Qual Life Res (2016) 25:183–192
DOI 10.1007/s11136-015-1067-7

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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Accepted: 7 July 2015 / Published online: 14 July 2015

Abstract
Purpose 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 associates with SRH at up to 8-year follow-up, stratified for CKD stages.
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 two groups: CKD1–2 and CKD3–5. Generalized estimating equations (GEE) were performed to identify associations of SRH at follow-up in both CKD groups.
Results Male gender, new-onset diabetes mellitus after KT (NODAT), 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.
Conclusions At up to 8-year follow-up, male gender, NODAT, a decrease in eGFR and Hb-value over time are associated with poorer SRH in CKD1–2. In such patients, we suggest monitoring slight deteriorations in eGFR and Hb-values. In CKD3–5, higher age, male gender and higher presence of CRAD are associated with poorer SRH at up to 8-year follow-up. In these patients, adequate treatment would slow down CRAD progression.

Keywords Anemia · Chronic kidney disease · Longitudinal design · Self-rated health · Kidney transplantation

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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 De Salvo et al. [7] and a systematic review by Spiegel et al. [8] both showed the importance of SRH along with traditional biomarkers and described SRH as a predictor of future health status and as an important outcome criterion in the evaluation of medical

treatment. Christian et al. [9] 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. So far, an association between older age and a higher likelihood of poor SRH has been shown as well [10]. Furthermore, Benjamin et al. [6] described the relationship between SRH and worse health outcomes as being stronger among males. The outcomes, based on the impact of SRH on mortality even after controlling for demographic and medical variables in dialyzed [11] and 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 the 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 (QoL) 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 QoL 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, the knowledge about the impact that a change in the hemoglobin (Hb) value has over a time longer than 1 or 2 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 Hb-value over time is associated with SRH at up to 8-year 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 PTA 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, 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, further 4 (1.3 %) participants were excluded due to exclusion criterion 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 1 presents more detailed information about the participants (Fig. 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 Institutional Ethics Committee of the University Hospital in Kosice approved the study. All data and information used from the documentation, including demographic and clinical, as well as completion of the questionnaire were used in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Measures

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

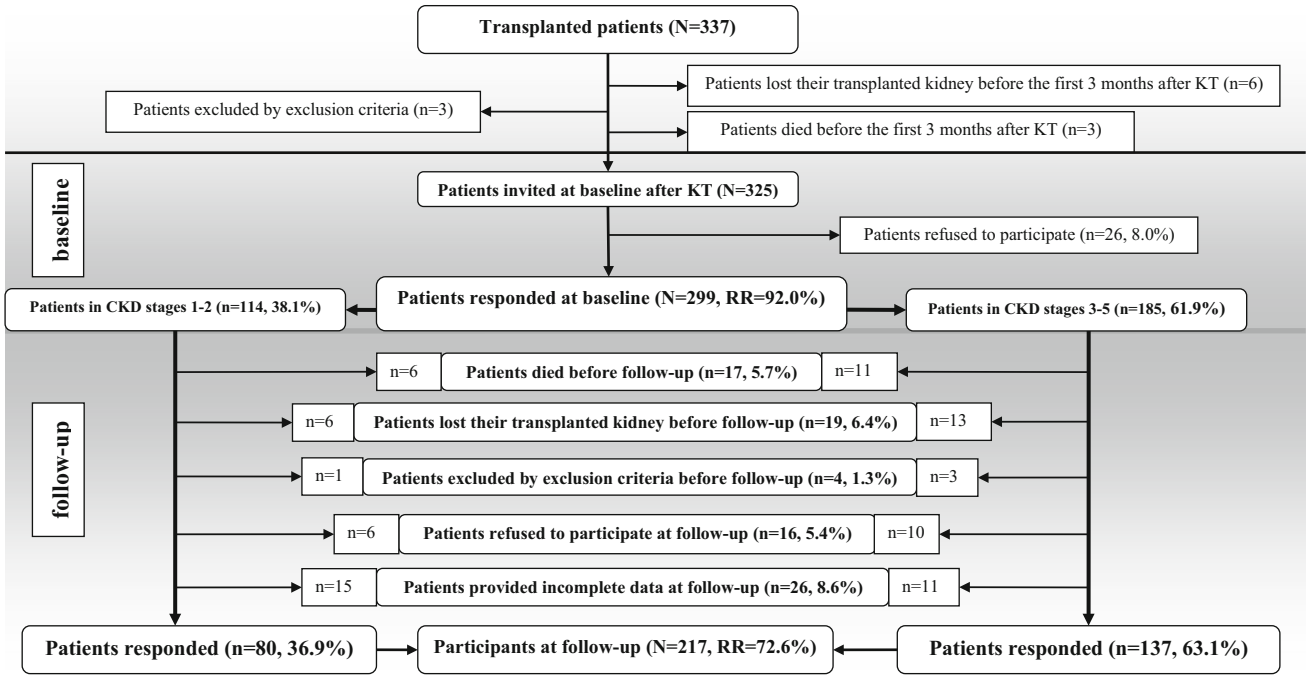

Fig. 1 Flowchart diagram of the participants. *CKD* Chronic kidney disease, *KT* kidney transplantation, *N/n* number, *RR* response rate

Self-rated health (SRH) was measured using the first question of the Short Form Health Survey (SF-36), which was designed for use in population surveys as a generic indicator of health status [6, 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 have been confirmed in Slovakia [25, 26] as well as in patients with renal disease, including those after KT [27, 28]. SRH has been previously used in health studies and has been found to be a reliable indicator of mortality and morbidity [6, 11, 12].

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 Hb (in gram-per-deciliters), therapy for anemia, acute rejection episodes, type of rejection treatment, chronic renal allograft dysfunction (CRAD), uroinfection (included pyelonephritis of 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—NODAT).

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]. The change over time in eGFR was determined by subtracting the absolute value at baseline from the absolute value at follow-up. As a result, a negative value of the change over time in eGFR means increasing kidney function over time and a positive value represents a worsening kidney function. The change over time in Hb-value was similarly calculated; however, a negative value of the change over time in Hb-value means worsening of PTA during the observation period and a positive change over time in Hb-value characterizes an improvement in PTA over time. Recently, "Kidney Disease Initiative for Global Outcomes" (KDIGO) proposed a new classification of CKDs [2, 4]; the classification reflects the impact of CKD (stages) for risk evaluation, diagnosis, patient management and treatment options. In order to explore the effect of the CKD staging on anemia, we stratified the sample into two groups: CKD stages 1–2 versus CKD stages 3–5.

Acute rejection episodes and CRAD 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 center is in line with standard recommendations issued by the KDIGO clinical practice guideline for the care of KT recipients [4].

Statistical analyses

First, frequencies, means and standard deviations were calculated for the sample description. The Mann–Whitney *U* test and Chi-squared 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 analyzed 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. [32] showed that GEE models provide a useful approximation of the truth. In line with this, GEE present a correlation matrix comparable to the way this type of matrix extends the normal equations for linear regression to those for a random intercept mixed effects linear model [31, 32]. The working covariance matrix was unstructured as there was no assumption of any pattern for the intra-subject correlation, and the robust estimator was selected due to its covariance remaining consistent even when the specification of the working correlation matrix is incorrect, as we might often expect. Based on these findings, the GEE were performed in order to identify the associations of SRH at up to 8-year follow-up. The independent variables in both stratified GEE models were all variables with $p < 0.1$ 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 stratification of GEE models according to CKD stages was selected due to the known impact of decreased kidney function on the Hb-value [2] in order to study the potentially differing associations between PTA and SRH independently of kidney function. The incorporated variables in both stratified GEE models were checked by multiple analyses to prevent collinearity. SPSS 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 CKD1–2 was from 1 to 6 years (mean 3.00 ± 1.4) and for CKD3–5 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 CKD1–2 and 97 (52.4 %) in CKD3–5. At follow-up, the prevalence of PTA was 75 (34.6 %) patients: 16 (20.0 %) in CKD1–2 and in 59 (43.1 %) in CKD3–5. The mean Hb-value increased nonsignificantly 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 CKD1–2; on the other hand, in CKD3–5 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 CKD3–5 only.

The mean SRH significantly differed over time ($p < 0.001$), as did the prevalence of CRAD ($p < 0.01$) and uroinfection ($p < 0.05$) in the whole sample. After stratification into the two CKD groups, the mean SRH significantly decreased ($p < 0.05$) in CKD1–2 and the prevalence of CRAD and uroinfection significantly increased in CKD3–5. Other variables did not significantly differ from baseline to follow-up. Table 1 displays more detailed information about the characteristics of the whole sample (Table 1). The associations of SRH at follow-up by CKD groups with each of the study variables are shown in Table 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 2 displays more detailed information about the characteristics of the significant medical variables and SRH at baseline and follow-up, stratified for CKD1–2 and CKD3–5 (Table 2).

Model 1: SRH at follow-up in CKD stages 1–2

Male gender ($B = -8.67$, 95 %CI 17.46; 0.12), the presence of NODAT ($B = -14.10$, 95 % CI 4.58; −15.71), a decrease in eGFR over time ($B = 1.02$, 95 % CI 0.92; 1.11) and a decrease in Hb-value over time ($B = 4.15$, 95 % CI 2.97; 5.33) contributed significantly to the GEE model on poor SRH at follow-up in CKD1–2 (Table 3).

Model 2: SRH at follow-up in CKD stages 3–5

Higher age ($B = -0.84$, 95 % CI 1.04; −0.61), male gender ($B = -6.73$, 95 % CI 13.41; −0.04) and CRAD ($B = -24.01$, 95 % CI 41.32; −11.78) contributed significantly to the GEE model on poor SRH at follow-up in CKD3–5 (Table 3).

Table 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 $\geq$ 12.0 g/l)	173 (57.9 %)	142 (65.4 %)
Mild (10.0 $\leq$ Hb $<$ 12.0 g/l)	98 (32.8 %)	56 (25.8 %)
Severe (Hb $<$ 10.0 g/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 %)
Anti-thymocyte globulin	4 (5.5 %)	5 (9.8 %)
Plasmapheresis	7 (9.6 %)	6 (11.8 %)
Plasmapheresis + i.v. immunoglobulin	9 (12.3 %)	5 (9.8 %)
Chronic renal allograft dysfunction	31 (10.4 %)#	**43 (19.8 %)#**

Table 1 continued

	Baseline ($N = 299$) N (%) or mean ± SD	Follow-up ($N = 217$) N (%) or mean ± SD
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 ($p < 0.1$) between SRH and each variable are flagged: * SRH in CKD stages 1–2, # SRH in CKD stages 3–5

Discussion

We explored whether a change in hemoglobin value over time is related to SRH in KT recipients at up to 8-year follow-up, stratified for CKD stages and controlled for demographic and medical variables. We found that male gender, the presence of NODAT, a decrease in the Hb-value and in graft function over time had a negative association with poor SRH at up to 8-year follow-up in patients after KT in CKD1–2. On the other hand, older age, male gender and CRAD had a negative association with poor SRH at up to 8-year follow-up in CKD3–5.

In patients with CKD1–2, the prevalence of PTA was approximately the same at baseline and at follow-up, and the mean Hb-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-year follow-up in patients with CKD1–2.

In contrast, in CKD3–5 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 Hb-value to normal in these CKD stages. SRH and eGFR in CKD3–5 slightly increased but remained significantly 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 8-year follow-up in CKD3–5. A change in the Hb-value over time was associated with SRH at up to 8-year follow-up in CKD1–2 only, and not in those with CKD3–5. 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. [33] in their study on the associations between anemia, ESA and QoL in a pre-dialyzed population. They included patients with an Hb-value lower than 10.0 g/dl, adequate iron stores and eGFR lower than 40 ml/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 QoL when the treatment was insufficient [33]. In parallel, Choukroun et al. [18], 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 QoL. 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 [18]. Therefore, our

Table 2 Characteristics of the variables stratified according to CKD stages estimated at baseline examination

	CKD stages 1–2		CKD stages 3–5	
	N (%) or mean ± SD		*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 ≥ 12.0 g/l)	85 (74.6 %)	64 (80.0 %)	88 (47.6 %)	78 (56.9 %)
Mild (10.0 ≤ Hb < 12.0 g/l)	17 (14.9 %)	11 (13.7 %)	81 (43.8 %)	45 (32.9 %)
Severe (Hb < 10.0 g/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 %)[$]
Chronic renal allograft dysfunction	4 (6.4 %)	7 (8.8 %)	27 (14.6 %)	36 (26.3 %)[$]
New-onset diabetes mellitus after transplantation	7 (6.1 %)	8 (10.0 %)	19 (10.3 %)	11 (8.0 %)

CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESA* erythropoiesis-stimulating agents, *Hb* hemoglobin, *N/n* number, *SD* standard deviation

[$] Significant differences ($p < 0.05$) between baseline and follow-up are flagged

findings might also be explained by an increase in the prevalence of anti-anemic 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 therapy, folic and ascorbic acid as well as cobalamin and pyridoxine. PTA therapy in our sample is in line with the standard recommendations by KDIGO 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 CKD3–5 and is therefore usually diagnosed and corrected in these patients. However, anemia is uncommon in patients with CKD1–2. These suggestions are in line with Bloom et al. [15], who found that anemia after successful KT has been underdiagnosed and consequently potentially undertreated. 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 immunosuppressant [2, 4]. In our sample, more than 90 % of the patients at baseline and 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 KT recipients regarding the long-term impact. Comparing the differences in significant associations stratified according to both CKD groups, the associations of a decrease in graft function over time and worse SRH were only found in CKD1–2. Interestingly, patients in more advanced stages of CKD did not show such associations. Similar results were found regarding NODAT: Its presence was associated with poor SRH at

Table 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 with the tested collinearity

Models for SRH at follow-up ($N = 217$)	Model 1 in CKD stages 1–2 ($n = 80$) QICC 875.45				Model 2 in CKD stages 3–5 ($n = 137$) QICC 856.79			
	B (95 % CI)	Wald χ^2	Collinearity		B (95 % CI)	Wald χ^2	Collinearity	
			Tolerance	VIF			Tolerance	VIF
Age	0.07 (−0.60; 0.21)$^{n.s.}$	0.91	0.92	1.09	−0.84 (−1.04; −0.61)***	12.54	0.76	1.32
Gender								
Female	Reference				Reference			
Male	−8.67 (−17.46; 0.12)*	3.74	0.99	1.01	−6.73 (−13.41; −0.04)*	4.83	0.91	1.10
SRH at baseline	0.40 (0.29; 0.51)$^{n.s.}$	4.56	0.86	1.17	0.19 (0.08; 0.31)$^{n.s.}$	11.30	0.75	1.33
Uroinfection								
No	Reference				Reference			
Yes	−0.62 (−2.34; −0.15)$^{n.s.}$	2.06	0.91	1.10	−7.52 (−9.64; −1.21)$^{n.s.}$	9.89	0.76	1.35
CRAD								
No	Reference				Reference			
Yes	−2.76 (−6.23; −1.03)$^{n.s.}$	3.65	0.92	1.09	−24.01 (−41.32; −11.78)**	15.78	0.77	1.32
NODAT								
No	Reference				Reference			
Yes	−14.10 (−4.58; −15.71)***	39.23	0.94	1.06	−11.75 (−5.21; −21,71)$^{n.s.}$	4.53	0.94	1.07
Change in eGFR over time	1.02 (0.92; 1.11)***	42.66	0.98	1.03	0.29 (−0.18; 0.24)$^{n.s.}$	0.75	0.97	1.03
Change in Hb-value over time	4.15 (2.97; 5.33)***	43.88	0.99	1.00	0.49 (−3.60; 1.32)$^{n.s.}$	1.35	0.99	1.00

n.s. not significant, *B* unstandardized coefficient B, *CI* confidence interval, *CKD* chronic kidney disease, *CRAD* chronic renal allograft dysfunction, *eGFR* estimated glomerular filtration rate, *Hb* hemoglobin, *NODAT* new-onset diabetes mellitus after transplantation, *QICC* corrected quasi-likelihood under independence model criterion, *SRH* self-rated health, *VIF* the variance inflation factor

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

follow-up in a well-functioning graft; on the other hand, no association between NODAT and SRH at follow-up was explored in the more advanced stages of CKD. So far, some studies have described the idea that NODAT is connected to graft worsening, which might be associated with poor SRH [4, 12, 35]. In addition, NODAT was confirmed as a predictor of graft loss, while the deterioration in graft function is also a known factor of worsening post-transplant anemia [4, 12]. Moreover, Ravindran et al. [35] found NODAT to be a well-recognized complication of solid organ transplantation, with a higher risk of graft loss and mortality. Nonetheless, we found in advanced CKD stages an impact of time since transplantation on the prevalence of CRAD and uroinfection (including pyelonephritis of the graft). In line with our results, Rebollo et al. [36] found poor QoL in transplant recipients with associated CRAD. Moreover, they showed that QoL in transplanted recipients with CRAD and PTA could be improved with adequate treatment by ESA [36]. These outcomes are similar to the findings from a retrospective randomized control trial by Choukroun et al. [18], in which they suggested that complete correction of PTA was associated with a significant reduction in the progression of CRAD as well as with improvement in QoL. 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 have a significant association with 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, CRAD, instead of the deterioration of kidney function and existing PTA, was associated with 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 CRAD 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 stratification of the sample into two groups according to CKD stages. This was done to prevent bias due to the impact of the graft function

on the Hb-value. Moreover, all consecutive patients originating from one major transplant center in Slovakia over a number of years were asked to participate in the study to prevent selection bias. An additional strength is the prospective follow-up from 1 to 8 years, which enabled us to explore the change in the Hb-value and in the kidney function over time and other factors closely linked to SRH in kidney transplant recipients by CKD stage.

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 and 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), which have an impact and decrease the Hb-value. These factors, therapy and inflammatory markers are associated with anemia; in addition, they play an important role in exploring the causes of PTA, which in turn is associated with SRH in CKD1–2. Therefore, these factors have to be considered in future research. Unfortunately, we did not have data about these markers at baseline, and the sample size of patients on anemia treatment was too small to be included to the relevant analyses in this study. Regrettably, this study has an observation design; thus, we have had no chance to participate in the therapy modality. It could be of interest to control for a potential effect of pre-transplantation SRH, as it may affect the well-being of KT recipients.

Recommendations

Our findings show that a decrease in the Hb-value as well as in the transplanted kidney function in KT recipients with CKD1–2 is important for their SRH. We therefore suggest earlier diagnosis and timely treatment of PTA to increase patients' well-being, QoL 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 QoL and survival should be considered as well.

Conclusions

Male gender, the presence of NODAT, a slight decrease in Hb-value and a negative change in eGFR over time were associated with poorer SRH at up to 8-year follow-up in patients after KT with CKD1–2, but not in patients with CKD3–5; in the latter group, higher age, male gender and CRAD were associated with poorer SRH.

Acknowledgments This study was funded by the Slovak Research and Development Agency under contract number APVV-0220-10 (70 %) and by the Agency of the Slovak Ministry of the Education, Science, Research and Sport of the Slovak Republic for the Structural Funds of the EU under Project Number ITMS: 26220120058 (20 %). Furthermore, this work was supported by the Medical Board of Fresenius Medical Care, Germany (10 %).

Compliance with ethical standards

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of interest Maria Majernikova, Jaroslav Rosenberger and Robert Roland are employees of Fresenius Medical Care—Dialysis Services Slovakia—and Daniele Marcelli of the Medical Board of Fresenius Medical Care, Germany; none of the authors has had any relationship with any company or funding source that might have an interest in the submitted work during the previous 3 years, and their spouses, partners or children do not have any financial relationships that may be relevant to the submitted work.

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