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ORIGINAL ARTICLE

Changes in clinical indicators related to the transition from dialysis to kidney transplantation—data from the ERA–EDTA Registry

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ABSTRACT

Background. Kidney transplantation should improve abnormalities that are common during dialysis treatment, like anaemia and mineral and bone disorder. However, its impact is incompletely understood. We therefore aimed to assess changes in clinical indicators after the transition from chronic dialysis to kidney transplantation.

Methods. We used European Renal Association–European Dialysis and Transplant Association Registry data and included adult dialysis patients for whom data on clinical indicators before and after transplantation (2005–15) were available. Linear mixed models were used to quantify the effect of transplantation and of time after transplantation for each indicator.

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Results. In total, 16 312 patients were included. The mean age at transplantation was 50.1 (standard deviation 14.2) years, 62.9% were male and 70.2% were on haemodialysis before transplantation. Total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and triglycerides increased right after transplantation but decreased thereafter. All other indicators normalized or approached the target range soon after transplantation and these improvements were sustained for the first 4 years of follow-up. In patients with higher estimated glomerular filtration rate (eGFR) levels (30–60 and >60 mL/min/1.73 m^2), the improvement of haemoglobin, ferritin, ionized calcium, phosphate, parathyroid hormone, HDL cholesterol, triglycerides, albumin and C-reactive protein levels was more pronounced than in patients with a lower eGFR (<30 mL/min/1.73 m^2).

Conclusions. Except for total cholesterol, LDL cholesterol and triglycerides, all clinical indicators improved after transplantation. These improvements were related to eGFR. Nevertheless, values remained out of range in a considerable proportion of patients and anaemia and hyperparathyroidism were still common problems. Further research is needed to understand the complex relationship between eGFR and the different clinical indicators.

Keywords: anaemia, dialysis, dyslipidaemia, inflammation, kidney transplantation, mineral metabolism

INTRODUCTION

Patients with end-stage kidney disease need renal replacement therapy (RRT) to maintain the balance of fluid and metabolic components in the body. Although kidney transplantation provides better patient survival and quality of life, most patients need to start RRT on dialysis treatment because of the lack of available donor kidneys [1].

In dialysis patients, disorders like anaemia and mineral and bone disorders are common. Patients treated with either haemodialysis or peritoneal dialysis need erythropoiesis-stimulating agents (ESAs), and even with administration of ESA, haemoglobin levels achieved may be suboptimal [2]. Mineral and bone disorders are also an important problem. The European multicentre COSMOS study (Current Management of Secondary Hyperparathyroidism: a Multicentre Observational Study) showed that only 77, 27 and 56% of haemodialysis patients achieved the target levels for calcium, phosphate and parathyroid hormone (PTH), respectively [3]. Furthermore, inflammatory markers such as C-reactive protein (CRP) are higher in dialysis patients and are associated with higher cardiovascular morbidity and mortality [4–7].

Kidney transplantation can improve many of these clinical indicators. Previous studies showed an increase in haemoglobin and albumin, a transient increase in cholesterol and a decrease in ferritin, phosphate and PTH levels [8–10]. However, these studies reported only on the first year post-transplantation and were performed in a single centre or country. To our knowledge, international studies with long-term follow-up have not yet been performed. In this study, we therefore used data from the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry to assess whether kidney transplantation is associated with changes in clinical indicators and how each clinical indicator changes over time after kidney transplantation. We focused on haemoglobin and iron status, mineral and bone metabolism, lipid profile, inflammation and malnutrition.

MATERIALS AND METHODS

Study population

National and regional renal registries within Europe provide yearly data on patients treated with RRT to the ERA-EDTA Registry [11]. The core dataset includes month and year of birth, sex, primary renal disease (PRD), treatment modality at the start of RRT, changes in RRT modality and date and cause of death. Recently the registry has extended its data collection with laboratory measurements. For this study we included the following national and regional renal registries that provided laboratory data for both dialysis and transplanted patients: Denmark (inclusion period 2005–15), Finland (2010–15), Norway (2005–15), Catalonia (Spain, 2010–15) and UK (England, Wales and Northern Ireland, 2005–15). All registries followed their national legislation with regard to ethics committee approval.

Patients ≥20 years of age who fulfilled the following criteria were included: first kidney transplantation between 2006 and 2015, ≥3 months of dialysis treatment before receiving a first kidney transplant and availability of one or more clinical indicator measurement while on dialysis within 1 year before kidney transplantation and one or more measurement within 4 years after transplantation.

Data collection and definitions

PRD was classified into six groups: glomerulonephritis (GN), diabetes mellitus, hypertension/renal vascular disease (HT/RVD), polycystic kidney disease, other causes of renal failure and unknown. To study the influence of time, the year of kidney transplantation was divided into the time periods 2006–10 and 2011–15.

The clinical indicators studied were categorized into four groups: anaemia (haemoglobin and ferritin), mineral and bone disorders (serum ionized calcium, phosphate and PTH), dyslipidaemia [total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides] and inflammation and malnutrition (serum albumin and CRP). Laboratory variables were determined according to local practice. An overview of the availability of clinical indicators is given in Supplementary data, Table S1. The registries of Denmark, Finland, Norway and Catalonia provided one laboratory measurement per patient per year. The Danish registry provided the date of each measurement, whereas these dates were unknown for the other registries. The UK Renal Registry provided one measurement per quarter (date unknown). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [12].

Statistical analysis

Patient characteristics were summarized using percentages, mean values with standard deviations (SDs) and median values

with interquartile ranges (IQRs). For the main analysis, data from all registries were combined. When multiple measurements per year were available, we calculated an average value per patient per calendar year. For the year of kidney transplantation, we only used measurements after transplantation. As this could only be determined for Denmark and the UK (used measurement in the quarter after quarter of transplantation), measurements in the year of transplantation represent only patients from these two countries.

To quantify the changes in the clinical indicators, we applied two different linear mixed models with and without adjustment for potential confounders (age at transplantation, sex, PRD, period of transplantation and country) using the SAS software 'proc mixed' procedure (SAS Institute, Cary, NC, USA). These models, also known as multilevel models, take into account the dependency between multiple measurements from the same patient. Model 1 examined the effect of kidney transplantation on the level of the clinical indicator, including the measurement in the year before and the first measurement after transplantation. Model 2 examined the effect of time after transplantation on the level of the clinical indictor, including only post-transplantation measurements.

For all clinical indicators we reported the percentages below, within and above the targets as defined in guidelines for dialysis patients [13–15] and for transplant recipients [16–18].

To show the short-term changes in clinical indicators, we performed further analyses including only Denmark and the UK, which provided the measurement date or period. These analyses present the course over time for haemoglobin, ferritin, phosphate, PTH and total cholesterol in 3-month periods between 1 year before and 4 years after transplantation. The linear mixed model was applied to identify at which time point clinical indicators had changed statistically significantly from the last time point pre-transplantation. Additional analyses were performed to examine changes in dyslipidaemia including only those registries with data for all lipid indicators (Denmark, Finland and Norway). Since the UK data comprised 75% of the dataset, sensitivity analyses excluding the UK were used to assess whether the results remained the same.

Subgroup analyses were performed for age at transplantation, sex, PRD, kidney donor source (living versus deceased) and time period (2006–10 versus 2011–15). Additional subgroup analyses were used to test for the association between eGFR (<30 versus 30–59 versus ≥60 mL/min/1.73 m^2), albumin (<35 versus 35–50 versus >50 g/L), CRP (<10 versus ≥10 mg/L) and PTH (<45 versus ≥45 pmol/L) levels 1 year post-transplantation and changes in the clinical indicators after transplantation.

All analyses were performed using SAS software (version 9.4; SAS Institute). We considered P-value <0.05 (two-sided) as statistically significant.

RESULTS

Patient characteristics

In total, 16312 patients were included in the study. Table 1 presents the demographic and clinical patient characteristics. The majority of patients were men (62.9%) and the mean age was 47.1 [standard deviation (SD) 14.1] years at the start of RRT and 50.1 (SD 14.2) years at transplantation. Haemodialysis was the most common dialysis modality (70.2%) and the median time on dialysis before transplantation was 2.3 years.

Table 1. Demographic and clinical characteristics of patients (N = 16 312)

Characteristics	Descriptive statistics
Gender, *n* (%)	
Male	10 257 (62.9)
Female	6055 (37.1)
Age at start RRT (years)	
Mean ± SD	47.1 ± 14.1
Age at kidney transplantation (years)	
Mean ± SD	50.1 ± 14.2
PRD, *n* (%)	
Diabetes	2620 (16.1)
HT/RVD	1416 (8.7)
GN	3581 (22.0)
Polycystic kidney disease	2170 (13.3)
Other causes	4088 (25.1)
Unknown	2437 (14.9)
Last dialysis modality before kidney transplantation, *n* (%)	
Haemodialysis	11 444 (70.2)
Peritoneal dialysis	4868 (29.8)
Countries/regions, *n* (%)	
Denmark	1068 (6.6)
Catalonia (Spain)	967 (5.9)
Finland	799 (4.9)
Norway	1144 (7.0)
UK (England, Wales, Northern Ireland)	12 334 (75.6)
Dialysis vintage at the time of kidney transplantation (years), median (IQR)	2.3 (1.2 – 4.1)
eGFR 1-year post-kidney transplantation (mL/min/1.73 m^2), mean ± SD	55.2 ± 22.5
<30, *n* (%)	1753 (11.3)
30–60, *n* (%)	8033 (51.8)
>60, *n* (%)	5719 (36.9)
Year of kidney transplantation, *n* (%)	
2006–10	7637 (46.8)
2011–15	8675 (53.2)
Clinical indicators before kidney transplantation, median (IQR)	
Haemoglobin (g/dL)	11.5 (10.9–12.2)
Ferritin (ng/mL)	340 (207–501)
Ionized calcium (mmol/L)	1.19 (1.14–1.24)
Phosphate (mmol/L)	1.63 (1.38–1.92)
PTH (pmol/L)	31.1 (17.0–53.4)
Total cholesterol (mmol/L)	4.15 (3.50–4.90)
HDL cholesterol (mmol/L)	1.17 (0.91–1.47)
LDL cholesterol (mmol/L)	2.15 (1.56–2.80)
Triglycerides (mmol/L)	1.40 (1.01–2.08)
Albumin (g/L)	39 (35–42)
CRP (mg/L)	3.0 (1.4–7.0)

Clinical indicators

Figure 1 shows the median levels of each clinical indicator in the year before transplantation, right after transplantation and in the years thereafter. In Table 2, the results of the mixed models are presented; it shows the unadjusted and adjusted effects of kidney transplantation on the clinical indicators (Model 1) and of time per year after transplantation (Model 2). The unadjusted and adjusted models yielded very similar results for all indicators. Below we present the results of the adjusted analyses.

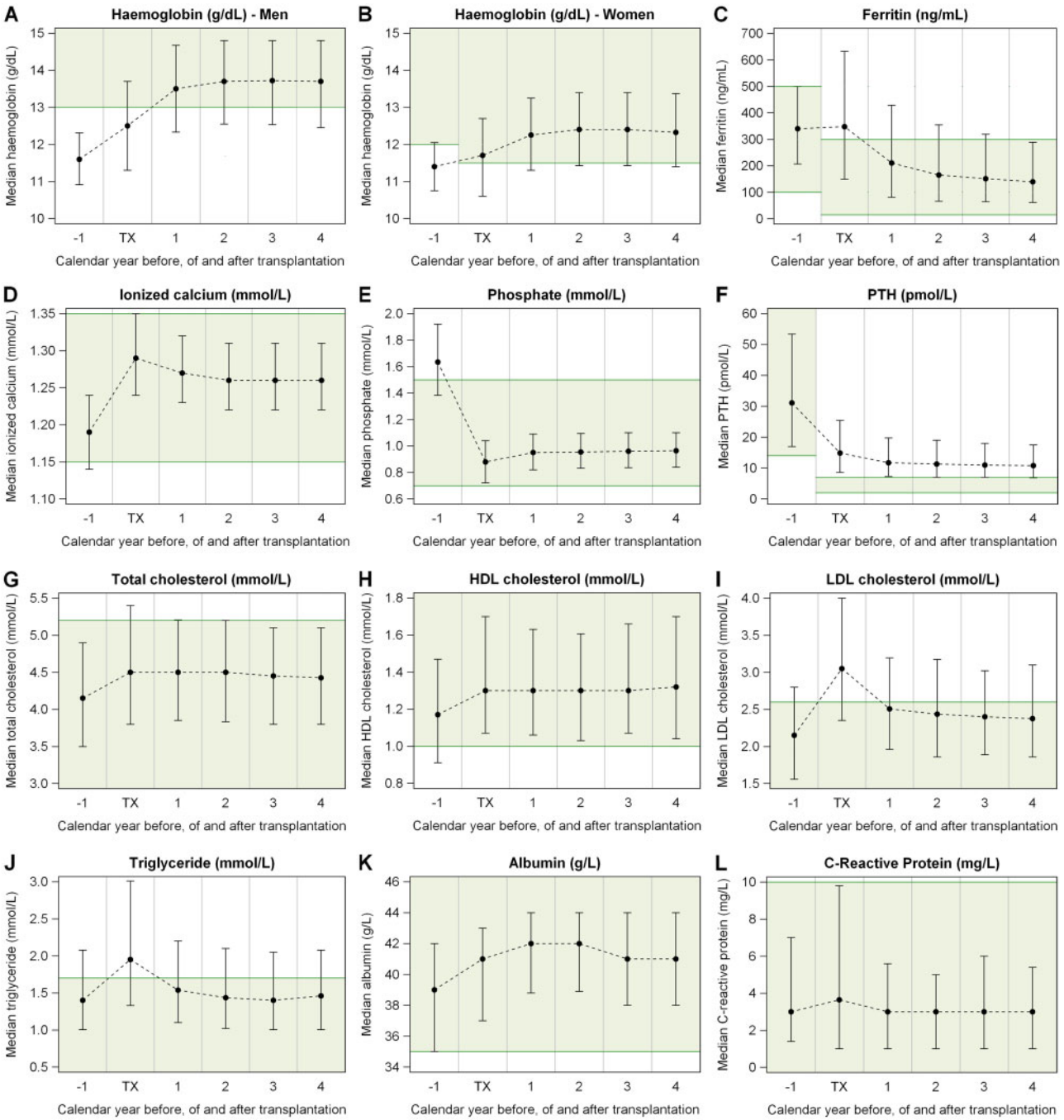

FIGURE 1: Median levels for each clinical indicator in the calendar year before, of and after kidney transplantation. Values in the year of kidney transplantation are based on measurements after kidney transplantation only. Vertical lines extend from the 25th to 75th percentiles. The grey area indicates the target range. If this was different for patients on dialysis, then the target range for dialysis patients is also shown.

Anaemia. Haemoglobin levels increased in the first year after kidney transplantation (Figure 1A and B) {0.90 g/dL [95% confidence interval (CI) 0.87–0.93]} and continued to increase 0.17 g/dL (95% CI 0.16–0.18) in each year thereafter (Table 2). The percentage of anaemic patients decreased from 75.7% before transplantation to 31.5% at 4 years after transplantation (Table 3). Also, ferritin increased after kidney transplantation [81.1 ng/mL (95% CI 71.6–90.5)]. However, thereafter it decreased [47.2 ng/mL/year (95% CI −50.0 to −44.4)] (Figure 1C and Table 2). The percentage of patients meeting the target for ferritin increased from 42.2% pre-transplantation to 72.9% at 4 years after transplantation (Table 3).

Mineral and bone disorders. Ionized calcium levels slightly increased after kidney transplantation and remained stable in the years thereafter (Figure 1D). The proportion of patients who met the target was relatively high and increased over 4 years (from 69.9% to 83.1%). Conversely, phosphate levels dropped after transplantation [0.76 mmol/L (95% CI −0.77 to −0.76)] and remained stable and within the target range post-transplantation

Table 2. Unadjusted and adjusted effects of kidney transplantation and time (in years) on clinical indicators

	Effect of kidney transplantation, estimate (95% CI)			
	Unadjusted		Adjusted[a]	
Clinical indicator	Effect of Tx	Effect of time per 1 year after Tx	Effect of Tx	Effect of time per 1 year after Tx
Haemoglobin (g/dL)	**0.95 (0.92; 0.97)**	**0.17 (0.17; 0.18)**	**0.90 (0.87; 0.93)**	**0.17 (0.16; 0.18)**
Ferritin (ng/mL)	**81.7 (72.3; 91.1)**	**−48.1 (−50.9; −45.3)**	**81.1 (71.6; 90.5)**	**−47.2 (−50.0; −44.4)**
Ionized calcium (mmol/L)	**0.09 (0.09; 0.10)**	**−0.01 (−0.01; −0.01)**	**0.09 (0.09; 0.10)**	**−0.01 (−0.01; −0.01)**
Phosphate (mmol/L)	**−0.76 (−0.77; −0.75)**	**0.02 (0.02; 0.02)**	**−0.76 (−0.77; −0.76)**	**0.02 (0.02; 0.02)**
PTH (pmol/L)	**−23.8 (−24.6; −23.0)**	**−0.95 (−1.08; −0.83)**	**−23.3 (−24.1; −22.4)**	**−0.93 (−1.06; −0.80)**
Total cholesterol (mmol/L)	**0.41 (0.39; 0.44)**	**−0.05 (−0.06; −0.04)**	**0.41 (0.39; 0.43)**	**−0.05 (−0.06; −0.05)**
HDL cholesterol (mmol/L)	**0.14 (0.12; 0.16)**	0.00 (0.00; 0.01)	**0.14 (0.12; 0.16)**	0.00 (0.00; 0.01)
LDL cholesterol (mmol/L)	**0.31 (0.22; 0.40)**	**−0.09 (−0.12; −0.07)**	**0.36 (0.27; 0.46)**	**−0.10 (−0.12; −0.07)**
Triglyceride (mmol/L)	**0.11 (0.04; 0.18)**	**−0.07 (−0.09; −0.05)**	**0.17 (0.10; 0.24)**	**−0.07 (−0.09; −0.05)**
Albumin (g/L)	**2.62 (2.42; 2.82)**	**−0.20 (−0.25; −0.14)**	**2.57 (2.38; 2.77)**	**−0.23 (−0.29; −0.17)**
CRP (mg/L)	−0.15 (−1.37; 1.07)	**−0.06 (−0.61; 0.49)**	0.43 (−0.81; 1.67)	0.12 (−0.45; 0.69)

[a]Models were adjusted for age at transplantation, sex, PRD, period of transplantation and country. Results in bold are statistically significant.
TX, kidney transplantation.

Table 3. Percentages of patients below, within or above the target range for clinical indicators in the calendar year before (−1), of (TX) and after kidney transplantation (1–4)

		Calendar year before, of and after kidney transplantation					
Clinical indicator	Level	−1 (%)	TX (%)	1 (%)	2 (%)	3 (%)	4 (%)
Haemoglobin[a] (g/dL)	Low	75.7 (83.1)	53.9	34.9	30.8	31.0	31.5
	Normal	24.3 (16.8)	45.8	64.6	68.6	68.6	68.1
	High	0 (0)	0.3	0.5	0.6	0.4	0.4
Ferritin[b] (ng/mL)	<15 (<100)	0.2 (7.6)	1.4	2.8	3.7	3.1	3.6
	15–300 (100–500)	42.2 (67.3)	43.8	58.9	66.2	70.3	72.9
	≥300 (≥500)	57.7 (25.1)	54.9	38.3	30.1	26.6	23.5
Ionized calcium (mmol/L)	<1.15	26.6	3.4	4.0	4.6	5.6	6.1
	1.15–1.35	69.9	74.8	81.6	84.8	82.3	83.1
	≥1.35	3.4	25.5	16.6	13.3	12.0	10.9
Phosphate (mmol/L)	<0.7	0.3	20.0	7.9	7.2	6.6	6.6
	0.7–1.5	35.5	78.2	90.5	91.0	91.4	91.3
	≥1.5	64.3	1.8	1.7	1.8	2.0	2.0
PTH[b] (pmol/L)	<2 (<14)	2.3 (19.3)	3.0	3.2	3.3	3.3	4.1
	2–7 (14–64)	5.4 (62.6)	14.7	19.4	20.9	21.4	21.8
	≥7 (≥64)	92.3 (18.1)	82.3	77.4	75.8	75.3	74.1
Total cholesterol (mmol/L)	<5.2	81.9	69.6	73.4	75.1	76.2	77.1
	≥5.2	18.1	30.4	26.6	24.9	23.8	22.9
HDL cholesterol (mmol/L)	<1.0	28.9	15.6	17.1	18.6	18.4	18.3
	≥1.0	71.1	84.4	82.9	81.4	81.6	81.7
LDL cholesterol (mmol/L)	<2.6	67.2	30.6	53.4	55.7	59.2	58.5
	≥2.6	32.8	69.4	46.6	44.3	40.9	41.5
Triglyceride (mmol/L)	<1.7	61.0	38.8	57.1	61.0	63.2	61.0
	≥1.7	39.0	61.2	42.9	39.0	36.8	39.0
Albumin (g/L)	<35	22.4	11.6	8.1	6.8	8.2	8.4
	35–50	77.3	88.1	90.9	92.1	90.7	91.1
	>50	0.3	0.3	1.0	1.2	1.0	0.4
CRP (mg/L)	<10	81.6	75.1	85.1	85.4	83.5	86.2
	≥10	18.4	24.9	14.9	14.6	16.5	13.8

[a]The normal range differs for men (low <13, normal 13–18, high >18 g/dL) and women (low <11.5, normal 11.5–16.5, high >16.5 g/dL). For patients on dialysis, reference values for dialysis patients were used (men: low <13, normal 13–17, high >17 g/dL; women: low <12, normal 12–17, high >17 g/dL).
[b]For patients on dialysis, reference values for dialysis patients (in parentheses) were used.
Values in the year of kidney transplantation are based on measurements after kidney transplantation only.
TX, kidney transplantation.

Table 4. Effect of kidney transplantation on clinical indicators in different subgroups

	Effect of kidney transplantation, estimate (95% CI)											
	Age at transplantation[a]		Sex[b]		PRD[c]				Kidney donor type[d]		Period of transplantation[e]	
Clinical indicator	<65	≥65	Men	Women	Diabetes	HT /RVD	GN	Other	Living	Deceased	2006–10	2011–15
Haemoglobin (g/dL)	**1.45**	0.96	**1.70**	0.84	1.36	1.50	**1.58**	1.27	**1.77**	1.23	1.20	**1.55**
	(1.42; 1.47)	(0.91; 1.01)	**(1.67; 1.72)**	(0.81; 0.87)	(1.30; 1.41)	(1.43; 1.57)	**(1.54; 1.62)**	(1.24; 1.30)	**(1.73; 1.81)**	(1.20; 1.25)	(1.17; 1.23)	**(1.52; 1.57)**
Ferritin (ng/mL)	**−68.1**	1.01	**−69.5**	−43.0	−50.7	−56.3	**−80.0**	−51.3	**−91.1**	−46.7	**−74.9**	−36.7
	(−73.9; −62.3)	(−14.9; 16.9)	**(−76.3; −62.7)**	(−51.9; −34.1)	(−65.8; −35.6)	(−77.5; −35.1)	**(−90.2; −69.9)**	(−58.8; −43.8)	**(−101; −80.8)**	(−53.1; −40.3)	**(−81.7; −68.1)**	(−45.6; −27.8)
Ionized calcium	0.08	0.07	0.10	0.07	0.09	0.08	0.08	0.07	0.09	0.08	0.08	0.08
(mmol/L)	(0.08; 0.08)	(0.06; 0.08)	(0.08; 0.09)	(0.07; 0.08)	(0.08; 0.10)	(0.07; 0.09)	(0.08; 0.09)	(0.07; 0.08)	(0.08; 0.09)	(0.07; 0.08)	(0.07; 0.08)	(0.07; 0.08)
Phosphate (mmol/L)	**−0.74**	−0.58	**−0.80**	−0.64	−0.64	−0.71	**−0.77**	−0.72	**−0.78**	−0.70	−0.74	−0.70
	(−0.75; −0.74)	(−0.59; −0.57)	**(−0.77; −0.76)**	(−0.65; −0.63)	(−0.65; −0.63)	(−0.72; −0.69)	**(−0.78; −0.76)**	(−0.73; −0.72)	**(−0.79; −0.77)**	(−0.70; −0.69)	(−0.74; −0.73)	(−0.71; −0.69)
PTH (pmol/L)	**−26.6**	−18.6	−25.1	−25.7	−21.7	**−26.0**	**−25.9**	**−26.0**	**−26.8**	−24.9	**−26.2**	−24.5
	(−27.1; −26.1)	(−19.5; −17.6)	(−25.7; −24.6)	(−26.4; −24.9)	(−22.8; −20.6)	**(−27.6; −24.4)**	**(−26.9; −25.0)**	**(−26.6; −25.4)**	**(−27.7; −26.0)**	(−25.4; −24.3)	**(−26.9; −25.6)**	(−25.1; −23.9)
Total cholesterol	0.52	0.65	**0.60**	0.44	0.55	**0.77**	0.48	0.51	0.48	0.57	0.67	0.52
(mmol/L)	(0.46; 0.58)	(0.55; 0.76)	**(0.55; 0.67)**	(0.34; 0.53)	(0.45; 0.65)	**(0.64; 0.91)**	(0.37; 0.59)	(0.44; 0.59)	(0.36; 0.60)	(0.51; 0.62)	(0.57; 0.77)	(0.46; 0.58)
HDL cholesterol	0.14	0.13	0.10	0.13	0.12	0.16	0.17	0.11	0.18	0.13	**0.20**	0.12
(mmol/L)	(0.12; 0.16)	(0.09; 0.16)	(0.12; 0.16)	(0.10; 0.17)	(0.09; 0.16)	(0.11; 0.21)	(0.13; 0.20)	(0.09; 0.14)	(0.14; 0.22)	(0.11; 0.15)	**(0.17; 0.24)**	(0.10; 0.14)
LDL cholesterol	0.34	0.36	**0.50**	0.16	0.38	**0.76**	0.20	0.31	**0.69**	0.28	0.26	0.36
(mmol/L)	(0.26; 0.41)	(0.23; 0.49)	**(0.38; 0.52)**	(0.03; 0.30)	(0.27; 0.49)	**(0.50; 1.02)**	(0.02; 0.38)	(0.22; 0.41)	**(0.54; 0.84)**	(0.20; 0.35)	(−0.02; 0.53)	(0.30; 0.42)
Triglyceride (mmol/L)	0.14	0.16	0.20	0.07	0.04	0.34	0.05	0.22	0.14	0.15	**0.46**	0.11
	(0.06; 0.22)	(0.02; 0.30)	(0.10; 0.27)	(−0.07; 0.21)	(−0.10; 0.18)	(−0.16; 0.84)	(−0.13; 0.23)	(0.13; 0.31)	(−0.06; 0.34)	(0.07; 0.23)	**(0.27; 0.65)**	(0.02; 0.19)
Albumin (g/L)	2.61	2.11	**2.30**	2.88	2.69	2.03	2.73	2.46	2.80	2.43	2.48	2.57
	(2.44; 2.78)	(1.77; 2.45)	**(2.10; 2.48)**	(2.62; 3.13)	(2.33; 3.05)	(1.60; 2.46)	(2.42; 3.04)	(2.23; 2.68)	(2.47; 3.14)	(2.26; 2.60)	(2.21; 2.75)	(2.39; 2.76)
CRP (mg/L)	0.56	1.24	0.00	1.69	1.07	−0.99	−1.05	1.56	0.85	0.73	0.06	0.91
	(−0.74; 1.87)	(−2.17; 4.64)	(−1.60; 1.63)	(−0.15; 3.53)	(−1.82; 3.96)	(−3.72; 1.73)	(−3.78; 1.68)	(−0.15; 3.28)	(−2.44; 4.14)	(−0.53; 1.98)	(−3.23; 3.35)	(−0.41; 2.23)

[a]Multivariate model included age at transplantation, sex, PRD, kidney donor type, period of transplantation, dialysis modality before transplantation and country.
[b]Multivariate model included age at transplantation, PRD, kidney donor type, period of transplantation, dialysis modality before transplantation and country.
[c]Multivariate model included age at transplantation, sex, kidney donor type, period of transplantation, dialysis modality before transplantation and country.
[d]Multivariate model included age at transplantation, sex, PRD, period of transplantation, dialysis modality before transplantation and country.
[e]Multivariate model included age at transplantation, sex, PRD, kidney donor type, dialysis modality before transplantation and country.
Results in bold are statistically significantly different from the other subgroup(s). RVD, renal vascular disease.

(Figure 1F and Table 2). The percentage of patients with target levels of phosphate improved from 35.5% pre-transplantation to 91.3% 4 years later (Table 3). Although PTH levels decreased after transplantation [23.3 pmol/L (95% CI −24.1 to −22.4)] and continued to decline yearly by 0.93 pmol/L (95% CI −1.06 to −0.80) (Figure 1G and Table 2), the majority of patients (74.1%) still had hyperparathyroidism 4 years post-transplantation (Table 3).

Dyslipidaemia. We observed an increase in the levels of all lipid indicators after transplantation (Figure 1H–K and Table 2). Thereafter, total cholesterol, LDL cholesterol and triglyceride levels slightly decreased yearly, whereas HDL cholesterol remained stable. The percentage of patients with hypercholesterolaemia increased right after transplantation (from 18.1% to 30.4%) and decreased thereafter (22.9% at 4 years). However, it remained higher than before transplantation (Table 3). Shortly after transplantation, 69.4% of patients had high LDL cholesterol (≥2.6 mmol/L) and this decreased to 41.5% at 4 years after transplantation, whereas the percentage of patients with hypertriglyceridaemia remained stable at ∼40% after a peak right after transplantation (61.2%). The percentage of patients achieving the target for HDL cholesterol increased from 71.1% to 81.7%.

Inflammation and malnutrition. Albumin levels increased by 2.57 g/L (95% CI 2.38–2.77) after kidney transplantation and thereafter slightly decreased 0.23 g/L (95% CI −0.29 to −0.17) per year (Figure 1L and Table 2). The percentage of patients meeting the albumin target increased from 77.3% pre-transplantation to 91.1% 4 years post-transplantation (Table 3). In contrast, CRP levels did not change. Elevated CRP levels (≥10 mg/L) were most common in the year of transplantation (24.9%) and decreased thereafter (13.8% at 4 years post-transplantation), which was lower than pre-transplantation (Table 3).

We explored the change of clinical indicators within the first year post-transplantation in an analysis including only Denmark and the UK and found that haemoglobin, ferritin, phosphate, PTH and total cholesterol levels significantly changed within 3 months after transplantation (Supplementary data, Figure S1). A sensitivity analysis including only Denmark, Finland and Norway, which had complete data on lipid profiles, showed that the patterns for all lipid indicators in these three countries were not different than those found in the main analysis. Finally, repeating the analysis without the UK showed similar patterns over time for all clinical indicators and did not change our conclusions.

Subgroup analyses

We found that haemoglobin levels showed a larger increase for younger versus older patients, men versus women, patients with GN versus those with other PRDs, those who received a kidney from a living versus a deceased donor and those who received their transplant between 2011–15 and 2006–10. Similarly, decreases in ferritin and phosphate levels were more pronounced in these subgroups (Table 4).

The improvements of haemoglobin, ferritin, ionized calcium, phosphate, PTH, HDL cholesterol, triglycerides, albumin and CRP levels were associated with eGFR 1 year post-transplantation, with better results in the subgroups with higher eGFR levels. Patients with albumin levels in the target range (35–50 g/L) had higher haemoglobin and HDL cholesterol and lower phosphate, PTH and CRP levels compared with those with lower albumin levels. Low CRP levels (<10 mg/L) were associated with high haemoglobin and albumin levels. Finally, lower phosphate levels and higher total and LDL cholesterol and triglyceride levels were found in patients with high PTH levels (≥45 pmol/L) when compared with those with lower levels (Figure 2 and Table 5).

DISCUSSION

In this study we assessed the patterns of clinical indicators related to anaemia, mineral and bone metabolism, inflammation and malnutrition during the transition period from dialysis treatment to kidney transplantation. All clinical indicators normalized or at least approached the target range soon after kidney transplantation. These improvements were sustained during 4 years of follow-up. Furthermore, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides increased directly after transplantation but decreased thereafter.

This study found an increase in haemoglobin levels in the first year post-transplantation. The percentage of anaemic patients decreased from 75.7% to 31.5% at 4 years after transplantation. Also, Jones *et al.* [19] showed for 530 patients that haemoglobin levels increased in the first 2 years after kidney transplantation and that the prevalence of anaemia decreased from 89.4% pre-transplantation to 44.3% post-transplantation. These findings were confirmed in some smaller studies [20, 21]. Although the transplanted kidney can improve haemoglobin levels, many patients still do not achieve the target levels [19, 22]. Likewise, we found a post-transplant anaemia prevalence of up to 30% in the 4-year follow-up period that was predominantly present in the subgroups with lower kidney function (eGFR <30 and 30–59 versus ≥60 mL/min/1.73 m^2). However, not only kidney function, but also male gender, African American race, low serum bicarbonate and the use of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and prednisone were shown to be associated with post-transplant anaemia [19, 20]. Based on these findings, we suggest that workup for other causes of anaemia could be useful for patients in whom the anaemia is not corrected within 1 year post-transplantation. In addition, we found that after transplantation, ferritin levels decreased and the percentage of patients meeting the target almost doubled. This finding could be explained by the fact that patients usually stop receiving intravenous iron after transplantation. However, other factors could play a role, because ferritin is not only representative for iron storage, it is also affected by infection, inflammation, liver disease and malignancy [23].

In line with previous studies [24, 25], we found an increase in ionized calcium levels in the first 3 months post-transplantation, which stabilized thereafter. Also, the percentage of patients within the normal range was stable. Hypophosphataemia is common in the early post-transplantation period, whereas phosphate levels commonly return to normal in the following year, with >90% of patients meeting the target [24, 26]. Similarly, phosphate levels decreased dramatically after transplantation and then slightly increased along the lower boundary of the target range for healthy individuals. Sirilak *et al.* [27] reported continuous renal phosphate loss during a median follow-up of 5.7 years and concluded that hyperparathyroidism might play a role in this phenomenon rather than the phosphaturic hormone fibroblast growth factor 23. The current findings support the recommendations from the Kidney Disease: Improving Global outcomes group to monitor calcium and phosphate regularly after kidney transplantation [28]. Furthermore, our study showed a dramatic decrease in PTH levels in the first 3 months post-transplantation, remaining stable thereafter. However, in the majority of transplant recipients, PTH levels were

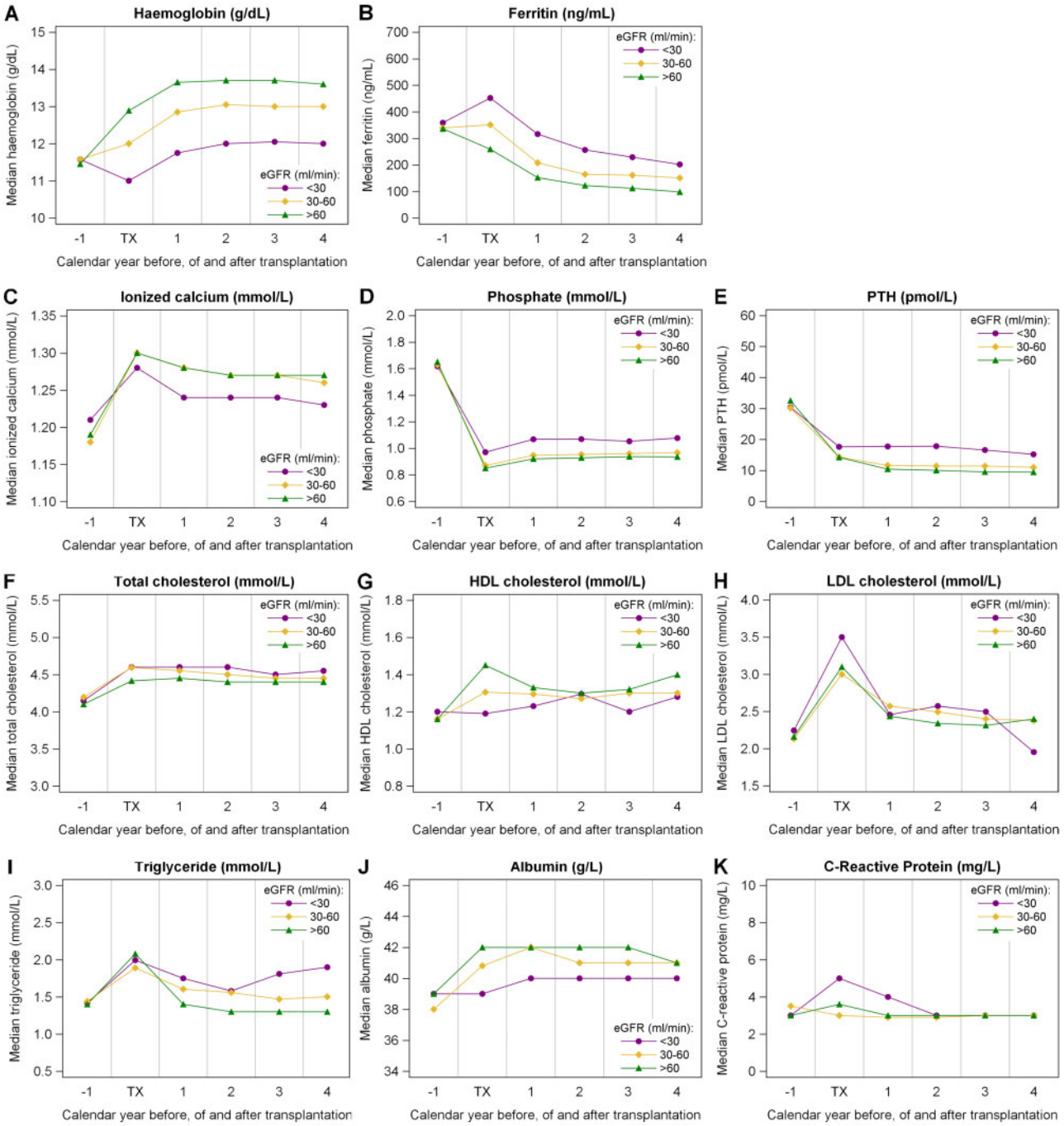

FIGURE 2: Median levels for each clinical indicator in the calendar year before, of and after kidney transplantation by eGFR level at 1-year post-transplant (<30, 30–59 and >60 mL/min/1.73 m^2). Values in the year of kidney transplantation are based on measurements after kidney transplantation only.

still higher than recommended for healthy individuals, which shows that even with good excretory function, the kidney allograft cannot normalize the PTH level [9, 10, 29, 30]. In most cases, tertiary hyperparathyroidism is probably the problem [31, 32]. The impact of hyperparathyroidism post-kidney transplantation is well recognized. Previous studies found associations between hyperparathyroidism and increased risk of fractures, graft loss, cardiovascular events and all-cause mortality [25, 29, 31, 32]. Thus the surveillance and treatment of hyperparathyroidism after transplantation may contribute to the prevention of poor outcomes in kidney transplant recipients.

This study showed an increase in total cholesterol, LDL cholesterol and triglycerides to levels higher than the target ranges only in the early post-transplantation period (3–6 months). Thereafter they decreased gradually into the target range, which could be due to lower doses of immunosuppressive drugs and/or the initiation of lipid-lowering therapy. Similarly, the percentages of patients with hypercholesterolaemia, high LDL cholesterol and hypertriglyceridaemia modestly increased the first year of transplantation. The increase in total cholesterol can be explained by an increase in LDL cholesterol. This finding is in line with other recent studies [10, 33]. In contrast, an older

Table 5. Effect of kidney transplantation on clinical indicators in different subgroups

	Effect of kidney transplantation, estimate (95% CI)									
	1-year post-transplant eGFR[a] (mL/min/1.73 m^2)			1-year post-transplant albumin[a] (g/dL)			1-year post-transplant CRP[a] (mg/L)		One-year post-transplant PTH[a] (pmol/L)	
Clinical indicator	<30	30–59	≥60	<35	35–50	>50	<10	≥10	<45	≥45
Haemoglobin (g/dL)	0.10 (0.05; 0.16)	**1.21 (1.19; 1.24)**	**2.05 (2.02; 2.08)**	1.01 (0.74; 1.28)	**1.85 (1.79; 1.90)**	**2.36 (1.82; 2.89)**	**1.69 (1.61; 1.76)**	1.08 (0.87; 1.30)	**1.39 (1.37; 1.42)**	0.66 (0.55; 0.77)
Ferritin (ng/mL)	11.1 (−56.6; 78.8)	**−129 (−163; −94)**	**−144 (−186; −102)**	10.9 (−157; 179)	−133 (−160; −105)	61.5 (−151; 274)	−130 (−160; −100)	−33.0 (−112; 47.0)	**−63.8 (−70.2; −57.4)**	−13.3 (−44.7; 18.2)
Ionized calcium (mmol/L)	0.05 (0.04; 0.06)	0.08 (0.08; 0.09)	**0.08 (0.07; 0.09)**	0.09 (0.08; 0.10)	0.08 (0.08; 0.08)	0.08 (0.03; 0.12)	0.08 (0.08; 0.08)	0.07 (0.06; 0.08)	0.08 (0.07; 0.08)	0.08 (−0.02; 0.18)
Phosphate (mmol/L)	−0.52 (−0.56; −0.48)	**−0.71 (−0.72; −0.69)**	**−0.73 (−0.75; −0.71)**	−0.59 (−0.64; −0.54)	**−0.70 (−0.71; −0.69)**	**−0.79 (−0.92; −0.66)**	−0.67 (−0.69; −0.66)	−0.70 (−0.74; −0.66)	−0.73 (−0.73; −0.72)	**−0.80 (−0.82; −0.78)**
PTH (pmol/L)	−8.0 (−2.3; −3.7)	**−19.5 (−20.8; −18.1)**	**−25.2 (−26.7; −23.8)**	−16.3 (−19.6; −13.1)	**−21.2 (−22.3; −20.1)**	−25.8 (−36.2; −15.5)	−20.4 (−21.7; −19.2)	−24.7 (−29.2; −20.1)	NA	NA
Total cholesterol (mmol/L)	0.60 (0.46; 0.74)	0.57 (0.50; 0.63)	0.47 (0.41; 0.53)	0.43 (0.25; 0.61)	0.58 (0.53; 0.63)	0.37 (−0.05; 0.80)	0.48 (0.42; 0.54)	0.67 (0.51; 0.84)	0.31 (0.29; 0.32)	**0.41 (0.33; 0.48)**
HDL cholesterol (mmol/L)	0.03 (−0.01; 0.07)	**0.13 (0.11; 0.16)**	**0.17 (0.15; 0.19)**	0.03 (−0.02; 0.09)	**0.15 (0.14; 0.17)**	**0.34 (0.13; 0.54)**	0.09 (0.07; 0.11)	0.07 (0.02; 0.13)	0.16 (0.14; 0.18)	0.10 (−0.04; 0.23)
LDL cholesterol (mmol/L)	0.13 (−0.14; 0.40)	0.44 (0.35; 0.53)	0.26 (0.16; 0.37)	0.30 (0.13; 0.47)	0.36 (0.28; 0.44)	0.00 (−0.89; 0.90)	0.28 (0.22; 0.35)	0.44 (0.18; 0.69)	0.25 (0.19; 0.32)	**1.03 (0.51; 1.56)**
Triglyceride (mmol/L)	**0.34 (0.14; 0.53)**	0.11 (0.04; 0.19)	0.03 (−0.04; 0.11)	0.09 (−0.19; 0.38)	0.14 (0.08; 0.20)	0.44 (−0.06; 0.95)	0.13 (0.07; 0.19)	0.09 (−0.13; 0.31)	−0.01 (−0.09; 0.06)	**0.71 (0.42; 1.00)**
Albumin (g/L)	0.53 (0.04; 1.02)	**2.66 (2.43; 2.88)**	**2.93 (2.71; 3.16)**	NA	NA	NA	**2.55 (2.34; 2.76)**	1.01 (0.47; 1.54)	2.87 (2.65; 3.08)	1.75 (0.01; 3.49)
CRP (mg/L)	**7.52 (1.64; 13.4)**	−1.11 (−2.72; 0.49)	0.56 (−0.97; 2.08)	**8.38 (2.30; 14.45)**	−0.18 (−1.42; 1.05)	0.01 (−8.08; 8.11)	NA	NA	−1.41 (−2.74; −0.07)	0.42 (−9.56; 10.4)

[a]Multivariate model included age at transplantation, sex, PRD, cohort of transplantation, dialysis modality before transplantation, kidney donor type and country.
Results in bold are statistically significantly different from the other subgroup(s).

study performed between 1976 and 1991 [34] showed persistently elevated total cholesterol, LDL cholesterol and triglyceride levels over a mean follow-up of 7 years. Possibly the patterns of lipid profiles differ over time due to a changing trend in immunosuppressive regimens. In the past, corticosteroids and cyclosporine, which were proven to induce hypercholesterolaemia, were used as the main regimens [35, 36], whereas the majority of clinicians nowadays choose tacrolimus, mycophenolate mofetil and as low as possible doses of corticosteroids [37].

Albumin levels increased early after transplantation, followed by a slight decline after 1 year. About 90% met the target and this proportion remained stable during the 4-year follow-up. A similar pattern was found by Guijarro *et al.* [7]. In addition, we found that CRP rose transiently in the year of transplantation and declined thereafter. This increase might be related with alloimmunity and ischaemia–reperfusion injury [38] and the occurrence of early post-transplant infection [39]. Surprisingly, we found that the great majority of patients was not inflamed and had normal CRP levels both before and after transplantation. This may be due to the better health status of patients selected for transplantation when compared with dialysis patients. However, it should be kept in mind that CRP may be measured only in those patients in whom an infection is suspected or needs to be excluded. Many studies found an association between high CRP and decreased long-term allograft function and increased risk of coronary events [4, 5, 40], supporting the idea that caution is required in case of elevated CRP levels in transplant recipients.

This study provides useful information about the course of clinical indicators directly and later post-transplantation, which reflects both kidney allograft function in recipients and the clinical practice of physicians in European countries. The major strengths of this study are the use of multinational data, long follow-up period and large sample size. However, there are also some limitations, most of which are related to the fact that this study was based on registry data. First, data on the use of medication were unavailable, whereas, in particular, immunosuppressive drugs, ESAs, iron supplementation, lipid-lowering therapies and vitamin D might have influenced the results. Second, clinical information, such as the occurrence of infections, allograft rejection or any illness that might have affected the levels of the clinical indicators, was unavailable. Third, there was considerable variation in the number of measurements of clinical indicators between countries/regions. We therefore performed sensitivity and subgroup analyses to examine the robustness of the results. Finally, we did not have information on the laboratory measurement methods used.

In conclusion, except for total cholesterol, LDL cholesterol and triglycerides, all other investigated clinical indicators improved after kidney transplantation. These improvements were related to eGFR. Nevertheless, values remained out of range in a considerable proportion of transplant recipients and particularly anaemia and hyperparathyroidism were still common problems. Datasets containing more clinical information, especially on the use of medication, are needed to understand the complex relationship between eGFR and the different clinical indicators.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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