Self-rated health and mortality after kidney transplantation

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Part II

Self-rated health as a health outcome

Chapter 5

Anemia has a negative impact on self-rated health in kidney transplant recipients with well-functioning grafts: findings from an 8-year follow-up study

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submitted

Abstract

Background

Anemia is a predictor of mortality and of self-rated health (SRH). However, studies on the relationship between SRH and changes in hemoglobin (Hb) value over time stratified by chronic kidney disease (CKD) stages are lacking. The aim is to explore whether a change in Hb-value over time predicts SRH at up to 8 years follow-up, stratified for CKD stages and controlled for demographic and medical variables.

Methods

A prospective study with a baseline measurement between the 3rd and 12th month after KT was performed on 337 consecutive patients. Demographic and clinical data were retrieved from medical records. CKD stages were estimated using the CKD-EPI formula and divided into 2 groups: CKD1-2 and CKD3-5. Generalized Estimating Equations (GEE) were performed to identify predictors of SRH at follow-up in both CKD groups.

Results

Male gender, a decrease in estimated Glomerular Filtration Rate (eGFR) and Hb-value over time contributed significantly to the GEE model on SRH at follow-up in CKD1-2. For SRH at follow-up in CKD3-5, older age, male gender and chronic renal allograft dysfunction (CRAD) contributed significantly to the GEE model.

Conclusion

At up to 8 years follow-up, male gender, a decrease in eGFR and Hb-value over time predicted poorer SRH in CKD1-2. In such patients, we suggest also monitoring slight deteriorations in eGFR and Hb-values. In CKD3-5, higher age, male gender and higher presence of CRAD predicted poorer SRH at up to 8 years follow-up. In these patients, adequate treatment would slow down CRAD progression.

Key words

anemia, chronic kidney disease, longitudinal design, self-rated health, transplantation

Introduction

Anemia has been generally considered to be a predictor of several health outcomes in the general population for decades now,[1] and anemia of renal origin might be a predictor of mortality as well.[2,3] The impact of post-transplant anemia (PTA) on mortality has also been previously proposed.[3-5]

Self-rated health (SRH) has also been identified as a predictor of mortality.[6] A meta-analysis by DeSalvo et al. (2006) and a systematic review by Spiegel et al. (2008) both showed the importance of SRH along with traditional biomarkers[7] and described SRH as a predictor of future health status and as an important outcome criterion in the evaluation of medical treatment.[8] Christian et al. (2011) concluded in their study on the relationship between SRH and medical indicators that SRH is not secondary to depressive symptoms, neuroticism, or changes in perceived health.[9] So far, an association between older age and a higher likelihood of poor self-reported health has been shown as well.[10] Furthermore, Benjamin et al. (2004) described the relationship between SRH and worse health outcomes as being stronger among males.[6] The outcomes, based on the impact of SRH on mortality even after controlling for gender, age and medical variables, such as a glomerular function in dialyzed[11] and in transplanted recipients,[12] have also been shown.

An association between the deterioration of kidney function and worse SRH has also been presented.[13,14] Moreover, previous findings in the transplanted population, based on a comparison between the impact of the absolute level of the graft function and the change in its function over time, showed that absolute level of graft function at baseline was not significantly associated with a patient's SRH at follow-up; however, its change over time was.[14] Similarly, an increase in anemia of renal origin was connected to a decrease in SRH and quality of life in the chronic kidney disease (CKD) population, including pre-dialyzed, dialyzed and transplanted patients.[15-17] The first study based on demonstrating the impact of erythropoiesis-stimulating agents (ESA) on well-being was performed by Revicki et al. 18 years ago.[17] They showed that ESA significantly enhanced the SRH of the pre-dialyzed CKD population.[17] A connection between adequate therapy for PTA, an improvement in quality of life and longer survival has been found in many – sometimes randomized – studies.[15-19]

Nonetheless, the influence of a change in medical findings over time on SRH in transplanted recipients has not yet been sufficiently described. The prevalence of PTA varies the most during the first post-transplantation year.[18,19] Additionally, there is still no well-known impact from a change in PTA over time on the long-term well-being at follow-up in the transplanted population. Thus far, knowledge about the impact that a change in the hemoglobin value has over a time longer than one or two years in relation to graft deterioration and SRH in varying CKD stages is still lacking. Hence, the aim of this study was to explore whether a change in the hemoglobin value over time predicts SRH at up to 8 years follow-up, stratified for CKD stages and controlled for demographic and medical variables.

Methods

Sample and procedure

A total of 337 consecutive patients who underwent KT between January 2002 and April 2010 at the Transplant Centre of Kosice in the eastern region of Slovakia were considered for participation in the study. The inclusion criterion was graft survival at 3 months after

KT, because the first 3 months after KT are usually considered as the most problematic period connected to dramatic changes, increased morbidity and even mortality.[20] Similarly, an improvement in SRH most often occurs at 6 months and remains unchanged for up to 2 years after KT.[21] Additionally, the degree of renal anemia during a period shorter than 3 months after successful transplantation depends on the pre- and peri-transplantation period.[2,4] Based on these findings, the baseline examination of participants occurred between the 3rd and 12th month after successful KT. The only exclusion criterion was the inability to answer questions during the interview due to severe dementia, or having mental retardation listed in the medical record. In line with this, 12 patients dropped out prior to reaching 3 months after KT: 3 (1.0%) of them died, 6 (1.9%) lost their transplanted kidney and 3 (1.0%) were excluded according to the exclusion criteria. Thus a total of 325 (96.4%) kidney transplant recipients after successful kidney transplant surgery were asked to participate at the baseline examination, and 26 (8.0%) of whom refused to participate. Thus, 299 (92.0%) patients were included in the analysis at baseline examination. The time to follow-up examination was up to 8 years (mean 2.8±1.7), in line with the study of Drent et al.[22] An additional 17 (5.7%) patients died and 19 (6.4%) lost their transplanted kidney before follow-up. At follow-up, a further 4 (1.3%) participants were excluded due to exclusion criterion because of severe stroke, 16 (5.4%) refused to participate and 26 (8.6%) provided incomplete data, resulting in 217 patients with a functional transplanted kidney (a response rate of 72.6%) who were enrolled in the study at the follow-up examination. Figure 5.1 presents more detailed information about the participants (Figure 5.1).

All participants were interviewed during regular outpatient clinical visits by trained personnel independent of the transplant team. Patients filled in a questionnaire, and demographic and medical data were retrieved from medical records at the time the SRH answer was provided through the questionnaire. All patients included in the study signed an informed consent prior to the study. The local Ethics Committee in Kosice approved the study.

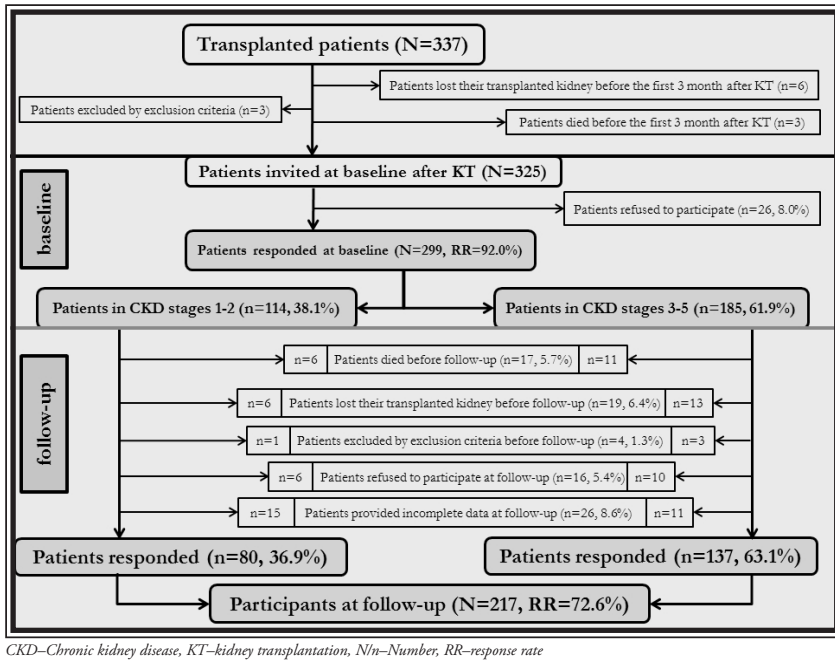
Measures

Demographic data included age and gender. Age was treated as the continuous variable. Female gender was set as the reference category.

Self-rated health (SRH) was measured using the first question of the Short Form Health Survey (SF-36).[23] It was transformed from scores between 1 (poor) and 5 (excellent) into a standard scale from 0 (poor health) to 100 (excellent health) in which a higher score indicates better health status.[23,24] The validity and reliability of the first item of the SF-36 has been confirmed in the Slovak Republic[25,26] as well as in patients with renal disease, including those after KT.[27,28]

Clinical data were retrieved from medical files. These included the primary diagnosis of kidney failure, duration on dialysis before KT (in years), source of transplanted kidney, its function immediately after KT, serum creatinine (laboratory methods by Scheffe), serum hemoglobin (Hb) (in gram per deciliters), therapy for anemia, acute rejection episodes, type of rejection treatment, chronic renal allograft dysfunction (CRAD), uroinfection (included pyelonephritis of the graft), immunosuppression treatment at the time of the interview and comorbidities (cardiovascular disease: coronary artery disease, severe cardiac failure, myocardial infarction; hypertension; and categories of diabetes mellitus: no diabetes mellitus, already existing diabetes mellitus and new-onset diabetes mellitus after KT).

Figure 5.1 Flow-chart diagram of the participants



CKD–Chronic kidney disease, KT–kidney transplantation, N/n–Number, RR–response rate

The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula (in milliliters per minutes).[29] Chronic kidney disease (CKD) stages from 1 to 5 were determined as recommended by guidelines.[2,4] After this, patients at baseline were stratified into two groups: the first group consisted of stages 1-2 CKD patients and the second group of stages 3-5 CKD patients according to the known impact of decreased kidney function on the Hb-value of renal origin.[2] Acute rejection episodes and chronic renal allograft dysfunction were diagnosed from biopsies according to the Banff 2009 update of diagnostic categories for renal allograft biopsies.[30] Patients received their immunosuppressive medication independently from this study based solely on the decision of their transplant nephrologists; the current practice in the transplant centre is in line with standard recommendations issued by the "Kidney Disease Improving Global Outcomes" (KDIGO) Clinical Practice Guideline for the care of kidney transplant recipients.[4]

Statistical analyses

First, frequencies, means and standard deviations were calculated for the sample description. The Mann-Whitney U-test and χ^2 test were used to check the differences between participants and non-participants as well as between the dependent variable (SRH at follow-up) and the other variables at baseline: age, gender, eGFR, Hb-value, uroinfection (including pyelonephritis of the graft), acute rejection episodes, CRAD and comorbidities. Next, SRH was analysed at follow-up by CKD group with each of the study variables. Finally, we performed Generalized Linear Models – Generalized Estimating Equations (GEE). GEE belong to the semi-parametric regressions and are standardly used to estimate the parameters of a generalized linear model

with a potential unknown correlation between the study outcomes.[31] Hubbard et al. showed that GEE models provide a useful approximation of the truth.[32] Based on these findings, the GEE were performed in order to identify the predictors of SRH at up to 8 years follow-up. The independent variables in both stratified GEE models were all variables with $p \leq 0.05$ in the bivariate analyses, and in line with our previous findings[14], we used as the independent variables the change in eGFR over time and the change in Hb-value over time as well instead of the eGFR and the Hb-value at baseline. The Statistical Package for the Social Science (IBM SPSS Inc. Chicago, IL, USA) version 20 was used for statistical analyses.

Results

No significant differences were found between participants and non-participants or between those who provided complete and incomplete data regarding age and gender at baseline and at follow-up.

The observation period for follow-up was from 1 to 8 years (mean 2.8±1.7); the observation period for CKD stages 1-2 was from 1 to 6 years (mean 3.00±1.4) and for CKD stages 3-5 was from 1 to 8 years (mean 3.24±1.7). PTA was found in 126 (42.1%) patients at baseline: 29 (25.4%) in CKD stages 1-2 and 97 (52.4%) in CKD stages 3-5. At follow-up, the prevalence of PTA was 75 (34.6%) patients: 16 (20.0%) in CKD stages 1-2 and in 59 (43.1%) in CKD stages 3-5. The mean hemoglobin value increased non-significantly over time from 12.3 at baseline to 12.7 at follow-up in the whole sample; after stratification of the sample into 2 groups, the mean Hb-value was 12.4 at baseline and 12.3 at follow-up in CKD stages 1-2; on the other hand, in CKD stages 3-5 it increased from 11.3 at baseline to 12.5 at follow-up. In line with these results, the prevalence of the therapy for anemia was significantly different ($p \leq 0.05$) from baseline to follow-up in CKD stages 3-5 only.

The mean SRH significantly differed over time ($p \leq 0.001$), as did the prevalence of CRAD ($p \leq 0.01$) and uroinfection ($p \leq 0.05$) in the whole sample. After stratification into the two CKD groups, the mean SRH significantly decreased ($p \leq 0.05$) in CKD stages 1-2 and the prevalence of CRAD and uroinfection significantly increased in CKD stages 3-5. Other variables did not significantly differ from baseline to follow-up. Table 5.1 displays more detailed information about the characteristics of the whole sample (Table 5.1). The associations of SRH at follow-up by CKD groups with each of the study variables are shown in Table 5.2. These variables were used as independent factors in the GEE models for SRH at follow-up, stratified according to the two groups of CKD. Table 5.2 displays more detailed information about the characteristics of the significant medical variables and SRH at baseline and follow-up, stratified for CKD stages 1-2 and CKD stages 3-5 (Table 5.2).

Model 1: SRH at follow-up in CKD stages 1-2
Male gender (B=-26.1, 95%CI -32.5;-19.7), a decrease in eGFR over time (B=0.8, 95%CI 0.4;1.1) and a decrease in Hb-value over time (B=2.3, 95%CI 1.6;3.0) contributed significantly to the GEE model on poor SRH at follow-up in CKD stages 1-2 (Table 5.3).
Model 2: SRH at follow-up in CKD stages 3-5
Higher age (B=-0.6, 95%CI -1.0;-1.1), male gender (B=-17.5, 95%CI -33.3;-1.7) and CRAD (B=-21.5, 95%CI -42.1;-0.9) contributed significantly to the GEE model on poor SRH at follow-up in CKD stages 3-5 (Table 5.3).

Table 5.1 Characteristics of the sample at baseline and at follow-up

		baseline (N=299) N(%) or mean±SD	follow-up (N=217) N(%) or mean±SD
Time after KT during reviewing (in years)		0.5±0.2	2.8±1.7
Age		48.3±12.2*#	50.6±12.1*#
Gender	Male	166(55.5%)*#	122(56.2%)*#
	Female	133(44.5%)	95(43.8%)
Primary diagnosis of kidney failure	Glomerulonephritis	108(36.1%)	74(34.1%)
	Tubulointerstitial nephritis	72(24.1%)	44(20.3%)
	Vascular disease	31(10.3%)	22(10.1%)
	Polycystic kidneys adult type	18(6.0%)	13(6.0%)
	Diabetic nephropathy	22(7.4%)	20(9.2%)
	Other or unknown	48(16.1%)	44(20.3%)
Duration on dialysis before KT (in years)		3.9±2.9	3.8±2.9
Source of transplanted kidney	Deceased donor	285(95.3%)	201(92.6%)
	Living donor	14(4.7%)	16(7.4%)
Function immediately after KT	Immediate	151(50.5%)	92(42.4%)
	Delayed	148(49.5%)	125(57.6%)
Self-rated health		45.6±26.1*	**52.1±24.7**
Estimated Glomerular filtration rate (ml/min)		50.1±17.9	49.8±20.4*
CKD stages	1	43(14.4%)	31(14.3%)
	2	71(23.8%)	49(22.6%)
	3a+3b	158(52.8%)	117(53.9%)
	4	23(7.7%)	17(7.8%)
	5	4(1.3%)	3(1.4%)
Hemoglobin (Hb) value (g/dl)		12.3±2.6*	12.7±1.9*
Post-transplant anemia	No anemia (Hb≥12.0g/l)	173(57.9%)	142(65.4%)
	Mild (10.0≤Hb<12.0g/l)	98(32.8%)	56(25.8%)
	Severe (Hb<10.0g/l)	28(9.3%)	19(8.8%)
Therapy for anemia	ESA	11(8.7%)	10(13.3%)
	Iron	45(35.7%)	44(58.7%)
	Folic acid	31(24.6%)	28(37.3%)
	Cobalamin	6(4.8%)	4(5.3%)
	Pyridoxine	7(5.6%)	8(10.7%)
	Ascorbic acid	13(10.3%)	11(14.7%)
Uroinfection (including pyelonephritis of graft) (during the last year)		80(26.8%)*	**63(29.0%)***
Acute rejection episodes		73(24.4%)	51(23.5%)
Type of rejection treatment	Steroids	53(72.6%)	35(68.6%)
	Antithymocyte globulin	4(5.5%)	5(9.8%)
	Plasmapheresis	7(9.6%)	6(11.8%)
	Plasmapheresis+i.v.immunoglobuline	9(12.3%)	5(9.8%)
Chronic renal allograft dysfunction		31(10.4%)#	**43(19.8%)#**
Immunosuppression treatment at the time of interview	CsA+MMF+P	211(70.6%)	149(68.7%)
	Tac+MMF+P	62(20.7%)	53(24.4%)
	Tac+MMF	8(2.7%)	6(2.8%)
	CsA+MMF	10(3.3%)	7(3.2%)
	SIR+MMF+P/ SIR+MMF	8(2.7%)	2(0.9%)
Comorbidity	Coronary artery disease	25(8.4%)	18(8.3%)
	Severe cardiac failure	19(6.4%)	16(7.4%)
	Myocardial infarction	7(2.3%)	8(3.7%)
	Hypertension	207(69.2%)	149(68.7%)
	Diabetes mellitus identified before KT	47(15.7%)	23(10.6%)
	New onset diabetes mellitus after transplantation	26(8.7%)*	19(8.8)
	CKD-MBD	41(13.7%)	31(14.3%)
	Other comorbidities:≥2	17(5.7%)	13(6.0%)

N/n–Number, SD–Standard deviation; AZA–azathioprine, CKD–Chronic kidney disease, CsA–cyclosporine A, ESA–erythropoiesis-stimulating agents, EVER–everolimus, MBD–Mineral bone disorder, MMF–mycophenolate mofetil/mycophenolate sodium, KT–kidney transplantation, P–prednisone, SIR–sirolimus, Tac–tacrolimus.
*Significant differences (p≤0.05) between baseline and follow-up are flagged: **bold font**. Determining the strength of the association (p≤0.05) between SRH and each variable are flagged: *-SRH in CKD stages 1-2, #-SRH in CKD stages 3-5.*

Table 5.2 Characteristics of the variables stratified according to CKD stages estimated at baseline examination

		CKD stages 1-2 (N(%) or mean±SD)		CKD stages 3-5 (N(%) or mean±SD)	
		baseline (n=114)	follow-up (n=80)	baseline (n=185)	follow-up (n=137)
Self-rated health		58.2±21.8	53.1±25.7$	43.8±25.4	46.4±24.9
eGFR (ml/min)		67.2±17.3	49.8±18.5$	42.1±11.5	49.9±20.7
Change in eGFR over time (ml/min)		-13.5±17.4		7.4±18.5	
Hb-value (g/dl)		12.4±3.5	12.3±2.1	11.3±2.5	12.5±1.8
Change in Hb-value over time (g/dl)		1.9±1.7		0.5±2.6	
Post-transplant anemia	No anemia (Hb≥12.0g/l)	85(74.6%)	64(80.0%)	88(47.6%)	78(56.9%)
	Mild (10.0≤Hb<12.0g/l)	17(14.9%)	11(13.7%)	81(43.8%)	45(32.9%)
	Severe (Hb<10.0g/l)	12(10.5%)	5(6.3%)	16(8.6%)	14(10.2%)
Therapy for anemia	ESA	2(6.9%)	1(6.3%)	9(9.3%)	9(15.3%)$
	Iron	16(55.2%)	10(62.5%)	29(29.9%)	34(57.6%)$
	Folic acid	17(58.6%)	9(56.3%)	14(14.4%)	19(32.2%)$
	Cobalamin	3(10.3%)	2(12.5%)	3(3.1%)	2(3.4%)
	Pyridoxine	4(13.8%)	3(18.7%)	3(3.1%)	5(8.5%)$
	Ascorbic acid	4(13.8%)	2(12.5%)	9(9.3%)	9(15.2%)
Uroinfection (including pyelonephritis of graft) (during the last year)		22(19.3%)	9(11.3%)	58(31.4%)	54(39.4%)$
Chronic renal allograft dysfunction		4(6.4%)	7(8.8%)	27(14.6%)	36(26.3%)$

CKD–Chronic kidney disease, eGFR–estimated Glomerular Filtration Rate, ESA–erythropoiesis-stimulating agents, Hb–Hemoglobin value, N/n–Number, SD–Standard deviation; Significant differences (p≤0.05) between baseline and follow-up are flagged: $

Table 5.3: Final GEE models in the cohort (stratified for two CKD groups: CKD stages 1-2 and CKD stages 3-5), containing significant predictors of SRH at follow-up

Models for SRH at follow-up (N=217)		Model 1 in CKD stages 1-2 (n=80) QICC 268.07		Model 2 in CKD stages 3-5 (n=137) QICC 788.66	
		B(95%CI)	Wald $\chi 2$	B(95%CI)	Wald $\chi 2$
Age		0.1(-0.63;0.83)n.s.	0.73	-0.58(-1.01;-1.14)**	6.78
Gender	Female	Reference		Reference	
	Male	-26.11(-32.51;-19.70)***	63.83	-17.50(-33.28;-1.72)*	4.72
SRH at baseline		0.20(-0.08;0.48)n.s.	1.95	0.25(-0.24;0.53)n.s.	3.21
Uroinfection	No	Reference		Reference	
	Yes	-15.06(-31.97;1.86)n.s.	3.04	-3.45(-7.17;0.27)n.s.	3.30
CRAD	No	Reference		Reference	
	Yes	-5.82(-8.28;-3.24)n.s.	2.38	-21.48(-42.11;-0.85)*	4.16
Change in eGFR over time		0.77(0.43;1.10)***	19.56	0.08(-0.19;0.35)n.s.	0.33
Change in Hb-value over time		2.33(1.63;3.03)***	42.89	1.42(-3.99;6.83 n.s.	0.27

*n.s–not significant, *-p<0.05, **-p<0.01, ***-p<0.001; B–Unstandardized Coefficient B, CI–Confidence Interval*
CKD–chronic kidney disease, CRAD–chronic renal allograft dysfunction, eGFR–estimated Glomerular Filtration Rate, Hb–hemoglobin, QICC–Corrected Quasi Likelihood under Independence Model Criterion, SRH–Self-rated health

Discussion

We explored whether a change in hemoglobin value over time predicts SRH in kidney transplant recipients at up to 8 years follow-up, stratified for CKD stages and controlled for demographic and medical variables. We found that male gender, a decrease in the hemoglobin value and in graft function over time predicted poor SRH at up to 8 years follow-up in patients after KT in CKD stages 1-2. On the other hand, older age, male gender and chronic renal allograft dysfunction predicted poor SRH at up to 8 years follow-up in CKD stages 3-5.

In patients with CKD stages 1-2 the prevalence of PTA was approximately the same at baseline and at follow-up, and the mean hemoglobin value seemed to be unchanged. No differences were found in the prevalence of therapy for anemia at baseline and at follow-up in patients with a well-functioning graft. In line with this, eGFR and SRH significantly decreased at up to 8 years follow-up in patients with CKD stages 1-2.

In contrast, in patients with CKD stages 3-5 regarding well-known outcomes in worsening anemia, the prevalence of therapy for anemia significantly increased. The treatment appeared to be sufficient because of a decrease in the prevalence of PTA and an increase in the hemoglobin value to normal in these CKD stages. SRH and eGFR in CKD stages 3-5 slightly increased but remained significant unchanged over time. This might be a reason why no significant association was found between a change in the Hb-value and graft function over time and SRH at up to eight years follow-up in CKD stages 3-5. A change in the Hb-value over time was associated with SRH at up to 8 years follow-up in CKD stages 1-2 only and not in those with CKD stages 3-5. These findings might partially explain the fact, that chronic anemia may per se be an additive or precipitating factor to transplant deterioration together with SRH worsening. We are thus far not aware of any other study publishing similar results in regard to the associations between a change in PTA over time and SRH at follow-up regarding long-term outcomes based on stratification of CKD stages.

Similar results were described by Alexander et al. (2007) in their study on the associations between anemia, ESA treatment and quality of life in a pre-dialyzed population.[33] They included patients with an Hb-value lower than 10.0g/dl, adequate iron stores and eGFR lower than 40ml/min.[33] They found that the prevalence of anemia rose from 2% at the earlier CKD stages via 5% in CKD stage 3 up to 50% in CKD stage 4 and was associated with a decreased quality of life when the treatment was insufficient.[33] In parallel, Choukroun et al. (2012), through a randomized controlled trial, provided evidence that a complete correction of PTA by ESA treatment with an Hb target higher than 13.0 g/d after 2 post-transplant years slows the decline in kidney function, prolongs graft survival and improves quality of life.[18] They showed that the mentioned Hb target was well tolerated and not associated with an increase in morbidity, such as the number of cardiovascular or thrombotic events. Therefore, our findings might also be explained by an increase in the prevalence of antianemic therapy in those patients with a decreasing Hb-value, more in the advanced stages of CKD compared with the well-functioning stages of CKD.

More than two-thirds of the participants were treated with a combination of two anti-anemia drugs, such as ESA, iron, folic and ascorbic acid as well as cobalamin and pyridoxine. Post-transplant anemia therapy in our sample is in line with the standard recommendations by KDIGO for clinical practice guidelines for anemia in CKD.[2] Such treatment could also explain the fact that a change in the Hb-value is not important for the SRH of patients with more advanced CKD: anemia is a well-known comorbidity of

CKD stages 3-5 and is therefore usually diagnosed and corrected in these patients. However, anemia is uncommon in patients with CKD stages 1-2. These suggestions are in line with Bloom et. al (2011), who found that anemia after successful KT has been underdiagnosed, and consequently potentially undertreated.[15] They suggested that worsening in individual health perception might be reduced by an increase in the Hb-value regarding sufficient ESA doses[15], but their Hb target with a significant impact on an improvement in SRH was lower than 12.5 g/dl. They suggested that the individual Hb target might be higher and primarily based on patients' perception of SRH.[15] To further complicate things, anemia after KT might be a side-effect of immunosuppressive treatment.[2,4] In our sample, more than 90% of the patients at baseline, as well as at follow-up, were treated by a combination containing mycophenolate mofetil (or mycophenolate sodium). The use of mycophenolate in particular might be connected to anemia.[4,34] Moreover, another severe non-renal etiology can reflect another severe illness, which could affect SRH as well.[6,8]

Other studies have shown the association between poor kidney function and worse SRH,[13,14] but thus far none has explored the association between kidney function and SRH related to CKD staging in kidney transplant recipients regarding the long-term impact. Comparing the differences in significant predictors stratified according to both CKD groups, the associations of a decrease in graft function over time and worse SRH were only found in CKD stages 1-2. Interestingly, patients in more advanced stages of CKD did not show such associations. However, we found in advanced CKD stages an impact of time since transplantation on the prevalence of chronic renal allograft dysfunction and uroinfection (including pyelonephritis of the graft). In line with our results, Rebollo et al. (2004) found poor quality of life in transplant recipients with associated chronic renal allograft dysfunction.[35] Moreover, they showed that quality of life in transplanted recipients with chronic renal allograft dysfunction and post-transplant anemia could be improved with adequate treatment by ESA.[35] These outcomes are similar to the findings from a retrospective randomized control trial by Choukroun et al. (2012), in which they suggested that complete correction of PTA was associated with a significant reduction in the progression of chronic renal allograft dysfunction as well as with improvement in quality of life.[18] These findings are known, and KDIGO guidelines recommended that patients be sufficiently treated to prevent graft loss.[4]

This study showed a decrease in glomerular function over time to be a significant predictor of worsening SRH at follow-up in a well-functioning graft as well as of a slight decrease in Hb-value over time; on the other hand, chronic renal allograft dysfunction, instead of the deterioration of kidney function and existing PTA, predicted a worsening of SRH at follow-up in the advanced stages of CKD. When there is sufficient treatment of PTA, and when hemoglobin is kept in the normal range, no impact of the change in hemoglobin value over time on SRH at follow-up is found, as we showed in the advanced stages of CKD. Our findings are in line with others showing that chronic allograft nephropathy might progress more rapidly in patients with PTA, though whether correction of anemia improves renal outcomes is still unknown.[18]

Strengths and limitations

The main strength of this study is the prospective follow-up for 8 years, which enabled us to explore the change in hemoglobin value and in kidney function over time and other factors as predictors of SRH in kidney transplant recipients by CKD stage. The stratification of the

sample into two groups of CKD according to CKD stages was done to prevent bias due to the impact of the graft function on hemoglobin value. Moreover, all consecutive patients originating from one major transplant centre in Slovakia over a number of years were asked to participate in the study to prevent selection bias.

Patients who dropped out are a limitation of this study; on the other hand, there were no differences in age and gender between participants and non-participants or between those who provided complete or incomplete data at baseline as well as at the follow-up examination. The variable observation period between minimum and maximum (1 and 8 years) might also be a limitation. The SRH interviews and testing of clinical data were not conducted immediately after transplantation to prevent false findings due to perioperative stress, complications and subjective anticipation or suspense. Therefore, patients who died or lost their transplanted kidney before the first 3 months after KT were not incorporated into the study. An additional limitation of this study might be the lack of certain other serum biomarkers (concentration of ESA, iron, ferritin, transferrin, vitamins, inflammatory markers, etc.) which have an impact and decrease the hemoglobin concentration. It could be of interest to control for a potential effect of pre-transplantation SRH, as it may affect the well-being of kidney transplant recipients.

Recommendations

Our findings show that a decrease in the Hb-value as well as of the transplanted kidney function in kidney transplant recipients with CKD stages 1-2 are important for their SRH. We therefore suggest diagnosing and treating post-transplant anemia to increase patients' well-being, quality of life and probability of survival. The results of this study should be verified in a larger multicenter sample to allow for generalization. We could then confirm whether treatment of anemia and subsequent improvement in Hb-value predicts SRH, or whether over a longer period after KT other variables become important. Furthermore, the pathways between other medical determinants associated with poor SRH, decreased quality of life and survival should be considered as well.

Conclusion

Male gender, a slight decrease in Hb-value and a negative change in graft function over time predicted poorer SRH at up to 8 years follow-up in patients after KT with CKD stages 1-2, but not in patients with CKD stages 3-5; in the latter group higher age, male gender and chronic renal allograft dysfunction predicted poorer SRH.

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