em tratamento conservador, a recuperação de uma fração significativa da TFG, além da retomada de importantes funções endócrinas e metabólicas, bem como melhor controle volêmico e pressórico. É considerada a melhor modalidade de terapia renal substitutiva sob diferentes aspectos (WOLFE 1999; PESAVENTO, 2009). A importante melhora da TFG, que na maioria das vezes reposiciona o paciente na categoria 1, 2, ou 3a da DRC, é acompanhada de grande melhora dos indicadores de qualidade de vida do paciente e de menor mortalidade, em comparação aos pacientes tratados com diálise (PESAVENTO, 2009).

A observação em longo prazo de pacientes transplantados renais demonstra a deterioração da função do enxerto ao longo dos anos, resultante de uma série de fatores agressores que podem ser didaticamente divididos em alogênicos e não-alogênicos (PASCUAL et al, 2002; FERNANDEZ FRESNEDO et al, 2009; CAPDEVILA PLAZA et al, 2009; EL-ZOGHBY et al, 2009; LEGENDRE et al, 2014).

Os PTR são sobreviventes de um longo processo de decaimento da TFG, acompanhado de graus variáveis de doença mineral óssea, disfunção do sistema nervoso autônomo, hiperatividade simpática e do sistema renina-angiotensina-

aldosterona, além do potencial efeito inflamatório da própria terapia renal substitutiva, notadamente no caso da hemodiálise, o que culmina na deterioração, por vezes acentuada, do endotélio nos diversos leitos arteriais (GILL, 2006; PLANTINGA et al, 2007, NEALE E SMITH, 2015).

Fatores de risco determinantes para a progressão da DRC, como hipertensão arterial, dislipidemia, diabetes mellitus, proteinúria e obesidade, podem seguir presentes, ou mesmo serem desencadeados a partir de efeitos colaterais da medicação imunossupressora, como no caso do diabetes pós transplante relacionado aos inibidores de calcineurina, ou à proteinúria relacionada ao uso do sirolimo (MARCÉN et al, 2009; SHIVASWAMY et al, 2016). Da mesma forma, podemos observar casos de recidiva de doenças glomerulares primárias anteriormente responsáveis pela perda da função dos rins nativos, e, mais raramente, a ocorrência de doenças glomerulares *de novo* (DJAMALI et al, 2006; NANKIVELL e KUYPERS, 2011; CANAUD et al, 2012).

Complicações advindas da perda gradual da função renal, como anemia, acidose metabólica, doença mineral óssea, hiperuricemia e hipovitaminose D, poderiam contribuir ulteriormente para um maior risco de decaimento da TFG ao longo dos anos, além de maior risco de complicações cardiovasculares e óbito (FERNANDEZ FRESNEDO et al, 2009; MARCÉN et al, 2009; EL-ZOGHBY et al, 2009).

Do ponto de vista imunológico, há constante exposição do enxerto a variados graus de resposta imune celular e humoral do receptor, o que pode desencadear episódios de rejeição aguda ou crônica (NANKIVELL e ALEXANDER, 2010; ZHANG, 2018). As drogas imunossupressoras atualmente utilizadas em associação para o tratamento de manutenção no transplante renal oferecem segurança cada vez maior

contra a ocorrência de rejeições graves, embora em muitos casos se verifique a presença de imunoativação, de forma subclínica, em trabalhos com biópsias protocolares do enxerto renal (REEVE et al, 2009; EINECKE et al, 2010; GOURISHANKAR et al, 2010).

Ao mesmo tempo em que conferem proteção contra fenômenos de natureza alo-imune, os imunossupressores, como o micofenolato mofetil, apresentam um potencial benefício ao atuarem na redução da ativação imunológica relacionada a fatores de risco tradicionais de lesão endotelial, como a força de cisalhamento (*shear stress*) verificada na hipertensão arterial sistêmica (ZATZ et al, 2002; FUJIHARA et al, 2010).

Em contraponto, importantes eventos adversos dos medicamentos imunossupressores, como no caso da fibrose intersticial em faixa caracteristicamente resultante do uso dos inibidores de calcineurina, ou de alterações metabólicas ligadas ao uso crônico da prednisona e do sirolimo, como dislipidemia e hiperglicemia, podem se fazer presentes (SAMANIEGO et al, 2006; REMUZZI et al, 2007; MARCÉN et al, 2009; LUAN et al, 2009; WEIR et al, 2010).

O paciente encontra-se, ainda, vulnerável a fatores de descompensação aguda da função renal, como desidratação, estenose de artéria renal, ação hemodinâmica de drogas como os próprios inibidores de calcineurina, ou os antiinflamatórios não-esteroidais, nefrite intersticial aguda, e a diversas formas de infecção, notadamente do trato urinário (CHAPMAN et al, 2005; DJAMALI et al, 2006; NANKIVELL e KUYPERS, 2011).

A exposição a todos estes fatores pode levar ao desenvolvimento de diferentes graus de fibrose intersticial, atrofia tubular, glomeruloesclerose, hiperplasia fibrointimal e hialinose arteriolar, que são reconhecidos em conjunto como uma entidade

denominada lesão crônica do enxerto (do inglês, *chronic allograft injury*), clinicamente correlacionada à perda lenta e gradual da função do enxerto frequentemente observada nos PTR em longo prazo (SOLEZ et al, 2007; SEMENTILLI et al, 2008; EL-ZOGHBY et al, 2009; FLETCHER et al, 2009; MENGEL, 2010; SIS et al, 2010, STEGALL et al, 2018).

2.1.2 Epidemiologia

O conceito de DRC do transplantado renal é relativamente recente, e encontra fundamento na observação de que, apesar da recuperação parcial da função renal, os PTR permanecem sob importante risco de progressão para DRC terminal, pela presença de diferentes lesões histológicas específicas, como demonstrado em trabalhos com biópsias protocolares, ou pela própria presença do enxerto renal, o que caracteriza uma alteração morfológica, mesmo em indivíduos com TFG normal (KARTHIKEYAN et al, 2003). Há pouco mais de uma década, o KDIGO propôs a classificação “doença renal do transplantado” (DRC-T), chamando atenção para a necessidade de uma abordagem completa, não somente da vertente imunológica, mas também dos aspectos relacionados aos fatores de risco ligados à própria DRC, como o controle da anemia, doença mineral óssea e hipertensão arterial, objetivando a prevenção da progressão da DRC nestes pacientes, através do cumprimento de metas semelhantes àquelas preconizadas para pacientes em tratamento conservador, muitas vezes referido como fase “pré dialítica” do tratamento da DRC (LEVEY et al, 2005).

A prevalência de DRC na população de transplantados renais varia, obviamente, de acordo com cada população estudada, e com o critério estabelecido

para sua avaliação (LEVEY et al, 2005). Ao considerarmos a presença de TFG < 60 mL/min/1,73m^2, encontramos na literatura que cerca de 60 a 78% dos PTR apresentam DRC (DJAMALI et al, 2006; COSTA DE OLIVEIRA et al, 2009; MARCÉN et al, 2009; SAMAAN et al, 2011). Quando a avaliação leva em consideração outros critérios, como hematúria glomerular e proteinúria, podemos encontrar até 90% dos pacientes com DRC (KARTHIKEYAN et al, 2003; LEVEY et al, 2005; CARMINATTI et al, 2016).

Apesar de haver relativamente poucos estudos, é bem estabelecida a presença de complicações relacionadas à DRC em PTR, notadamente naqueles em categorias mais avançadas da DRC (DJAMALI et al, 2006; COSTA DE OLIVEIRA et al, 2009; CARMINATTI et al, 2016).

A prevalência de hipertensão arterial sistêmica (HAS), por exemplo, varia conforme as características de cada população estudada, notadamente a TFG do enxerto renal, estando aproximadamente entre 60 e 90% (OPELZ e DOHLER, 2005; AKBARI et al, 2007; COSTA DE OLIVEIRA et al, 2009; WEIR et al, 2015). Conforme observado por Akbari et al, a prevalência de HAS não controlada efetivamente é bastante elevada em pacientes com DRC categoria 5, tanto em PPD (57%) quanto em PTR (60%) (AKBARI et al, 2007). Em outro estudo, Carpenter et al demonstraram a prevalência de HAS não controlada em 44% de PTR pertencentes a diferentes categorias de DRC (CARPENTER et al, 2012).

A presença de proteinúria varia bastante de acordo com o cenário em que é descrita, assim como seu significado (PONTICELLI et al, 2012; HALIMI, 2013). Em pacientes com pouco tempo de transplante e com função renal preservada, sua prevalência tende a ser bastante baixa, ao passo que, em pacientes com tempo maior de transplante, e pior função do enxerto, pode chegar a estar presente em 30 a 45%

(MANFRO, 2011; KARTHIKEYAN et al, 2003; PONTICELLI et al, 2012; HALIMI, 2013). O significado da proteinúria nestes pacientes é muitas vezes indeterminado, podendo, por exemplo, corresponder a graus variáveis de lesão crônica do enxerto relacionada a resposta aloimune, recidiva de doença glomerular presente no rim nativo, ou, ainda, a podocitopatia induzida por imunossupressores, notadamente o sirolimo (PONTICELLI et al, 2012; HALIMI, 2013).

Oliveira et al, em um interessante estudo brasileiro, demonstraram a variação da prevalência de anemia conforme a categoria da DRC, sendo de 10% em pacientes na categoria 3, 26% na categoria 4, e 50% na categoria 5 (COSTA DE OLIVEIRA et al, 2009). Ao analisar dados relativos somente a PTR com DRC categoria 5, Akbari et al encontraram prevalência de anemia em 31%, dado corroborado por outro importante estudo, de Karthikeyan et al, que situa esta prevalência em 27% para pacientes na categoria 4, e 33% para pacientes na categoria 5 da DRC (KARTHIKEYAN et al, 2003; AKBARI et al, 2007).

Fator classicamente determinante de morbimortalidade cardiovascular, a dislipidemia pode ser encontrada em mais de 60% dos PTR, embora esta prevalência também possa apresentar variações conforme a categoria de DRC e a população estudada (GUIJARRO et al, 1995; AKBARI et al, 2007; COSTA DE OLIVEIRA et al, 2009; CARMINATTI et al, 2016). A presença do tratamento com estatina, quando indicada, foi descrita como desigual entre PTR e PPD por Akbari et al, no estudo comparativo canadense previamente citado, com maior cobertura de tratamento no grupo PPD, embora em outro estudo transversal mais recente, conduzido pela nossa equipe, a distribuição do tratamento tenha sido semelhante (AKBARI et al, 2007; CARMINATTI et al, 2016). Ainda segundo Akbari et al, a prevalência de hiperfosfatemia em pacientes com DRC categoria 5 foi idêntica (21%), quando

comparados PTR e PPD, mas somente 28% dos PTR estavam recebendo tratamento com quelante de fósforo, comparado a 87% de pacientes tratados no grupo de PPD (AKBARI et al, 2007). Em estudo do nosso grupo, os PTR, com melhor perfil de filtração glomerular, apresentaram 16% de hiperfosfatemia, contra 27% no grupo PPD, mas a taxa de pacientes com hiperfosfatemia não tratada, bastante elevada, foi estatisticamente semelhante entre os grupos, sendo de 80% nos PTR e 67,8% nos PPD (CARMINATTI et al, 2016).

Com base nestas observações, o interesse no estudo dos fatores envolvidos na progressão da DRC em transplantados renais vem naturalmente crescendo, ao mesmo tempo em que existem relativamente poucos estudos que descrevem o impacto destes fatores e, principalmente, do controle clínico dos mesmos, na função do enxerto e na sobrevida do paciente em longo prazo (DJAMALI et al, 2006).

2.1.3 Progressão da DRC em Transplantados Renais

A partir do melhor domínio das estratégias de imunossupressão, com a redução do impacto dos episódios de rejeição aguda na sobrevida do enxerto, o estudo dos fatores implicados no decaimento da função do enxerto em longo prazo, em especial daqueles fatores reconhecidos como tradicionalmente relacionados à progressão da DRC, oferece um importante nicho de pesquisa clínica para a comunidade transplantadora (KARTHIKEYAN et al, 2003; MARCÉN et al, 2009).

Os PTR representam uma população selecionada em relação aos PPD e aos pacientes em diálise, mas com alto risco de nova progressão para perda da TFG e disfunção endotelial (WOLFE et al, 1999; GILL, 2006). O decaimento anual esperado da TFG, em PTR, é da ordem de 2 mL/min/ano (DJAMALI et al, 2003; KUKLA et al,

2007). Em um estudo brasileiro, focado na progressão da DRC em PTR, Samaan et al descreveram uma coorte retrospectiva de 567 pacientes, encontrando 61,9% destes com TFG inferior a 60 mL/min/1,73m^2 já ao final do primeiro ano pós-transplante, com média de decaimento da TFG de 2,38 mL/min/ano, entre o primeiro e o quinto anos pós-transplante (SAMAAN et al, 2011).

Dois interessantes estudos comparativos entre PTR e PPD descrevem maior sobrevida renal no grupo de PTR, registrando, em um deles, mortalidade comparável entre as duas populações, e no outro, maior mortalidade no grupo de PTR (DJAMALI et al, 2003; KUKLA et al, 2008). Como sabemos, o estado crônico de imunossupressão dos PTR facilita a ocorrência de infecções e neoplasias, muito embora o risco cardiovascular observado nesta população seja caracteristicamente bastante elevado, contribuindo de forma importante para a mortalidade geral dos PTR (DJAMALI et al, 2006; OJO, 2006; FISHMAN, 2007; RAMA e GRINYÓ, 2010).

Diante do reconhecimento de que a função do enxerto é preditora da ocorrência de eventos cardiovasculares e da mortalidade em PTR, a exemplo do que ocorre nos PPD, torna-se fundamental o estudo mais detalhado dos fatores de progressão da DRC nos PTR (MEIER-KRIESCHE et al, 2003). De forma geral, a literatura ainda não estabelece claramente se a intervenção sobre os fatores de risco “tradicionais” para progressão da DRC nos PPD teria o mesmo impacto nos PTR, e há ainda relativa escassez de evidência em favor desta hipótese (MANGE et al, 2000; OPELZ et al, 2005).

A exemplo do que ocorre nos PPD, foi demonstrado que a piora da função do enxerto, de causa multifatorial, está relacionada ao pior controle da pressão arterial, e que, por sua vez, o controle inadequado da pressão arterial é um fator de risco independente para o decaimento da função do enxerto renal (OPELZ et al, 2005). Um

estudo italiano avaliou o benefício do bloqueio do sistema renina-angiotensina no controle adequado da hipertensão arterial e da proteinúria, dois dos principais fatores de risco para progressão para DRC terminal. Os autores mostraram redução da incidência combinada de eventos cardiovasculares e perda da função do enxerto em PTR, de forma semelhante ao que se observa com rins nativos (PAOLETTI et al, 2013). Entretanto, outros estudos relatam dados conflitantes acerca deste benefício em longo prazo (HEINZE et al, 2006; OPELZ et al, 2006; PONTICELLI et al, 2013; KNOLL et al, 2016).

No caso do controle da dislipidemia, ainda não foi demonstrado de forma contundente o efeito da redução do colesterol total e do LDL na redução da mortalidade de causa cardiovascular em PTR (SUNDER-PLASSMANN et al, 2012). O tratamento da hiperuricemia, possivelmente um fator de risco adicional para a progressão da DRC, também não demonstrou impacto na redução da incidência de desfechos duros cardiovasculares, ou em comprovada redução do decaimento da função do enxerto em longo prazo nesta população, até o momento (MAZALI e MAZZALI, 2011; HUANG et al, 2012).

A reposição de eritropoetina para controle da anemia, por sua vez, parece ter impacto na preservação da função do enxerto (CHOUKROUN et al, 2012). De forma semelhante ao que ocorre em PPD, no entanto, o uso de eritropoetina com alvo terapêutico de níveis de hemoglobina superiores a 12,5 g/dL foi relacionado a maior mortalidade, em função dos efeitos colaterais relacionados ao uso de maiores doses de eritropoetina (HEINZE et al, 2009).

Da mesma forma como ocorre em PPD, pode-se inferir que o adequado controle da doença mineral óssea possa contribuir na redução da incidência de eventos duros cardiovasculares em PTR (STEINER et al, 1993; KALANTAR-ZADEH

et al, 2012; TRILLINI et al, 2014). Apesar disto, não se dispõe, até o momento, de estudos que demonstrem claramente este benefício, ou que demonstrem melhora da sobrevida do enxerto, assim como no caso do controle da acidose metabólica observada em categorias mais avançadas, em transplantados renais (GORAYA et al, 2013; TRILLINI et al, 2014).

Em suma, podemos verificar a escassez de estudos acerca do impacto da intervenção sobre os fatores de risco e complicações clínicas, relacionados à progressão da DRC, na sobrevida do enxerto e dos PTR. Os dados disponíveis são muitas vezes controversos, e variam conforme os desenhos dos estudos e as populações estudadas, o que torna necessário um maior aprofundamento que permita demonstrar claramente o impacto positivo de cada intervenção, de forma isolada, bem como de uma abordagem multidisciplinar, mais completa, naqueles desfechos (OPELZ et al, 2005).

O cuidado pós transplante, seguindo os consensos clínicos disponíveis, deve ser objetivamente pautado no controle de fenômenos de natureza aloimune e na aderência ao tratamento imunossupressor por parte do paciente, assim como na redução do risco cardiovascular, com ênfase nos fatores clássicos de progressão para DRC terminal e suas complicações, com especial atenção para se evitar a adoção de polifarmácia, que poderia acarretar a ocorrência de interações medicamentosas e redução da própria aderência do paciente ao tratamento (LEVEY et al, 2005; DE GEEST et al, 2011; GORDON et al, 2013). Neste cenário, o entendimento mais completo e individualizado das características clínicas e sociais de cada paciente vem sendo facilitado a partir da adoção das equipes multidisciplinares (CURTIS et al, 2005; DEW et al, 2007; BISSONNETTE et al, 2013).

2.1.4 Tratamento Multidisciplinar da DRC-T

Dois importantes estudos, publicados pelo mesmo grupo de estudo canadense, demonstram benefício da abordagem multidisciplinar no acompanhamento de PTR (AKBARI et al, 2007; BISSONNETTE et al, 2013). Akbari et al descrevem a cobertura mais completa de complicações relacionadas à DRC em PPD, acompanhados por equipe multidisciplinar, como por exemplo a presença de tratamento com eritropoetina para pacientes com anemia, quando comparados a PTR acompanhados somente pelo médico (AKBARI et al, 2007). Bissonnette et al, mais recentemente, descreveram redução na frequência de hospitalizações e maior facilidade na obtenção de metas específicas de tratamento da DRC, como, por exemplo, a manutenção do nível adequado de hemoglobina, em uma coorte de PTR avaliada antes e após a adoção do tratamento multidisciplinar (BISSONNETTE et al, 2013).

Como demonstrado por Akbari et al, no estudo comparativo de duas coortes de 72 pacientes primeiramente citado, parece existir menor foco por parte das equipes de acompanhamento pós-transplante renal com a progressão da DRC quando comparado à abordagem empregada em PPD, o que é evidenciado pelo menor uso de medicação antiproteinúrica, tratamento inadequado de hipertensão arterial e dislipidemia apesar de indicação clínica precisa, deficiência na reposição de eritropoetina, e maior demora na referência para confecção de acesso vascular para hemodiálise (AKBARI et al, 2007).

Este comportamento poderia ser, em parte, justificado pela maior atenção naturalmente dispensada pelas equipes transplantadoras aos fenômenos imunológicos relacionados ao transplante renal (AKBARI et al, 2007). Esta observação é reforçada por outros autores, e oferece um importante questionamento acerca da

qualidade do acompanhamento clínico atualmente dispensado aos PTR, notadamente quanto ao controle dos fatores de risco tradicionais de progressão da DRC e mortalidade nesta população (KARTHIKEYAN et al, 2003; MARCÉN et al, 2009; JARDINE et al, 2011; NANKIVELL e KUYPERS, 2011).

O acompanhamento do paciente com DRC por uma equipe multidisciplinar está comprovadamente associado a melhores resultados em longo prazo, no tratamento de PPD (THANAMAYOORAN et al, 2005; HEMMELGARN et al, 2007; VASSALOTTI et al, 2016). Da mesma forma, o efeito positivo desta abordagem pode ser observado em alguns estudos em PTR (BASTOS et al, 2008; MARCÉN et al, 2009). Dentre os fatores provavelmente associados a esta observação, pode-se destacar a prática mais racional da prescrição médica, observando pontos prioritários, a partir da observação multiprofissional do paciente. Como consequência, relata-se melhor aderência ao tratamento, com menor incidência de efeitos adversos relacionados ao tratamento medicamentoso (PRENDERGAST e GASTON, 2010; GORDON et al, 2013).

Na literatura, no entanto, não há estudos que analisam comparativamente, de forma clara, ao longo de um período de seguimento, a performance do tratamento da DRC oferecido a PPD e PTR, se ambas estas coortes estiverem sob cuidado multidisciplinar. Em estudo realizado no nosso grupo de pesquisa, Pinheiro et al analisaram comparativamente, em dois momentos distintos, uma população de 76 PTR com doador vivo, em que 78,5% apresentaram TFG < 60 mL/min/1,73m^2, e outra de 260 PPD (96,4% de pacientes com FG < 60 mL/min/1,73m^2), encontrando menor velocidade de decaimento da TFG, e implementação mais efetiva das medidas recomendadas para tratamento da DRC, no grupo de PTR (PINHEIRO et al, 2004; BASTOS et al, 2008). Em outro estudo do mesmo grupo, de natureza transversal, Carminatti et al demonstraram que o modelo multidisciplinar de atenção aos PTR é

capaz de propiciar distribuição relativamente equânime do tratamento específico das complicações relacionadas à DRC, ao comparar um grupo de PTR a um grupo de PPD (CARMINATTI et al, 2016).

O transplante renal é reconhecidamente uma excelente forma de terapia renal substitutiva. A manutenção da viabilidade do enxerto requer o empenho constante de uma equipe de saúde qualificada, que atente não somente às questões relacionadas à imunologia do transplante, mas também, de forma importante, ao tratamento direcionado aos fatores de risco clássicos de progressão da DRC. A compreensão disto por parte do próprio paciente, e sua plena colaboração com a equipe de saúde, são também fundamentais neste contexto (DJAMALI et al, 2006). Ao avaliarmos a qualidade do tratamento dispensado pela equipe a cada complicação da DRC, a capacidade de atingir as metas específicas preconizadas para o controle de cada uma destas complicações, e, possivelmente, o impacto destas variáveis na sobrevida renal e do paciente, de forma comparativa entre uma coorte de PTR e uma coorte de PPD, esperamos poder reunir dados de interesse acerca da adoção do modelo multidisciplinar de acompanhamento da DRC em pacientes transplantados renais.

3 HIPÓTESE

Segundo a literatura, é comum que os PTR não recebam cuidado multidisciplinar da forma como os PPD tradicionalmente recebem, o que se traduz em melhor qualidade de tratamento das complicações e fatores de risco para progressão da DRC nos PPD, e o modelo de atenção multidisciplinar pode contribuir para melhores resultados do que o modelo não-multidisciplinar no acompanhamento de PTR. Ao colocar estas teorias à prova, oferecendo seguimento multidisciplinar tanto para uma coorte de PPD como para uma coorte de PTR, esperamos observar semelhante distribuição e efetividade do tratamento específico das complicações e fatores de risco para progressão da DRC entre os grupos, bem como reduzidas taxas de progressão da DRC e elevadas taxas de sobrevida da função renal e dos pacientes acompanhados em ambas as coortes.

4 JUSTIFICATIVA

Poucos estudos oferecem uma análise comparativa do tratamento clínico direcionado às complicações da DRC em PTR e PPD, com foco em sua qualidade e no seu possível impacto na sobrevida renal e na sobrevida dos pacientes. Encontramos, na literatura, apenas um estudo comparativo, transversal, da qualidade do tratamento das complicações da DRC entre estas duas populações, sendo ambas acompanhadas por uma equipe multidisciplinar. O presente estudo, de coorte retrospectivo, é o primeiro que visa avaliar, de forma comparativa, a taxa anual de progressão da DRC, sobrevida da função renal livre de diálise, mortalidade, prevalência de fatores de risco para progressão e complicações advindas da DRC, disponibilidade do tratamento destas complicações, e cumprimento de metas de tratamento estabelecidas na literatura, entre uma população composta de 101 PTR, e outra composta de 101 PPD, ambas em acompanhamento com equipe multidisciplinar, composta de nefrologistas, enfermeiros, nutricionistas, assistentes sociais e psicólogos.

5 OBJETIVOS

5.1 Objetivo principal

Comparar a prevalência de complicações e fatores de risco para progressão da DRC, a frequência de pacientes que recebem tratamento específico para cada uma delas quando indicado, e a frequência de pacientes que atingem as metas de tratamento preconizadas pelas diretrizes nacionais e internacionais de tratamento da DRC, entre uma população composta de PTR e outra formada por PPD, sendo ambas acompanhadas por uma equipe multidisciplinar.

5.2 Objetivos secundários

Comparar a taxa de progressão da DRC entre os grupos, através da análise do decaimento anual da taxa de filtração glomerular.

Comparar a sobrevida dos pacientes entre ambas as populações.

Comparar a sobrevida da função renal, livre de diálise, entre ambas as populações.

6 CASUÍSTICA E MÉTODOS

6.1 Desenho do Estudo

Realizamos um estudo retrospectivo, de coorte.

6.2 Amostra e coleta de dados

6.2.1 Composição da amostra

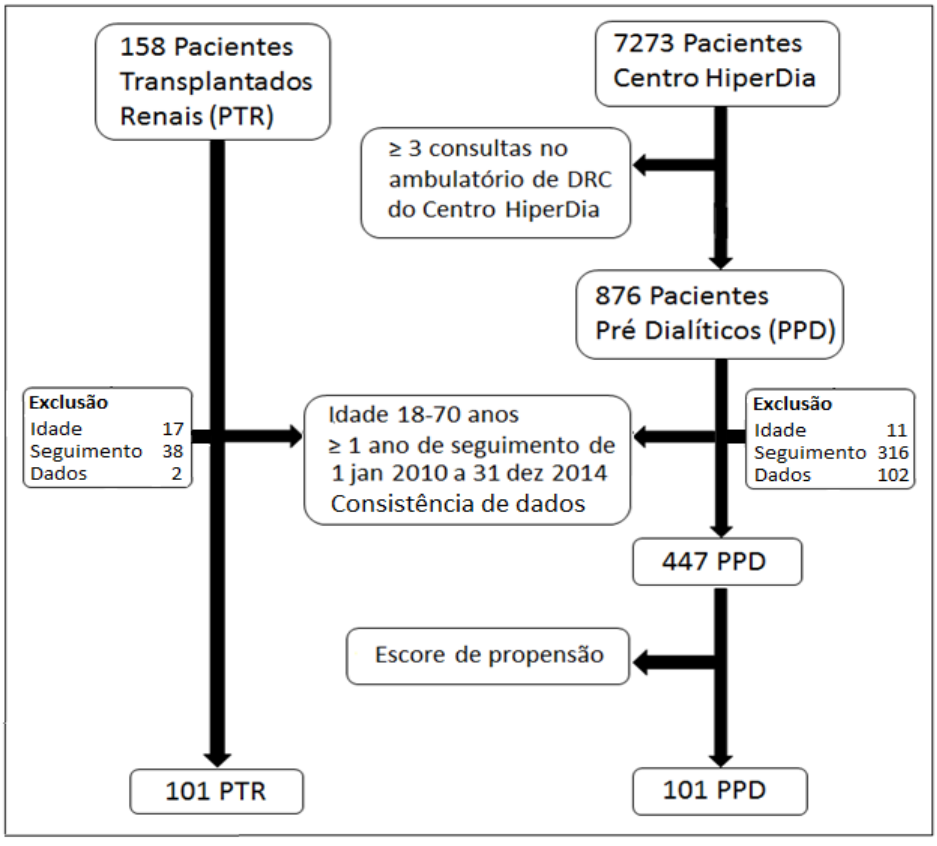
A amostra foi composta por pacientes dos ambulatórios de doença renal crônica do Centro Hiperdia da Fundação Instituto Mineiro de Estudos e Pesquisas em Nefrologia (IMEPEN) e de Pós Transplante Renal do Hospital Universitário da Universidade Federal de Juiz de Fora (HU-UFJF), localizados em Juiz de Fora - MG. No Centro Hiperdia são atendidos pacientes portadores de doença renal crônica, pertencentes a todas as categorias desta doença, encaminhados de centros da atenção primária. No ambulatório de Pós Transplante Renal, são atendidos pacientes transplantados no HU-UFJF e no Hospital Dr. João Felício, porém acompanhados pela mesma equipe. Nos dois serviços, os pacientes recebem acompanhamento multidisciplinar, por equipe composta de nefrologistas, enfermeiros, nutricionistas, assistentes sociais e psicólogos, e o protocolo de atendimento médico segue as diretrizes nacionais e internacionais vigentes (SBN, 2004; KDIGO, 2013).

6.2.2 Critérios de Inclusão

A amostra de pacientes do presente estudo foi constituída de duas populações de indivíduos adultos, entre 18 e 70 anos de idade, de ambos os sexos, e portadores de DRC. A primeira foi composta por todos os 101 pacientes transplantados renais com ao menos 1 ano de acompanhamento, no período compreendido entre 1 de

janeiro de 2010 e 31 de dezembro de 2014, no Serviço de Transplante Renal do HU-UFJF. A segunda, foi formada por 101 pacientes portadores de DRC, em tratamento pré-dialítico, seguidos no ambulatório de doença renal crônica do Centro Hiperdia Fundação IMEPEN, selecionados através do método de escore de propensão, a partir do total de 447 pacientes com ao menos 1 ano de seguimento neste ambulatório, no mesmo período compreendido entre 1 de janeiro de 2010 e 31 de dezembro de 2014, conforme demonstrado na Figura 1. As variáveis utilizadas para o escore de propensão foram: idade, índice de massa corporal (IMC), hipertensão arterial, diabetes, coronariopatia, doença cerebrovascular, doença vascular periférica, insuficiência cardíaca, sexo, raça, obesidade e categoria da DRC.

Figura 1 – Composição da amostra do estudo.



6.2.3 Critérios de Exclusão

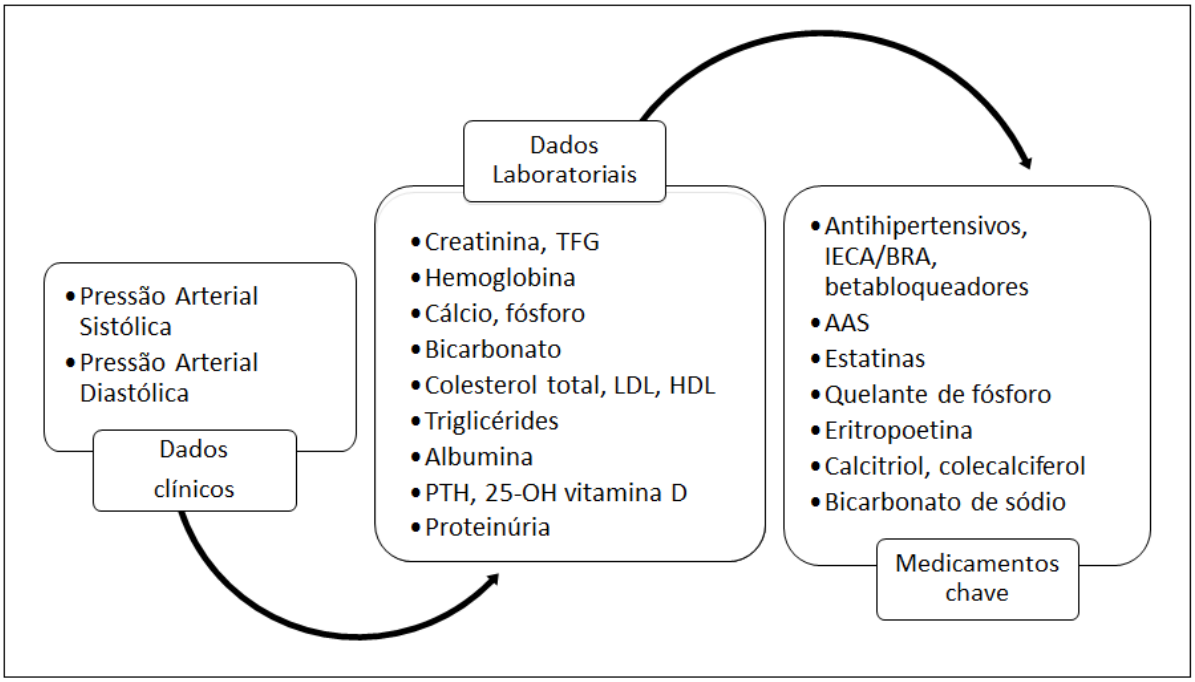
Pacientes cujos prontuários médicos revelassem inexistência de dados clínicos ou laboratoriais fundamentais à análise estatística proposta no estudo, de forma a impedir tecnicamente sua utilização, foram excluídos do mesmo. Os dados considerados essenciais para a inclusão dos pacientes no estudo foram: data de nascimento, peso, altura, data do transplante (para PTR), e pelo menos 2 valores de creatinina sérica e de pressão arterial sistólica e diastólica.

6.2.4 Coleta de dados

Os dados foram coletados dos prontuários médicos, relativos aos atendimentos realizados semestralmente entre 1 de janeiro de 2010 e 31 de dezembro de 2014. Em cada ponto, foram colhidas informações referentes a dados clínicos e laboratoriais, e ao uso de medicamentos chave para o tratamento, conforme disposto na Figura 2.

O estudo foi submetido e aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Juiz de Fora, sob o registro de parecer número 275/2011, em 15 de dezembro de 2011. Houve dispensa do termo de consentimento livre e esclarecido (TCLE), por se tratar de estudo que consiste apenas de consulta a dados de prontuários médicos.

Figura 2 – Dados clínicos, laboratoriais e referentes ao tratamento, coletados semestralmente do prontuário médico de cada paciente.



6.3 Variáveis estudadas

6.3.1 Sócio-demográficas

Foram colhidas informações referentes a: sexo, idade, raça (auto-referida), e tempo de seguimento no ambulatório de DRC pré-dialítica, ou de pós-transplante (meses).

6.3.2 Etiologia da DRC

Foi considerado o diagnóstico registrado no prontuário, incluindo: nefroesclerose hipertensiva, doença renal diabética, doença glomerular crônica, doença renal policística do adulto, etiologia indeterminada, ou outras causas

(englobando acidente ofídico, uropatia obstrutiva e nefropatia de refluxo vésico-ureteral).

6.3.3 Presença de comorbidades

Foram computados os seguintes diagnósticos, conforme diagnóstico do médico assistente registrado em prontuário: hipertensão arterial, diabetes mellitus, obesidade, doença coronariana, doença vascular periférica, doença cerebrovascular, insuficiência cardíaca, e vício relacionado ao tabaco.

6.3.4 Função renal

Avaliamos a função renal pelos valores de creatinina (mg/dL) e pela TFG, estimada pela equação do estudo CKD-EPI – *Chronic Kidney Disease Epidemiology Collaboration* (LEVEY et al, 2009), sem considerar a variável raça negra. Os pacientes foram classificados a partir da TFG nas categorias da DRC nos pontos de interesse do estudo (KDIGO, 2013).

6.3.5 Avaliação laboratorial

Consistiu de resultados de exames de rotina, que permitiram avaliar as complicações e alvos do tratamento da DRC: hemoglobina (g/dL), cálcio (mg/dL), fósforo (mg/dL), PTH intacto (pg/mL), bicarbonato (mEq/L), albumina (g/dL), colesterol total (mg/dL), LDL (mg/dL), HDL (mg/dL), triglicérides (mg/dL), proteinúria em urina de 24h (mg/24h) e vitamina D (ng/dL) (SBN, 2004; KDIGO, 2013).

6.3.6 Tratamento da DRC

Identificamos, durante o período de seguimento, se cada paciente: 1. apresentou alguma das alterações de indicadores de controle clínico e laboratorial (ou "complicações") relacionadas à DRC; 2. recebeu o tratamento direcionado para cada complicação; 3. até o final do seguimento, o paciente pôde se enquadrar dentro das metas de tratamento, de acordo com as diretrizes brasileiras de DRC (SBN, 2004).

Detalhamos abaixo as categorias de dados referentes ao tratamento dos pacientes estudados:

- Medidas clínicas: controle da pressão arterial sistólica e diastólica (pressão arterial sistólica < 140 mmHg, ou 130 mmHg para pacientes diabéticos com proteinúria superior a 300 mg/24h, e pressão arterial diastólica < 90 mmHg, ou 80 mmHg para pacientes diabéticos com proteinúria superior a 300 mg/24h), uso de medicações hipotensoras recomendadas (e em especial IECA, BRA e betabloqueadores), uso de ácido acetilsalicílico (AAS), uso de estatinas e uso de quelante de fósforo, reposição de eritropoetina, reposição de 25-OH vitamina D ou 1,25-OH vitamina D e reposição de bicarbonato de sódio.
- Adequação ou inadequação dos dados laboratoriais às metas preconizadas: presença de anemia (hemoglobina < 11,0 g/dL, até 31 de dezembro de 2013, ou 10 g/dL, após 1 de janeiro de 2014), hipocalcemia (cálcio < 8,5 mg/dL), hiperfosfatemia (fósforo > 4,5 mg/dL para pacientes com DRC categorias 1 a 4, ou 5,5 mg/dL, para pacientes com DRC categoria 5), acidose metabólica (bicarbonato < 22 mEq/L), hipercolesterolemia (colesterol total > 200 mg/dL, ou LDL > 100 mg/dL),

hipertrigliceridemia (triglicérides >150 mg/dL), hipoalbuminemia (albumina <3,5 g/dL), hipovitaminose D (25-OH vitamina D <30 ng/mL), hiperparatireoidismo (PTH >450 pg/mL), e proteinúria significativa (proteinúria >1,0 g/24h).

6.3.7 Aspectos imunológicos do transplante renal

Colhemos dados acerca das características imunológicas dos pacientes transplantados renais, como descrito a seguir:

- Imunossupressão: medicamentos utilizados no esquema de manutenção pós-transplante durante o período de acompanhamento (tacrolimo, ciclosporina, micofenolato, azatioprina, sirolimo, everolimo e prednisona).
- Características imutáveis: tipo de doador (vivo relacionado, vivo não-relacionado, ou falecido), compatibilidade HLA (número de discordâncias, variando de 0 a 6), e tempo decorrido em terapia dialítica.
- Fatores intercorrentes: presença de episódios de rejeição aguda, infecções, e ocorrência de diabetes pós-transplante.

6.3.8 Desfechos

Os desfechos considerados foram os seguintes: paciente ativo, encaminhamento para terapia renal substitutiva, e óbito. Também foi considerada a variação da TFG no tempo, ou *slope* de TFG.

6.4 Análise estatística

Inicialmente, a partir do total de 447 PPD elegíveis para o estudo, foi realizada a seleção de 101 com características demográficas semelhantes aos 101 PTR incluídos no estudo. Esta seleção foi realizada pelo método de escore de propensão, que consiste em uma regressão logística levando em consideração as variáveis clínico-demográficas idade, índice de massa corporal (IMC), hipertensão arterial, diabetes, coronariopatia, doença cerebrovascular, doença vascular periférica, insuficiência cardíaca, sexo, raça, obesidade e categoria da DRC, seguida da determinação da probabilidade, ou propensão, de cada indivíduo do grupo de PPD apresentar uma distribuição destas variáveis que seja o mais semelhante possível àquela observada no grupo de PTR, possibilitando a seleção de 101 PPD a partir do método de escolha do "vizinho mais próximo" (*nearest neighbor matching*), condicional às covariáveis acima descritas (RUBIN, 1997).

Após a definição das duas populações de estudo, foi realizada análise descritiva dos dados demográficos, clínicos e laboratoriais coletados, expressos em média (com desvio padrão) ou mediana (mínimo-máximo), ou percentagem, de acordo com a característica da variável. Para avaliar a normalidade, utilizamos o teste de Kolmogorov-Smirnov. As características sócio-demográficas, clínicas e laboratoriais dos PPD foram comparadas com as dos PTR, através de Teste t ou qui quadrado, conforme indicado.

Para a análise comparativa da sobrevida renal e da sobrevida dos pacientes, foi utilizado o método de Kaplan-Meier. A análise da variação da TFG no tempo foi realizada através de um modelo linear misto, que permite agregar um componente de variação longitudinal intra individual e um componente de variação inter individual, resultando na determinação do *slope* da TFG, ou seja, do valor correspondente ao

padrão de tendência de variação da TFG durante o tempo de observação do estudo, para cada uma das duas populações estudadas, permitindo sua comparação (WEST et al, 2007).

Na seção correspondente à avaliação do tratamento da DRC, cada paciente foi avaliado para a presença, ou ausência, de cada uma das alterações de indicadores de controle clínico e laboratorial anteriormente especificadas, levando em consideração o valor da variável correspondente à entrada do paciente no estudo, ou o primeiro valor correspondente àquela variável, na sequência do acompanhamento. A seguir, foi determinado se o paciente recebeu o tratamento correspondente àquela complicação durante o seguimento, e se, até o final do acompanhamento, o paciente atingiu a meta preconizada para aquela situação clínica. Desta forma, pudemos comparar a frequência de pacientes que receberam o tratamento correspondente a cada complicação específica, e a de pacientes que atingiram cada meta de tratamento dentro de ambas populações. A seguir, estas frequências foram ponderadas de acordo com o tempo, em meses, em que os pacientes de cada população permaneceram dentro de cada meta de tratamento preconizada, como medida de efetividade de tratamento.

Consideramos estatisticamente significante um valor de $p < 0,05$. Para as análises, foram utilizados os softwares SPSS 15.0 (IBM Corp. Released 2015. IBM Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) e Stata versão 13 (StataCorp. 2013*. Stata Statistical Software: Release 13.* College Station, TX: StataCorp LP.).

7 RESULTADOS

Apresentamos, como resultados deste projeto de pesquisa, o artigo de revisão intitulado “Chronic kidney disease progression in kidney transplant recipientes: a focus on traditional risk factors”, publicado na revista “Nephrology” (Apêndice 1), e o artigo “Similar quality in chronic kidney disease multidisciplinary follow-up between kidney transplant and pre-dialysis patients”.

Similar quality in chronic kidney disease multidisciplinary follow-up between kidney transplant and pre-dialysis patients

Abstract

Background. Multidisciplinary clinics are established as the best approach for pre-dialysis patients (PDP), but only a few studies depict its impact in kidney transplant recipients (KTR), mostly through comparisons between multidisciplinary and non-multidisciplinary clinics.

Methods. In this retrospective cohort study, we compared patient and kidney function survival, glomerular filtration rate (GFR) decline, prevalence of complications related to chronic kidney disease (CKD) throughout follow-up, percentage of patients without specific treatment at any point in time, percentage of clinical visits without specific treatment for those complications, and percentage of time within therapeutic goals in 101 KTR and 101 propensity score-matched PDP, all followed by a multidisciplinary team, new in the literature.

Results. Time within therapeutic goals was similar between groups, except for diastolic blood pressure (83.4% vs 77.3%, RR 0.92, CI 0.88-0.97, p = 0.002) and hypertriglyceridemia (67.7% vs 58.2%, OR 0.85, CI 0.78-0.93, p <0.001), longer controlled in PDP, and for proteinuria, longer controlled in KTR (92.7% vs. 83.5%, RR 1.1, CI 1.05-1.16, p <0.001). Patient survival and GFR decline (0.81 mL/min/year in KTR vs 1.07 mL/min/year in PPD, p = 0.48, CI -0.04-0.08) were similar, though PDP progressed earlier to dialysis (9.9% vs 6.9%, log-rank p <0.001).

Conclusions. Time within most evaluated therapeutic goals was similar between groups, suggesting that multidisciplinary approach is a valid strategy towards good

quality clinical management of CKD-related complications in KTR, as established in PDP.

Keywords: Chronic Kidney Disease, Multidisciplinary, Transplant, Interprofessional Relations, Patient Care Management, Disease Progression, Risk Factors.

Introduction

Kidney transplant is the best modality of renal replacement therapy for end-stage chronic kidney disease (CKD) patients, in terms of lower overall mortality, better quality of life, and better control of CKD-related complications and comorbidities, such as hypertension, anemia, bone mineral disorder, metabolic acidosis and hypervolemia [1,2].

As stated by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, kidney transplant recipients (KTR) are a particular subset of CKD patients which, in addition to alloimmune phenomena and potentially life-threatening immunosuppression drug side effects, undergo variable periods of CKD progression and dialysis, with severe endothelial derangement and high risk for cardiovascular hard endpoints and new progression to category 5 CKD, sharing some clinical similarities with pre-dialysis patients (PDP) [3,4,5].

Long-term patient and graft survival had a modest improvement during the last decades [6,7]. Although alloimmune features, such as HLA compatibility, donor-specific antibodies, rejection episodes and graft function at 1 year posttransplant, are the major determinants in long-term kidney function survival, there is growing interest in classical clinical factors, such as hypertension, proteinuria, anemia, diabetes, dyslipidemia, bone mineral disorder and metabolic acidosis, which can contribute to CKD progression, notably after the first year posttransplant [8,9,10].

Multidisciplinary clinics are established as the best model for clinical management of pre-dialysis patients (PDP) [11,12]. Conversely, reduced attention is directed to classical CKD-related complications that contribute to CKD progression in KTR, and few studies describe the impact of multidisciplinary approach for treatment

of CKD in KTR, mostly through comparisons between multidisciplinary and non-multidisciplinary clinics [13,14].

The present study evaluates the effect of multidisciplinary post-transplant approach on obtaining good quality of CKD treatment for KTR, by comparing CKD progression and treatment of CKD-related complications to what is observed in PDP, when both cohorts are followed in a multidisciplinary clinic.

Materials and Methods

Setting, study population and data collection

In this retrospective study, we included patients followed at the nephrology unit of the Núcleo Interdisciplinar de Estudos, Pesquisas e Tratamento em Nefrologia (NIEPEN) of the Federal University of Juiz de Fora, Brazil, between 1st January 2010 and 31st December 2014. At this clinic, a multidisciplinary team of nephrologists, nurses, dietitians, social assistants and psychologists routinely assists PDP in CKD of all categories, and KTR. Inclusion criteria were age between 18-70 years, and a follow-up >1 year post-transplant in the case of KTR, and >1 year from the beginning of follow-up at the clinic for PDP. Non-inclusion criteria were lack of birth date, weight, height, transplant date for KTR, or at least two measures of serum creatinine plus two measures of systolic and diastolic blood pressure (BP) in the first year of follow-up. From the total of 876 PDP and 158 KTR, 447 PDP and 101 KTR matched the inclusion criteria and were pre-selected for entering the study. Further, 101 of the 447 PDP were selected through a “nearest neighbor” propensity score matching model, which considered the variables age, gender, race, body mass index, obesity, CKD category, hypertension, diabetes, coronary artery disease, cerebrovascular disease, peripheral

artery disease and congestive heart failure, resulting in the studied sample of 101 PDP and 101 KTR (Figure 1) [15]. Clinical and laboratorial data were collected from medical records.

All procedures were approved by the local Ethics Committee (approval number 275/2011, December 15th, 2011), and were in accordance with the ethical standards of the institutional research committee and with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards. For this retrospective study, formal consent was dispensed.

Variables and measurements

Demographic data included age, gender, race (self-reported), primary cause of CKD, comorbidities (hypertension, diabetes, obesity, cardiovascular disease and smoking) and specific characteristics of KTR (time on dialysis, donor type, HLA matches, and immunosuppressive drugs). Glomerular filtration rate (eGFR) was estimated applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [16].

CKD-related complications were defined as follows: systolic hypertension (systolic BP >140 mmHg, or >130 mmHg in diabetic patients with proteinuria >300 mg/24h, or use of anti-hypertensives), diastolic hypertension (diastolic BP >90 mmHg, or >80 mmHg in diabetic patients with proteinuria >300 mg/24h, or use of anti-hypertensives), clinically significant proteinuria (proteinuria >1 g/24h), anemia (serum hemoglobin <11 g/dL until 31st December 2013, or <10 g/dL after 1st January 2014, or use of erythropoietin), hypocalcemia (serum calcium <8.5 mg/dL), hyperphosphatemia (serum phosphate >4.5 mg/dL for patients in CKD categories 1-4, or >5.5 mg/dL for patients in CKD category 5, or phosphate chelation), hyperparathyroidism (PTH >450

pg/mL or use of 1,25-OH vitamin D), hypovitaminosis D (25-OH vitamin D <30 ng/mL or use of 25-OH vitamin D), hypercholesterolemia (total cholesterol >200 mg/dL or use of statins), elevated LDL (LDL cholesterol >100 mg/dL or use of statins), low HDL (HDL cholesterol <50 mg/dL for women and <55 mg/dL for men), hypertriglyceridemia (serum triglycerides >150 mg/dL), hyperuricemia (uric acid >8.0 mg/dL or use of allopurinol), and metabolic acidosis (blood bicarbonate <22 mEq/L or use of sodium bicarbonate), according to the Brazilian and international guidelines for CKD management [5,17].

We compared the percentage of patients with the aforementioned CKD-related complications, both at baseline and throughout follow-up, between KTR and PDP. Then, we assessed the percentage of follow-up visits in which patients from each group were receiving specific treatment for those complications, as a measure of treatment quality, and compared the percentage of follow-up visits in which patients from each group were within each therapeutic goal, as a measure of treatment performance.

Statistical analysis

Statistical analysis consisted of a comparative description of clinical and laboratorial characteristics between the two cohorts, by means (± standard deviation) or medians (and range), after analysis of sample normality by the Kolmogorov-Smirnov and Shapiro-Wilk tests, and frequencies for categorical variables. For each clinical complication and untreated complication, we assessed frequencies, odds ratio or relative risk, confidence interval (CI) and p value (regarding a 95% CI). Chi-square, or t-test, were used, as indicated for each subset of variables. Kaplan-Meier analysis was employed for assessing patient and kidney function survival free of dialysis, compared by log-rank test. A mixed linear model permitted the comparative analysis of glomerular

filtration rate decay between the two cohorts. Softwares employed in the analyses were SPSS 20.0 (IBM, Chicago, Illinois, USA), Stata 13.0 (Stata Corporation, College Station, Texas, USA) and MedCalc (MedCalc Software, B-8400, Ostend, Belgium).

Results

Demographics

The study included 101 PDP and 101 KTR (Figure 1). After propensity score selection of PDP, baseline characteristics such as GFR, cardiovascular comorbidities and CKD category distribution were matched, though KTR were younger than PDP (43.4 ± 12.5 vs. 50.2 ± 13.5 years), with lower body mass index (24.7 ± 4.4 vs. 26.1 ± 4.4), longer average follow-up (55.7 ± 12.1 vs. 31.6 ± 11.5 months), and predominance of white race (74.2 vs 54.4, p = 0.003). Among PDP, the predominant cause of CKD was hypertensive nephrosclerosis, whereas in KTR it was chronic glomerulonephritis (Table 1).

Most KTR had living related donors (84.2%), and 3 HLA matches (54.5%). The median time on dialysis was 20 months (0-112 months), and 12 transplants were preemptive. Delayed graft function occurred in 5.9% of KTR. Throughout follow-up, acute rejection was observed in 9.9%, and new-onset diabetes in 17.8%. Immunosuppression consisted more often of prednisone (89.1%), mycophenolate (73.2%) and tacrolimus (56.4%). Most KTR were on triple therapy (89.1%), and 79.1% received calcineurin inhibitors (Table 2).

Use of key medications for CKD-related complications

Throughout the follow-up, overall use of erythropoietin (28.7% vs 3.96%, p <0.001) was more common in KTR, whereas use of cholecalciferol (48.5% vs 2.97%, p <0.001), was more frequent in the PDP group. The prescription of other classes of medications for the treatment of CKD-related complications was similar between groups (Table 1).

Hypertension and blood pressure control

At baseline, mean systolic (137.6 ± 25.3 vs. 125.1 ± 13.1 mmHg, p <0.001) and diastolic BP (85.5 ± 13.9 mmHg vs. 80.0 ± 11.0 mmHg, p = 0.002) were higher in PDP (Table 1). There was a trend towards higher prevalence of both systolic and diastolic hypertension in PDP at baseline, but those differences were no longer observed throughout the whole period of follow-up (Table 3). The percentage of time in which both cohorts were kept within systolic BP goal was similar, though diastolic BP was more often observed within the established goal in PDP (83.4% vs 77.3%, RR 0.92, CI 0.88-0.97, p = 0.002).

Proteinuria and anemia

Baseline median proteinuria was not different between groups (Table 1). Prevalence of significant proteinuria (>1 g/24h) throughout the whole follow-up was similar between both cohorts (Table 3). A trend towards longer periods with untreated significant proteinuria was observed in KTR (17.2% vs. 7.5%, RR 2.27, CI 0.76-6.73, p = 0.137), though KTR were more often observed to obtain the treatment goal (92.7% vs. 83.5%, RR 1.1, CI 1.05-1.16, p < 0.001) (Table 3).

At baseline, mean hemoglobin was significantly higher in PDP (13.5 ± 1.5 g/dL vs. 12.7 ± 1.6 g/dL, p <0.001) (Table 1). Prevalence of anemia was higher in KTR both

at baseline (22.8% vs 6.9%, OR 3.95, CI 1.61-9.71, p <0.001) and during follow-up (38.6% vs 15.8%, RR 2.43, CI 1.46-4.06, p <0.001), though the overall percentage of untreated patients was statistically not different between groups, and, conversely, time elapsed with untreated anemia was much lower in KTR than in PDP (11.3% vs 73.9%, OR 0.15, CI 0.1-0.23, p <0.001) (Table 3). Both cohorts, however, were kept within desired hemoglobin goals in more than 92% of follow-up observations, with no statistical difference between them (Table 3).

Lipid abnormalities

Mean baseline HDL cholesterol tended to be higher in PDP (50.4 ± 14.7 mg/dL vs. 46.4 ± 13.5 mg/dL, p = 0.056), but mean total cholesterol and mean LDL cholesterol were similar (Table 1). Prevalence of hypercholesterolemia and elevated LDL was similar between groups, both at baseline and during follow-up (Table 3). PDP endured larger periods of time without treatment of hypercholesterolemia (22.9% vs 15.7%, OR 0.68, CI 0.52-0.89, p = 0.005), though both cohorts were similarly within total cholesterol specified goals, during follow-up (Table 3). Untreated elevated LDL, and LDL values to be found out of clinical goals were not different between groups (Table 3). Conversely, among KTR, hypertriglyceridemia tended to be more common at baseline, was more common throughout follow-up (78.2% vs 51.0%, OR 1.53, CI 1.23-1.9, p <0.001), and was less commonly observed to be within the clinical goal (58.2% vs 67.7%, OR 0.85, CI 0.78-0.93, p <0.001) (Table 3).

Bone mineral disorder

Baseline calcium levels were statistically, though not clinically, different between groups (9.4 ± 0.7 mg/dL in PDP vs. 9.7 ± 0.7 mg/dL in KTR, p = 0.033), and there were

no differences in baseline phosphorus, PTH and 25-OH vitamin D between groups (Table 1). Prevalence of hyperphosphatemia was similar at baseline, and, although time spent with untreated hyperphosphatemia was significantly higher in KTR (56.1% vs 30.0%, RR 1.86, CI 1.01-3.44, p = 0.044), both cohorts elapsed circa 95% of clinical checkups within desired phosphate ranges (Table 3).

Hyperparathyroidism with need for clinical treatment (>450 pg/mL) was rather uncommon (5.7% in PDP and 4.3% in KTR) in both cohorts throughout follow-up, no differences in treatment coverage were observed, and both groups stayed within PTH goals in over 95% of observed time (Table 3). Vitamin D deficiency tended to be more commonly observed in PDP at baseline (76.1% vs 59.2%, OR 0.45, CI 0.18-1.13, p = 0.091), but this trend was not observed during follow-up, and, although time with untreated deficiency was similar between groups, KTR tended to fulfill vitamin D goals more often (49.4% vs 39.2%, RR 1.25, CI 0.96-1.64, p = 0.09) (Table 3).

Other metabolic parameters

Baseline mean uric acid was similar between groups, and, although prevalence of hyperuricemia was higher in PDP (30.3% vs 14.0%, OR 0.37, CI 0.18-0.76, p = 0.006), the same difference was not observed during the length of follow-up. Time passed with untreated hyperuricemia was greater in KTR (60.4% vs 35.4%, RR 1.7, CI 1.31-2.21, p <0.001), time within laboratorial uric acid goal was similar in KTR and PDP (Table 3).

Prevalence of metabolic acidosis was similar between cohorts, both at baseline and during follow-up, and, though untreated metabolic acidosis tended to be more often observed in KTR, serum bicarbonate was place within desired range similarly between the groups (Table 3).

Clinical endpoints

Kaplan-Meier analysis revealed comparable mortality between the cohorts (3.9% in both cohorts, p = 0.064) (Figure 2). Infections were significantly more common in KTR (50.4% vs. 6.9%, p <0.001), cardiovascular events were uncommon in both cohorts (0.9% in KTR vs. 1.9% in PDP, p = 0.56), and cancer was twice as common in PDP, though not significantly (5.9% vs. 2.9%, p = 0.306). Glomerular filtration rate decay was low and did not differ between groups (0.81 mL/min/year in KTR vs 1.07 mL/min/year in PPD, p = 0.48, CI -0.04-0.08) (Figure 2). We observed PDP more likely to progress to dialysis (9.9% vs 6.9%, log-rank p <0.001), and the survival of a combined endpoint with death and dialysis tended to be worse among PDP (13.9% vs 10.9%, log-rank p = 0.052) (Figure 2). Patients from both cohorts who progressed to dialysis were younger, with lower baseline GFR, and more often had glomerulonephritis as the primary cause of CKD (Table 4).

Discussion

Multidisciplinary teamwork provides the most complete approach, and best possible long-term results, for care of patients with chronic conditions, such as CKD [18]. KTR are a particular subset of CKD patients in which CKD-related complications and risk factors for CKD progression are concurrent with major immunological concerns [10]. The importance of multidisciplinary approach for treatment of CKD in KTR has been suggested by few studies that compare multidisciplinary and non-multidisciplinary post-transplant clinics [14]. In this retrospective study, we compared a group of KTR and a group of PDP, matched by propensity score, both receiving

multidisciplinary follow-up. The cohorts had similar estimated GFR, CKD category distribution, prevalence of diabetes and of cardiovascular comorbidities, but KTR were younger and had a longer mean follow-up. Time within most therapeutic goals was similar between groups, with exception of diastolic BP and hypertriglyceridemia, longer controlled in PDP, and proteinuria, longer controlled in KTR. Patient survival and GFR decay were also similar between groups, although PDP showed a trend to more likely progress to dialysis.

Anemia was more common and more often being treated in KTR throughout follow-up, partly because most anemic KTR were already in use of erythropoietin at the beginning of the study, whereas most PDP were incident patients. The similar percentages of patients from each cohort left with untreated anemia at any point in time reinforces that observation. Overall, we observed 13.8% of KTR with untreated anemia at any point in time, compared to 16.8% of PDP, whereas Akbari et al, in a transversal study, described 59% of KTR without multidisciplinary care, and 21% of PDP with multidisciplinary care, to be with untreated anemia [13].

In turn, the finding that significant proteinuria was more often within goals in KTR should be considered with caution, since the meaning of proteinuria in PDP is usually not the same as in KTR. Especially after the first year post-transplant, proteinuria could represent a number of concurrent conditions implied in tubulo-interstitial derangement of the graft, in the context of multifactorial chronic allograft nephropathy, such as alloimmune response, recurrent or *de novo* glomerulonephritis, or adverse effects of immunosuppressive medication, notably m-TORi [19,20].

Interestingly, we also observed a downslope of estimated GFR in the first 6 to 12 months of follow-up in the PDP cohort, followed by a less steepy curve, which probably reflects introduction and dose adjustment of antihypertensive medication,

particularly ACEi or ARB, in incident patients entering the PDP cohort. This observation is paralleled by the fact that mean systolic and diastolic BP were higher in PDP at baseline, which did not persist throughout follow-up. Overall, both cohorts had systolic and diastolic BP controlled for more than 75% of the observation period. Although straight comparison cannot be drawn, due to the different nature of available studies, Carpenter et al described controlled BP (<130/80 mmHg) in 56% of KTR, whereas Bissonnette et al found 65% of systolic and 88% of diastolic BP to be controlled in KTR with GFR <30 mL/min/m^2 under multidisciplinary care, and Akbari et al reported 40% of controlled BP among KTR in category 5 of CKD without multidisciplinary care [13,14,21].

The higher prevalence and poorer control of hypertriglyceridemia in KTR were probably related to side effects of immunosuppressive drugs, such as prednisone, calcineurin inhibitors and mammalian target of rapamycin inhibitors (m-TORi) [22]. Although untreated hypercholesterolemia was less observed in KTR, concerns regarding avoidance of polypharmacy, potentially harmful drug interactions, and side effects, may have probably inhibited the use of fibrates in KTR. Similar findings are reported by Akbari et al, who described hypertriglyceridemia in 67% of KTR without multidisciplinary treatment and 50% of PDP under multidisciplinary care, whereas in the present study we found hypertriglyceridemia in 67.7% of KTR and 58.2% of PDP, despite multidisciplinary follow-up being available in both cohorts [13].

In the present study, polypharmacy avoidance could also partly explain why KTR were kept for larger periods with untreated hyperphosphatemia and hyperuricemia. Despite that, no differences were observed in the percentage of clinical visits in which both phosphate and uric acid were within goals, between the cohorts. Again, as a comparison, Akbari et al described untreated hyperphosphatemia in 71.4%

of category 5 KTR in non-multidisciplinary setting, and in 13.3% of category 5 PDP under multidisciplinary care [13]. Bissonnette et al, from the same Canadian study group, later described 73% KTR under multidisciplinary treatment, as opposed to 25% KTR in non-multidisciplinary setting, using phosphate chelators, despite clinical targets for hyperphosphatemia being easily attained in both cohorts, respectively in 90% and 85%, without statistical difference [14].

Patient survival was similar between groups. The observed GFR decline was very slow, and similar in both cohorts, although PDP progressed earlier to dialysis [3,23]. Considering the particular nature of the KTR sample we studied, which mostly received living, related-donor grafts, and in base of whose characteristics the cohort of PDP was selected through propensity score matching, the results we described must be carefully compared to those from other authors [7,13]. Still, we could demonstrate that, throughout follow-up, the percentage of time within most therapeutic goals was similar between groups, positively testing the hypothesis that multidisciplinary care can aggregate good quality for CKD treatment in KTR, similarly to what has longer been observed in PDP, and previously suggested [13,18].

Another important limitation of the study is its single-center, retrospective, non-randomized nature, with a relatively small, convenience sample of prevalent KTR compared to mostly incident PDP, possibly accounting for protection against hard endpoints in the KTR group. To correct demographic disparities, we employed “nearest neighbor” propensity score matching, obtaining the better possible sample of PDP, from a larger cohort, to match KTR [15]. Despite not being possible to fully match the cohorts by age, body mass index and length of follow-up, we could equalize both cohorts in terms of GFR and CKD stage, as well as prevalence of diabetes and cardiovascular comorbidities.

Few well-designed studies depict the beneficial impact of multidisciplinary care of KTR, when compared to non-multidisciplinary clinics [13,14], and only one cross-sectional study demonstrates comparable quality of multidisciplinary treatment directed towards CKD-related complications in PDP and KTR [24]. The present study was the first to compare the quality of treatment of CKD-related complications, throughout a follow-up period, between a group of KTR and a group of PDP, when both were under multidisciplinary care.

In conclusion, the percentage of time within most of the evaluated therapeutic goals, patient survival and GFR decline were similar between groups, although PDP more likely progressed to dialysis. The observed results show a good performance of multidisciplinary approach for clinical management of CKD-related complications in KTR, in comparison with PDP, suggesting that a multidisciplinary clinic is a valid strategy for good quality follow-up of KTR.

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Table 1. Demographic and clinical characteristics of PDP and KTR.

	PDP (N = 101)	**KTR (N = 101)**	**p**
Demographics			
Age (years)	50.2 ± 13.5	43.4 ± 12.5	<0.001
Female gender (%)	37.6	31.7	0.46
White race (%)	54.4	74.2	0.003
Body mass index (kg/m^2)	26.18	24.78	0.025
Follow-up (months)	31.61	55.77	<0.001
Renal function			
Creatinine (mg/dL)	1.62 ± 0.61	1.59 ± 0.53	0.735
eGFR (mL/min/1.73m^2)	51.69 ± 20.18	53.27 ± 16.88	0.548
CKD category at baseline (%)			
1	2.9	2.9	
2	24.8	29.7	
3a	40.6	36.6	
3b	22.8	24.8	
4	8.9	5.9	
5	0	0	
Primary cause of CKD (%)			
Hypertensive	43.6	20.8	
Glomerulonephritis	12.9	40.6	
Diabetes	4.0	2.0	
Adult polycystic kidney disease	11.9	5.0	
Other	6.9	5.9	

Undetermined	20.8	25.7	
Comorbidities at Baseline (%)			
Hypertension	92.1	86.1	0.175
Diabetes	4.95	2.97	0.251
Obesity	20.8	11.9	0.088
Coronary artery disease	6.93	6.93	1.0
Peripheral artery disease	2.97	0.99	0.315
Cerebrovascular disease	4.95	1.98	0.251
Congestive heart failure	5.94	3.96	0.519
Smoking	9.9	8.9	0.808
Baseline clinical characteristics			
Systolic blood pressure (mmHg)	137.6 ± 25.3	125.1 ± 13.1	<0,001
Diastolic blood pressure (mmHg)	85.5 ± 13.9	80.0 ± 11.0	0.002
Hemoglobin (g/dL)	13.5 ± 1.5	12.7 ± 1.67	< 0.001
Proteinuria (mg/24h)	169(10-5650)	184(15-1500)	0.071
Total cholesterol (mg/dL)	189.8 ± 43.4	186.6 ± 37.8	0.598
LDL cholesterol (mg/dL)	115.0 ± 35.8	109.7 ± 28.3	0.291
HDL cholesterol (mg/dL)	50.4 ± 14.7	46.4 ± 13.5	0.056
Triglycerides (mg/dL)	138.1 ± 78.1	151.4 ± 96.8	0.33
Calcium (mg/dL)	9.4 ± 0.7	9.7 ± 0.7	0.033
Phosphorus (mg/dL)	3.6 ± 0.7	3.4 ± 0.8	0.124
PTH (pg/mL)	63 (7.6-784)	76.7 (19-530)	0.886
Cholecalciferol (ng/mL)	23.5 (2-42)	24.4 (16.7-38)	0.872
Albumin (g/dL)	4.0 ± 0.5	4.2 ± 0.5	0.144
Bicarbonate (mEq/L)	24.6 ± 3.6	23.3 ± 2.6	0.113
Uric Acid (mg/dL)	6.6 ± 1.6	6.3 ± 1.5	0.246

Overall use of key medications (%)			
Anti-hypertensive	94.0	90.1	0.298
ACEi or ARB	87.1	78.2	0.127
Betablockers	45.5	38.6	0.32
ASA	17.8	15.8	0.707
Statins	49.5	61.3	0.092
Phosphate binder	5.94	4.95	0.757
1,25 OH Vitamin D	4.95	2.97	0.476
Cholecalciferol	48.5	2.97	< 0.001
Erythropoietin	3.96	28.7	< 0.001
Bicarbonate	14.8	19.8	0.355
Allopurinol	16.8	10.9	0.227

[1] Data are shown as percentages, means ± standard deviation, or medians. Continuous variables were compared using t-test or Mann-Whitney test, and frequencies with Chi-square or Fisher test. [2] PDP = pre-dialysis patients. KTR = kidney transplant recipients. eGFR = estimated glomerular filtration rate, according to the CKD-EPI formula. CKD = chronic kidney disease. ACEi = angiotensin converting enzyme inhibitors. ARB = angiotensin receptor blocker. ASA = acetylsalicylic acid.

Table 2. Specific clinical characteristics of KTR.

Donor Type (%)	
Living related	84.2
Living unrelated	11.9
Deceased	3.9
HLA matches (%)	
0-2	26.7
3	54.5
6	18.8
Median time on dialysis (months)	20 (0 – 112, 12 preemptive transplants)
Complications during follow-up (%)	
Delayed graft function	5.94
Acute rejection	9.9
Post-transplant Diabetes	17.8
Immunosuppression (%)	
Prednisone	89.1
Tacrolimus	56.4
Cyclosporine	23.7
Micophenolate	73.2
Azathioprine	26.7
Rapamycin	32.6
Everolimus	8.9
Triple medication	89.1
Calcineurin inhibitor	79.1

[1] Data are shown as percentages or as means ± standard deviation.

[2] KTR = kidney transplant recipients. HLA = human leukocyte antigen.

Table 3. CKD-related complications, treatment distribution and achievement of specific therapeutic goals in PDP and KTR groups throughout follow-up.

	PDP (%)	KTR (%)	RR/OR	CI	p
Hypertension and blood pressure control					
Baseline Systolic Hypertension	92.1	85.1	0.49*	0.19-1.22	0.126
Systolic Hypertension in follow-up	94.1	92.1	0.97	0.9-1.05	0.579
Systolic BP within goal	75.7	76.5	1.01	0.95-1.06	0.695
Baseline Diastolic Hypertension	92.1	86.1	0.53*	0.21-1.33	0.18
Diastolic Hypertension in follow-up	94.1	93.1	0.98	0.92-1.06	0.774
Diastolic BP within goal	83.4	77.3	0.92	0.88-0.97	0.002
Proteinuria and anemia					
Baseline Proteinuria > 1g/day	11.8	7.9	0.64*	0.24-1.67	0.36
Proteinuria > 1g/day in follow-up	22.6	23.7	1.05	0.62-1.75	0.845
Patients with Untreated Proteinuria	3.2	6.9	2.14	0.57-8.06	0.257
Time with Untreated Proteinuria	7.5	17.2	2.27	0.76-6.73	0.137
Proteinuria within goal	83.5	92.7	1.1	1.05-1.16	<0.001
Baseline Anemia	6.9	22.8	3.95*	1.61-9.71	0.002
Anemia in follow-up	15.8	38.6	2.43	1.46-4.06	<0.001
Patients with Untreated Anemia	13.8	16.8	1.21	0.63-2.32	0.559
Time with Untreated Anemia	73.9	11.3	0.15	0.1-0.23	<0.001
Hemoglobin within goal	92.0	92.8	1.008	0.97-1.03	0.614
Lipid abnormalities					
Baseline Hypercholesterolemia	61.4	59.4	0.92*	0.52-1.61	0.774
Hypercholesterolemia in follow-up	76.2	78.2	1.02	0.88-1.19	0.737
Patients with Untreated Hypercholest.	40.6	38.6	0.95	0.67-1.33	0.773
Time with Untreated Hypercholest.	22.9	15.7	0.68	0.52-0.89	0.005

Total Cholesterol within goal	66.4	69.9	1.05	0.97-1.13	0.188
Baseline elevated LDL cholesterol	82.0	76.2	0.7*	0.35-1.39	0.316
Elevated LDL cholesterol in follow-up	92.0	88.1	0.95	0.87-1.05	0.358
Patients with Untreated elevated LDL	60.6	51.5	0.83	0.65-1.06	0.15
Time with Untreated elevated LDL	35.6	31.0	0.87	0.73-1.03	0.117
LDL cholesterol within goal	40.3	45.7	1.13	0.98-1.3	0.07
Baseline Hypertriglyceridemia	28.0	37.6	1.55*	0.85-2.8	0.147
Hypertriglyceridemia in follow-up	51.0	78.2	1.53	1.23-1.9	<0.001
Triglyceridemia within goal	67.7	58.2	0.85	0.78-0.93	<0.001
Bone mineral disorder					
Baseline Hyperphosphatemia	5.5	4.9	0.89*	0.25-3.2	0.865
Hyperphosphatemia in follow-up	12.7	19.8	1.55	0.8-2.99	0.191
Patients w/ Untreated Hyperphosphat.	7.4	18.8	2.52	1.11-5.73	0.026
Time with Untreated Hyperphosphat.	30.0	56.1	1.86	1.01-3.44	0.044
Phosphatemia within goal	94.9	95.5	1.006	0.97-1.03	0.654
Baseline Hyperparathyroidism	1.4	2.9	2.05*	0.18-23.2	0.559
Hyperparathyroidism in follow-up	5.7	4.3	0.76	0.17-3.27	0.713
Patients with Untreated Hyperparat.	2.8	4.4	1.52	0.26-8.82	0.639
Time with Untreated Hyperparat.	30.0	25.0	0.83	0.24-2.8	0.768
PTH within goal	95.3	95.7	1.003	0.95-1.05	0.873
Baseline Hypovitaminosis D	76.1	59.2	0.45*	0.18-1.13	0.091
Hypovitaminosis D in follow-up	84.1	77.8	0.92	0.74-1.15	0.489
Patients with Untreated Hypovit. D	53.4	66.6	1.24	0.89-1.73	0.188
Time with Untreated Hypovit. D	28.3	33.3	1.17	0.82-1.68	0.368
25-OH Vitamin D within goal	39.2	49.4	1.25	0.96-1.64	0.09
Other metabolic parameters					
Baseline Hyperuricemia	30.3	14.0	0.37*	0.18-0.76	0.006
Hyperuricemia in follow-up	40.4	39.0	0.96	0.68-1.35	0.839

Patients with Untreated Hyperuricemia	28.3	34.0	1.2	0.79-1.82	0.385
Time with Untreated Hyperuricemia	35.4	60.4	1.7	1.31-2.21	<0.001
Uricemia within goal	83.9	87.2	1.03	0.98-1.09	0.146
Baseline Metabolic Acidosis	17.5	19.4	1.13*	0.46-2.78	0.783
Metabolic Acidosis in follow-up	28.1	34.7	1.23	0.73-2.08	0.425
Patients with Untreated Met. Acidosis	3.5	12.5	3.56	0.8-15.84	0.095
Time with Untreated Met. Acidosis	2.6	8.5	3.3	0.74-14.7	0.116
Serum Bicarbonate within goal	86.4	90.1	1.04	0.96-1.13	0.316

[1] Data are shown as percentages. Frequencies were compared using Chi-square or Fisher´s test. [2] PDP = pre-dialysis patients. KTR = kidney transplant recipients. OR = odds ratio. RR = relative risk. CI = confidence interval. BP = blood pressure. LDL = low-density lipoprotein. HDL = high-density lipoprotein. * OR (odds ratio).

Table 4. Demographic characteristics and progression to dialysis.

	PDP with dialysis (N = 10)	PDP without dialysis (N = 91)	KTR with dialysis (N = 7)	KTR without dialysis (N = 94)
Primary cause of CKD				
Glomerulonephritis	60.0	7.7	57.1	39.3
Hypertension	20.0	46.1	0.0	22.3
Diabetes	10.0	3.3	14.3	1.1
Polycystic kidney disease	0.0	13.2	0.0	5.3
Other	10.0	6.6	14.3	5.3
Undetermined	0.0	23.1	14.3	26.6
Baseline renal function				
Creatinine (mg/dL)	2.58 ± 0.89	1.51 ± 0.47	2.24 ± 1.00	1.54 ± 0.45
eGFR (mL/min/1.73m^2)	33.4 ± 12.4	53.7 ± 19.9	37.23 ± 13.0	54.4 ± 16.6
Demographics				
Female gender (%)	30.0	38.5	57.1	29.8
Age (years)	36.6 ± 11.0	51.8 ± 12.9	36.3 ± 11.8	43.9 ± 12.5
Donor type (%)				
Living related	-	-	85.7	85.1
Living unrelated	-	-	14.3	11.7
Deceased	-	-	0.0	3.2

[1] Data are shown as percentages, or means ± standard deviation.
[2] PDP = pre-dialysis patients. KTR = kidney transplant recipients.
eGFR = estimated glomerular filtration rate, according to the CKD-EPI formula.
CKD = chronic kidney disease.

Figure 1. Sample composition. Patient selection according to inclusion and exclusion criteria.

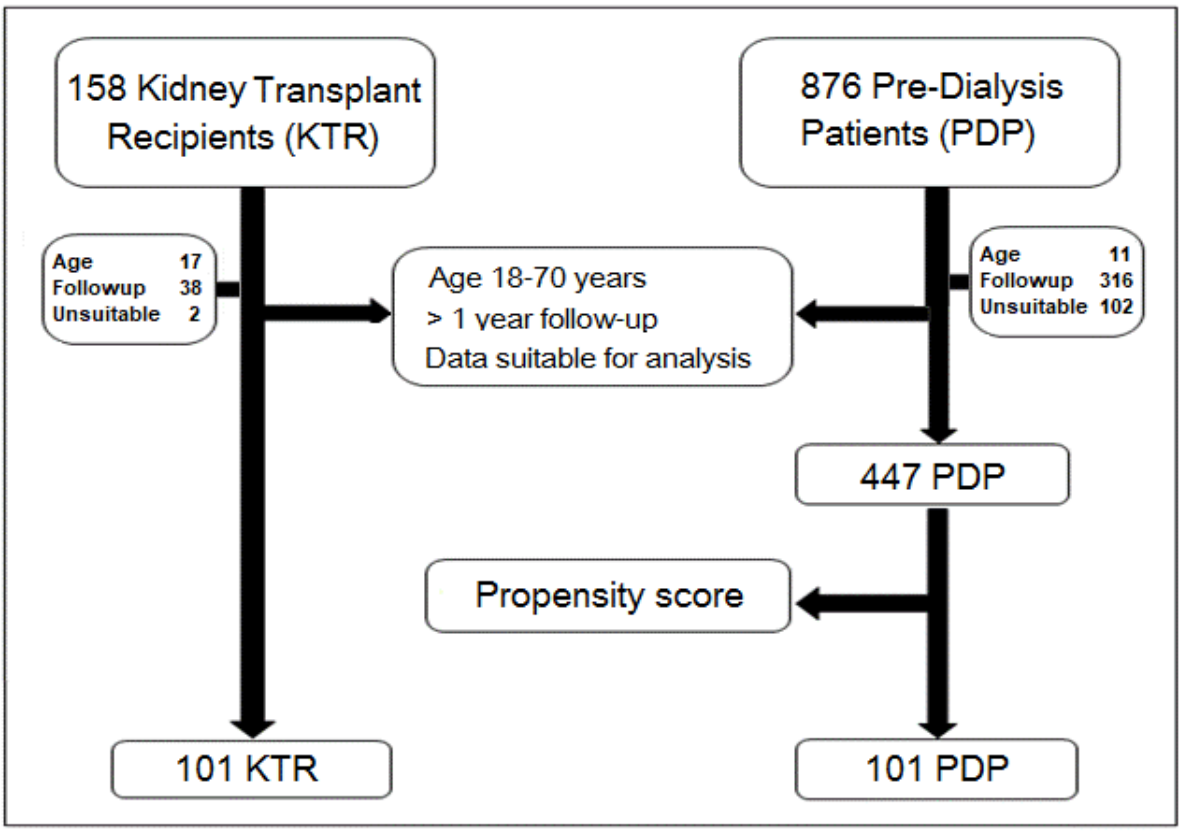
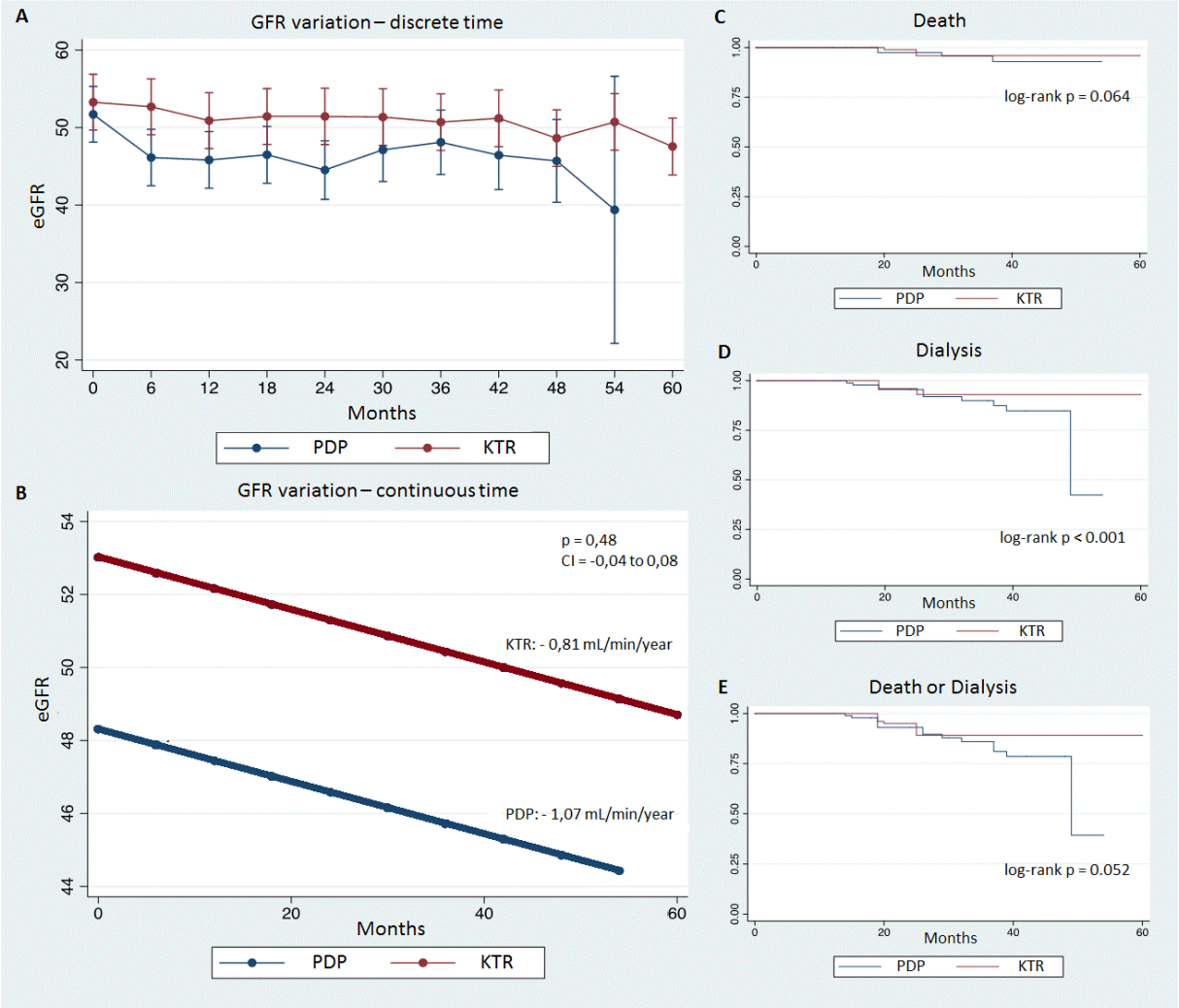


Figure 2. Glomerular filtration rate variation with discrete (A) and continuous time (B), and Kaplan-Meier curves for death (C), dialysis (D) and death or dialysis (E).



8 CONCLUSÕES

1. No presente trabalho, em que tanto a coorte de PPD quanto a de PTR foram acompanhadas por equipe multidisciplinar, encontramos distribuição e efetividade do tratamento das complicações relacionadas à DRC, em sua maioria, semelhantes entre os grupos estudados.

2. Diferenças observadas na prevalência de anemia devem-se, em parte, à maior prevalência de PTR já em uso de eritropoietina no início do estudo, enquanto a maior parte dos PPD eram incidentes. A maior prevalência e pior controle de hipertrigliceridemia nos PTR relaciona-se provavelmente a efeitos adversos da medicação imunossupressora.

3. Mesmo levando em consideração as características demográficas da coorte PTR, composta em sua maioria de pacientes transplantados a partir de doadores vivos relacionados, demonstramos taxas de decaimento da TFG e de mortalidade bastante reduzidas, embora a coorte de PPD tenha demonstrado maior tendência a evoluir com necessidade de tratamento dialítico.

4. Os resultados deste trabalho demonstram boa performance do modelo multidisciplinar no tratamento das complicações da DRC em PTR, comparativamente aos PPD, fornecendo evidência de que o modelo de assistência multidisciplinar pode contribuir para melhorar a qualidade do seguimento clínico dos PTR.

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APÊNDICE 1 – Artigo publicado

Progression of chronic kidney disease in kidney transplant recipients: a focus on traditional risk factors

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Running title: CKD progression in kidney transplant.

ABSTRACT

Kidney transplant recipients are a subset of patients with chronic kidney disease that remain at high risk for progression to dialysis and mortality. Recent advances in immunosuppression have only partially improved long-term graft and patient survival. Discovery of new immunosuppressive regimens is a slow and resource-intensive process. Hence, recognition and management of modifiable allogeneic and non-allogeneic risk factors for progression to chronic kidney disease among kidney transplant recipients is of major interest for improving long-term outcomes. Graft survival is mainly determined by the quality of the allograft and by the patient's alloimmune response, which is influenced by human leukocyte antigen matching and the presence of donor-specific antibodies. Alloimmune responses manifest as acute and chronic forms of cell- and antibody-mediated rejection, which can be worsened by patient nonadherence or inadequate immunosuppression. However, donor and patient ages, glomerular disease recurrence, time on dialysis, pre-existing cardiovascular burden, medication side-effects, and traditional risk factors such as hypertension, proteinuria, anemia, dyslipidemia, diabetes, and bone mineral disorder, which can ultimately lead to severe endothelial derangement, also contribute to graft loss and mortality. These traditional risk factors, common to pre-dialysis patients, often are considered of secondary importance when compared to alloimmunity and immunosuppression concerns. In this review article, we focus on the epidemiological, pathophysiological, and therapeutic features of non-allogeneic risk factors for chronic kidney disease. We also discuss the benefit of adopting a multidisciplinary approach to pursue the same therapeutic targets recommended for pre-dialysis patients.

Keywords: Chronic kidney disease, Kidney transplant, Multidisciplinary, Progression, Risk factors

Introduction

Kidney transplant offers patients with end stage renal disease (ESRD) the chance for improved renal function, as evidenced by recovery of glomerular filtration rate (GFR) and endocrine functions such as erythropoiesis. These patients also benefit from lower mortality rates, improved physical independency, and better quality of life, compared to patients in dialysis.[1,2] Better immunosuppression strategies lowered acute rejection rates and improved short-term graft survival, whereas long-term graft survival has shown less significant improvements in recent years.[3]

Kidney transplant recipients (KTR) are a select subset of patients among patients with chronic kidney disease (CKD), that are generally younger and have less cardiovascular comorbidities.[4] However, variable times spent in dialysis can lead to serious endothelial derangement and higher cardiovascular risk.[4] Most KTR experience varying degrees of bone mineral disorder, autonomic dysfunction with sympathetic hyperactivity, renin-angiotensin-aldosterone overstimulation, and further cytokine-mediated endothelial damage related to dialysis.[5]

CKD progression in KTR, notably after the first year post-transplant, involves a complex network of allogeneic and non-allogeneic risk factors, including hypertension, proteinuria, anemia, dyslipidemia, and bone mineral disorder. As with pre-dialysis patients (PDP), these factors contribute to GFR decline and mortality.[6,7] In this paper, we discuss the key epidemiological and therapeutic aspects of traditional CKD-related risk factors in KTR.

Literature review

A literature search for the terms “kidney transplantation”, “progression” and “chronic kidney disease”, using the PubMed database, resulted in 1884 studies primarily included for review. Of those, 32 articles written in English and specifically referring to epidemiology or risk factors for CKD progression in KTR, were selected. Established guidelines for specific treatment targets and recommendations, and further relevant issues related to this review were specifically assessed, accounting for a total of 42 selected references. Pooled treatment recommendations, even those contained in guidelines, are often based on weak evidence, or extrapolated from PDP to KTR.

CKD progression and mortality in KTR

Every KTR is, by definition, a patient with CKD (CKD-T), due to the presence of the allograft and the numerous risk factors for CKD progression that remain or appear posttransplant.[8] Sixty to 78% of KTR have a GFR<60 mL/min/1.73m^2, and up to 90% of KTR are considered to have CKD if proteinuria or glomerular hematuria are present.[9,10,11]

The average GFR decline in KTR is 1.2-2.5 mL/min/year, which is slower than in PDP, although mortality rates are similar or higher in KTR.[4,12] The chronic state of immunosuppression carries a high risk of infections and cancer, but, above all, the cardiovascular risk is very high, since KTR have been exposed to varying degrees of endothelial derangement, during pre-dialysis and later in dialysis.[9,13]

Renal function independently predicts mortality, notably due to cardiovascular causes, and, conversely, death with a functioning graft is a major cause of graft loss.[14,15] Abrupt GFR decline, especially early after transplantation, prompts aggressive investigation and treatment, as it could mean rejection of the allograft. Late,

slow GFR decline often results from a complex mixture of alloimmune and non-alloimmune factors. Traditional CKD-related factors, classified as non-alloimmune, often receive secondary attention.[9,14,15]

Transplant-related risk factors

One of the most important determinants of long-term graft function is GFR at 1 year post-transplant.[15] Graft quality, which is influenced by demographic features as donor age or expanded criteria donors, and delayed graft function (DGF), seen in 20-70% of KTR, are hallmarks of early and potentially permanent graft dysfunction.[15,16] DGF is associated with pre-existing donor-specific alloantibodies (DSA) and ischemia-reperfusion lesions, which are directly related to cold ischemia time. Early acute rejection of the allograft may also occur, and contribute to later development of tubulo-interstitial fibrosis.[17,18]

Advances in immunosuppression lowered the incidence of acute rejection to 10-15% in the first year post-transplant.[18] Nearly 80-90% of acute rejections are cell-mediated, which usually respond well to methylprednisolone.[19] In turn, late vascular antibody-mediated rejections are usually more severe, especially when related to newly-formed DSA.[18,19] Chronic antibody-mediated rejection, in turn, presents an ominous long-term prognosis and treatment is rarely effective.[17,19] Recurrence of primary glomerulonephritis is another important cause of graft loss, especially late post-transplant. Its incidence varies greatly in the literature, and some forms manifest early and more severely, while others present more insidiously, at times being diagnosed only by surveillance biopsies.[20]

In this setting, stronger net immunosuppression confers protection against immune activation, but can lead to infections and cancers, whose description is beyond the scope of this article.[13] Additionally, serious medication adverse effects can occur, as calcineurin inhibitor (CNI)-induced interstitial band fibrosis, new-onset diabetes due to CNI-induced pancreatic toxicity plus steroid-induced insulin resistance and proliferation signal inhibitors (PSI) toxicity, mycophenolate-induced diarrhea, or PSI-related podocyte lesions that translate into persistent proteinuria.[21]

Exposure to all these risk factors can ultimately lead to different degrees of interstitial fibrosis, tubular atrophy, glomerulosclerosis, fibro-intimal hyperplasia, and arteriolar hyalinosis, together known as *chronic allograft injury*. This condition clinically corresponds to slow and gradual loss of graft function. Additionally, KTR can present with chronic, CKD-related, and acute forms of GFR impairment, thus rendering the pattern of CKD progression more unpredictable than that observed in PDP (Figure 1).[22]

CKD-related risk factors

Hypertension

Progressive GFR loss after kidney transplant is associated with worsening of hypertension, which is present in 60-90% KTR.[10,23] Alternatively, inadequate blood pressure (BP) control independently predicts loss of GFR.[14] Uncontrolled hypertension is present in 44-60% of KTR, depending on CKD categories.[23,24]

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, KTR are particularly at risk for CKD progression. Hence, BP of 130/80 mmHg, lifestyle changes including weight loss and low sodium intake, targeting urinary sodium <150 mEq/24h, are suggested (grade 2C).[25]

In KTR, primary hypertension coexists with sodium retention and the vascular effects of steroids and CNI, but practitioners should suspect secondary causes of uncontrolled BP, such as renal artery stenosis, if the response to treatment is suboptimal, and treat accordingly.[25,26] To date, neither white-coat nor masked hypertension have been thoroughly assessed in KTR, and ambulatory BP monitoring could provide more reliable data.[27]

As stated in KDIGO, any class of antihypertensive medication can be employed, although angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) are suggested when proteinuria is present (not graded) (Table 1).[25,27]

Proteinuria

Proteinuria is infrequent in the early post-transplant period when graft function is mostly preserved, but reaches 30-45% in KTR that develop CKD-T in later years.[11,28] Early low-grade proteinuria can be residual from native kidneys, indicate pre-existing donor or ischemia-reperfusion lesions, predict transplant glomerulopathy in the context of antibody-mediated rejection, hallmark endothelial derangement prior to cardiovascular hard endpoints, or even precede the diagnosis of new-onset diabetes.[30,31] Persistent and more significant proteinuria can be caused by tubulo-interstitial derangement of the graft in multifactorial chronic allograft injury, recurrent or *de novo* glomerulonephritis, or PSI-induced podocyte lesions.[28] Clinical history may suggest the cause of proteinuria, but graft biopsy should be performed to guide treatment, especially if changes in the pattern of proteinuria are detected.[29]

Some studies demonstrated the benefit of ACEi and ARB in controlling proteinuria, with emphasis on the combined endpoints of cardiovascular events and loss of graft function in KTR, similar to what is known in PDP.[29,30] Long-term benefits

of RAS blockade in KTR, however, are not clearly established in the literature, since other authors have reported an absence of beneficial effect on GFR, possibly because proteinuria in KTR is multifactorial and presents differing prognoses among different patients and scenarios.[28,31,32] Despite being difficult to determine the exact cause in each case, proteinuria resulting from hyperfiltration is potentially present in most patients.[28] Consequently, the KDIGO (not graded) suggests administration of ACEi or ARB in adult patients with proteinuria >1g/day and in patients <18 years old with proteinuria >600 mg/m²/day.[25]

Anemia

The prevalence of anemia in KTR is 10% in CKD-T categories 3a and 3b, 26% in category 4, and 31-50% in category 5.[10,11,23] Iron deficiency from CKD-related cytokines such as hepcidin, or gastrointestinal or uterine blood loss should be assessed and corrected through intravenous iron supplementation, with a target of 20% transferrin saturation and 100 mg/dL ferritin levels.[33] Other causes of anemia, such as viral infections (cytomegalovirus, parvovirus B19), bone marrow toxicity from immunosuppressant drugs (azathioprine, mycophenolic acid), or antihypertensive medications (ACEi and ARBs) should be clinically managed as well.[25]

Treatment with erythropoietin positively impacts graft function, however, as in PDP, excessive use of erythropoietin (effecting haemoglobin levels >12.5 g/dL) increases mortality due to thrombotic and hypertensive side effects.[34] According to the KDIGO guidelines (not graded), erythropoietin should be initiated when haemoglobin levels fall below 10 g/dL, with an optimal target between 11-12 g/dL (Table 1).[33]

Dyslipidemia

Hypercholesterolemia and elevated LDL cholesterol are classically associated with cardiovascular mortality, and dyslipidemia is found in over 60% of KTR. This can be explained by genetic factors, diabetes, metabolic syndrome, and immunosuppressant drug adverse effects, mainly sirolimus, but also prednisone and, to a lesser degree, CNI.[11,23]

The benefit of statins on cardiovascular mortality can be inferred in KTR, although reductions in death-censored graft survival were not thoroughly demonstrated given the richly multifactorial scenario of CKD-T.[35] Some studies, however, show a significant number of dyslipidemic KTR without statin treatment, even when clinically indicated.[23,36]

Adverse effects of statins and fibrates, such as myopathy, liver toxicity, drug interactions with immunosuppressive drugs and diarrhea, can limit their use in KTR, partly justifying those data.[9,23] Still, targets of <200 mg/dL for total cholesterol, <100 mg/dL for LDL cholesterol, and <150 mg/dL for triglycerides should be pursued through dietary and lifestyle changes, use of statins as indicated, and careful selection of patients in which fibrates could be of benefit (Table 1).[9,25]

Diabetes

Diabetes is very common among KTR, since a good proportion of KTR are previously diabetic and around 20-25% of KTR develop post-transplant diabetes mellitus (PTDM), due to direct toxicity of CNI towards pancreatic beta cells, steroid-induced peripheral insulin resistance, or PSI toxicity.[37] Treatment of PTDM includes either insulin or oral antidiabetic drugs and follows the same targets as pre-transplant diabetes, with recommended glycosylated haemoglobin <6.5%.[37]

Special attention must be given to micro- and macrovascular complications, including regular ophthalmological follow-ups and periodic complete cardiovascular check-ups, as PTDM increases the mortality risk two-fold, with greater impact among KTR younger than 55 years old (Table 1).[37]

Bone mineral disorder and metabolic acidosis

As a result of pre-transplant CKD, KTR can present with various forms of bone disease, including renal osteodystrophy, adynamic bone, and corticosteroid-borne osteopenia and osteoporosis.[38] Since bone mineral disorder plays a major role in endothelial dysfunction and cardiovascular mortality in PDP, adequate control of hyperparathyroidism could logically slow CKD progression and lower mortality in KTR, although to date there are no studies clearly demonstrating that.[38]

In a Canadian study, the prevalence of hyperphosphatemia in category 5 CKD-T was 21%, identical to that in CKD category 5 PDP. However, only 28% of KTR received phosphate chelation, compared to 87% in the PDP group.[23] In another, Brazilian study, only 20% of KTR received specific treatment for hyperphosphatemia at 1-year post-transplant.[36]

According to the KDIGO guidelines (2C), KTR should receive phosphate chelation and 1,25-OH vitamin D supplementation in the activated vitamin form and/or its pro-form as indicated, targeting the same references for phosphate (<4,5 mg/dL for patients with category 1 to 4 CKD-T, and <5,5 mg/dL for patients with category 5 CKD-T), PTH (<450 pg/mL), and 25-OH vitamin D (>30 ng/dL) as with PDP.[33] Treatment of osteoporosis with bisphosphonates is indicated by the KDIGO guidelines (2D).[25] However, the risk for adynamic bone disease and, particularly in category 4 and 5 CKD-T patients, potential nephrotoxicity, should be considered.[38]

In metabolic acidosis, the benefit of bicarbonate supplementation to slow CKD progression in PDP has been better established.[39] Despite the lack of compelling data in KTR, control of metabolic acidosis targeting serum bicarbonate >20-22 mEq/L should be implemented (Table 1).[39]

Patient adherence and lifestyle changes

Massive research, development, and implementation efforts for state-of-the-art therapies are useless if KTR are not motivated to follow specific recommendations. Hence, transplant teams must make patients aware that they play an extremely important part in the care-taking process, and that their actions will positively or negatively affect graft function and mortality, among other outcomes.[40]

Although KTR are a selected subset of CKD patients, often more active and compliant than many of their dialysis counterparts, treatment nonadherence is noted in over one third of KTR.[41] Moreover, 10-33% of KTR are smokers, 60% are obese or overweight, and dietary transgression with sedentary behaviour is very common.[40]

Surveillance of nonadherence, through methods such as the Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS), which considers immunosuppressive medication blood levels as well as self-reported and physician information to identify patients skipping, delaying or reducing medication dosages, or practicing drug holidays, is fundamental.[41]

In this setting, adoption of multidisciplinary teams, including nurses, physicians, dietitians, social workers, and psychologists, allows better observation of each patient´s primary issues and development of more reasonable and individualized treatment decisions. This ultimately leads to improved understanding and adherence to treatment

by patients, with clear advantages in long-term follow-up performance compared to patients managed by non-multidisciplinary teams (Table 1).[42]

Multidisciplinary approach

It has been suggested that adoption of the multidisciplinary approach could be highly beneficial for attaining specific CKD treatment goals in KTR, similar to the model adopted in pre-dialysis.[11,23] Despite the relevance of allogeneic and immunosuppression concerns in KTR, it has been reported that these patients often fail to receive adequate attention to CKD-related risk factors for disease progression, especially when kidney transplant teams are not multidisciplinary.[11,12,23]

Akbari et al. described a more complete distribution of specific treatments for CKD-related complications in category 5 PDP followed by a multidisciplinary team, compared to CKD category 5 KTR followed by non-multidisciplinary staff. In particular, KTR received considerably less anti-proteinuric medications, erythropoietin, and statins when clinically indicated, and had overall worse blood pressure control.[23]

Recently, the same authors demonstrated that 68% of KTR under multidisciplinary care obtained 7 of 9 control targets for CKD-related risk factors, compared to 10% of KTR without multidisciplinary care, with an overall 66% reduction in hospital admissions.[42] Alternatively, comparable quality of treatment for CKD-related complications between KTR and PDP, when both groups were under similar multidisciplinary treatments, has been part of our experience.[36]

In fact, multidisciplinary teams facilitate a number of needs for KTR including: access to medications and exams, discussing risks and concerns related to medication and dietetic patterns, motivation to pursue cardinal clinical targets such as blood

pressure and glucose control, offer valuable logistical help and counselling with intercurrent problems, and assist with organization of family and social support. In total, the multidisciplinary team helps patients to overcome technical and social pitfalls that may not always be easily sensed or solved by physicians alone.[41,42]

Summary

Relatively few studies consider the clinical impact of multidisciplinary interventions on traditional CKD-related risk factors for progression of CKD in KTR, which is clearly a tempting field for research.[14] Post-transplant care should be based on strict control of alloimmune phenomena, patient compliance with immunosuppressive treatment, reduction of cardiovascular risk and adequate control of the same complications and risk factors for CKD progression found in pre-dialysis, such as hypertension, proteinuria, anaemia, dyslipidemia, diabetes, metabolic acidosis, and bone mineral disorder, all ultimately related to chronic allograft injury and death with functioning graft.[9]

Even though recognition of all possible aspects of the pathophysiology of CKD-T, not every one of the risk factors will eventually be treatable. Therefore, individualizing each situation is fundamental, as there is not one treatment plan that will be appropriate for all patients. Practitioners should also avoid polypharmacy, which could lead to drug interactions, adverse effects, and nonadherence.[41] Rational management of the clinical and social characteristics of each individual patient is better achieved through the adoption of multidisciplinary post-transplant teams, as the patient´s collaboration is fundamental for pursuing optimal clinical treatment goals that will positively impact the survival endpoints.[9,42]

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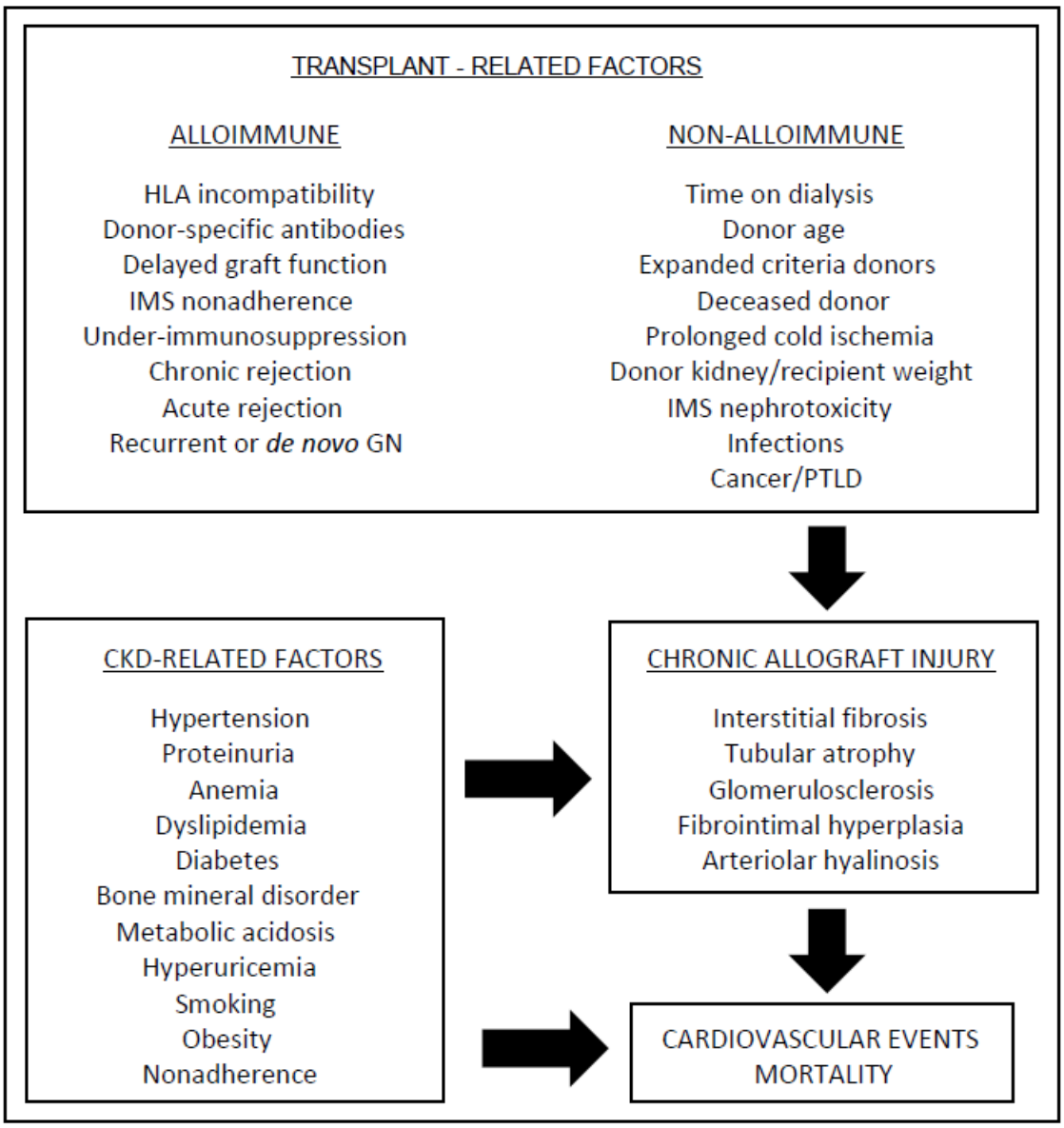
Figure 1. Risk factors for chronic allograft injury and mortality in KTR



Abbreviations: HLA (human leukocyte antigen), IMS (immunosuppressive medication), GN (glomerulonephritis), PTLD (posttransplant lymphoproliferative disease), CKD (chronic kidney disease).

Table 1. Clinical targets and recommendations for the management of CKD-related risk factors in KTR.

Risk fator	Targets	Recommendations
Hypertension	uNa+ < 150 mEq/24h BP < 130x80 mmHg	Lower Na+ ingestion, lose weight, keep BP diary Use ACEi or ARB, β-blocker, consider spironolactone for CV prevention Consider CCB for afferent arteriolar vasodilation Consider association of diuretic, direct vasodilators for further BP control
Proteinuria	< 500 mg/24h	Use ACEi or ARB, consider spironolactone Multifactorial, hence target difficult to attain (ex. PSI-induced podocitopathy)
Anaemia	Hb 11-12 g/dL TS > 20% Ferritin > 100 mg/dL	Start erythropoietin if Hb < 10 mg/dL, ideally not exceed Hb > 12.5 mg/dL EV iron supplementation as needed, caution with hemochromatosis If persisting anaemia, consider viral infection (PVB19, CMV) or drug side-effects (ACEi/ARB, azathioprine + allopurinol, mycophenolate)
Dyslipidaemia	TC < 200 mg/dL LDLc < 100 mg/dL TG < 150 mg/dL	Nutritional counselling, lose weight, use statins, consider association of fibrates (observe risk of rhabdomyolysis, liver toxicity and diarrhea) Control may be difficult to attain (ex. PSI-induced dyslipidaemia)
Bone Mineral Disorder	PTH < 300 pg/mL P < 4.5 mg/dL (CKD 1-4), or < 5.5 (CKD stage 5) 25-OH vit. D > 30 ng/dL	Start 1,25-OH vitamin D if PTH > 450 pg/mL Lower phosphate ingestion through nutritional counselling, use phosphate chelation with sevelamer or CaCO3 if P above range despite diet Supplement 25-OH vitamin D if < 30 ng/dL, morning sun exposure
Diabetes	HbA1c < 6.5%	Lower calorie ingestion, physical activity, use oral antidiabetics as needed (ex. metformin, glimepiride), consider insulin Motivate patient to keep glucose diary, to detect daily glucose variations Periodical ophthalmological and diabetic foot check-ups
Metabolic Acidosis	HCO3- > 20-22 mEq/L	Supplement oral bicarbonate as needed
Other	Smoking Obesity Adherence	Psychological counselling, nicotine patches, Bupropion (supervised) Physical exercise, nutritional counselling Multidisciplinary approach to highlight the importance of treatment

Abbreviations: uNa+ (urinary sodium), Na+ (sodium), BP (blood pressure), ACEi (angiotensin converting enzyme inhibitor), ARB (angiotensin receptor blocker), CV (cardiovascular), CCB (calcium channel blocker), PSI (proliferation signal inhibitor), Hb (haemoglobin), TS (transferrin saturation), EV (endovenous), PVB19 (parvovirus B19), CMV (cytomegalovirus), TC (total cholesterol), LDLc (LDL cholesterol), TG (triglycerides), PTH (parathyroid hormone), P (phosphorus), CKD (chronic kidney disease), CaCO3 (calcium carbonate), HbA1c (glycosylated haemoglobin), HCO3- (serum bicarbonate).

APÊNDICE 2 – Aprovação pelo Comitê de Ética em Pesquisa local.

UNIVERSIDADE FEDERAL DE JUIZ DE FORA
PRO-REITORIA DE PESQUISA
COMITÊ DE ÉTICA EM PESQUISA - CEP/UFJF
36036900- JUIZ DE FORA - MG – BRASIL

Parecer nº 275/2011 **2ª VIA**

Protocolo CEP-UFJF: **2516.256.2011** **FR: 462849** **CAAE**: 0249.0.180.000-11
Projeto de Pesquisa: "Análise comparativa entre o tratamento da doença renal crônica em paciente com pré-diálise e transplantados renais"
Area Temática: *Grupo III*
Pesquisador Responsável: Moisés Carminatti
Data prevista para o término da pesquisa: agosto de 2013
Instituição Proponente: Universidade Federal de Juiz de Fora

Análise do protocolo:

Itens Avaliados			Sim	Não	P	NA
Justificativa	O estudo proposto apresenta pertinência e valor científico		X			
	Objeto de estudo está bem delineado		X			
Objetivo(s)	Apresentam clareza e compatibilidade com a proposta		X			
Material e Métodos	Atende ao(s) objetivo(s) proposto(s)		X			
	Informa	Tipo de estudo	X			
		Procedimentos que serão utilizados	X			
		Número de participantes	X			
		Justificativa de participação em grupos vulneráveis				X
		Critérios de inclusão e exclusão	X			
		Recrutamento	X			
		Coleta de dados	X			
		Tipo de análise	X			
		Cuidados Éticos	X			
Revisão da literatura	Atuais e sustentam o(s) objetivo(S) do estudo		X			
Resultados	Informa os possíveis impactos e benefícios		X			
Cronograma	Agenda as diversas etapas de pesquisa		X			
	Informa que a coleta de dados ocorrerá após aprovação do projeto pelo comitê		X			
Orçamento	Lista a relação detalhada dos custos da pesquisa		X			
	Apresenta o responsável pelo financiamento		X			
Referências	Segue uma normatização		X			
Instrumento de coleta de dados	Preserva o sujeito de constrangimento		X			
	Apresenta pertinência com o(s) objetivo(s) proposto(s).		X			
Termo de dispensa de TCLE	Solicita dispensa		X			
Termo de assentimento	Apresenta o termo em caso de participação de menores					X
TCLE	Está em linguagem adequada, clara para compreensão do sujeito					X

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	Apresenta justificativa e objetivos					X
	Descreve suficientemente os procedimentos					X
	Apresenta campo para a identificação dos sujeitos					X
	Informa que uma das vias do TCLE deverá ser entregue ao sujeito					X
	Assegura liberdade do sujeito recusar ou retirar o consentimento sem penalidades					X
	Garante sigilo e anonimato					X
	Explicita	Riscos e desconfortos esperados				X
		Ressarcimento de Despesas				X
		Indenização diante de eventuais danos decorrentes da pesquisa				X
		Forma de contato com o pesquisador				X
		Forma de contato com o CEP				X
		Como será o descarte de material coletado (no caso de material biológico)				X
		O arquivamento do material coletado pelo período mínimo de 5 anos				X
Pesquisador (es)	Apresentam titulação e experiência compatível com o projeto de pesquisa		X			
	Apresenta comprovante do Currículo Lattes do pesquisador principal e dos demais participantes.		X			
Documentos	Carta de Encaminhamento à Coordenação do CEP		X			
	Folha de Rosto preenchida		X			
	Projeto de pesquisa, redigido conforme Modelo de Apresentação de Projeto de Pesquisa padronizado pela Pró-Reitoria de Pesquisa (PROPESQ)		X			
	Declaração de infraestrutura e de concordância com a realização da pesquisa, assinada pelo responsável pelo setor/serviço onde será realizada a pesquisa		X			

P= parcialmente **NA=Não se aplica**

Diante do exposto, o Comitê de Ética em Pesquisa – CEP/UFJF, de acordo com as atribuições definidas na Res. CNS 196/96, manifesta-se pela aprovação do protocolo de pesquisa proposto, devendo o pesquisador entregar o relatório no final da pesquisa.

Situação: Projeto Aprovado

Juiz de Fora, 15 de Dezembro de 2011

Lainer C. Serrano
Coordenadora em exercício– CEP/UFJF

RECEBI
DATA: 07/03/2016
ASS: _____

APÊNDICE 3 – Apresentação em congresso científico.