Calcium and phosphate levels after kidney transplantation and long-term patient and allograft survival

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ABSTRACT

Background. Non-traditional cardiovascular risk factors, including calcium and phosphate derangement, may play a role in mortality in renal transplant. The data regarding this effect are conflicting. Our aim was to assess the impact of calcium and phosphate derangements in the first 90 days post-transplant on allograft and recipient outcomes.

Methods. We performed a retrospective cohort review of all-adult, first renal transplants in the Republic of Ireland between 1999 and 2015. We divided patients into tertiles based on serum phosphate and calcium levels post-transplant. We assessed their effect on death-censored graft survival and all-cause mortality. We used Stata for statistical analysis and did survival analysis and spline curves to assess the association.

Results. We included 1525 renal transplant recipients. Of the total, 86.3% had hypophosphataemia and 36.1% hypercalcaemia. Patients in the lowest phosphate tertile were younger, more likely female, had lower weight, more time on dialysis, received a kidney from a younger donor, had less delayed graft function and better transplant function compared with other tertiles. Patients in the highest calcium tertile were younger, more likely male, had higher body mass index, more time on dialysis and better transplant function. Adjusting for differences between groups, we were unable to show any difference in death-censored graft survival and all-cause mortality. We used Stata for statistical analysis and did survival analysis and spline curves to assess the association.

Conclusions. Hypophosphataemia and hypercalcaemia are common occurrences post-kidney transplant. We have identified different risk factors for these metabolic derangements. The calcium and phosphate levels exhibit no independent association with death-censored graft failure and mortality.

Keywords: calcium, graft survival, mortality, phosphate, renal transplant

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INTRODUCTION

Outcomes in renal transplant have improved considerably since the early days of transplantation, thanks to improved immunosuppression, better surgical technique and improved tissue matching [1, 2]. However, while patients who received a renal transplant have increased survival and improved quality of life compared with those on dialysis therapy, they still have significant morbidity and mortality compared with the general population [3, 4]. Kidney transplant recipients are four times more likely to be admitted to hospital than the general population and five times more likely to die of cardiovascular disease (CVD), even after adjusting for diabetic status [5–7].

Traditional risk factors for ischaemic heart disease (IHD) such as age, hypertension smoking and diabetes tend to underestimate the risk of IHD in renal transplant recipients, raising the possibility of non-traditional risk factors playing a role in IHD in transplant patients [8]. CVD following renal transplantation is thought to be due to a combination of atheroma, left ventricular hypertrophy and vascular calcification [4].

Vascular calcification is the abnormal deposition of calcium salts in the tissues of the vasculature due to derangements in calcium and phosphate metabolism and is highly prevalent in chronic kidney disease (CKD) and end stage renal disease (ESRD) [9, 10]. Vascular calcification in CKD is thought to be due to hyperphosphataemia and associates with poor clinical outcomes, such as mortality and CVD [11, 12]. ESRD is associated with elevated levels of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) and with low levels of calcitriol, which in turn contribute to hyperphosphataemia and hypocalcaemia [13, 14]. Following renal transplantation, there can be rapid shifts in these molecules leading to hypophosphataemia and hypercalcicaemia post-transplant [15, 16].

A number of studies have assessed the effect of post-operative serum phosphate and calcium levels on long-term outcomes and mortality in kidney transplant recipients. However, results have been conflicting, with some studies showing that higher serum phosphate may predict higher mortality in kidney transplant recipients and others reporting no effect on mortality while still others report a U-shaped association with graft and recipient survival [17–19]. However, the clinical implications of post-transplant calcium and phosphate levels remain unclear, and hypophosphataemia may simply reflect good graft function. Our aim was to assess the impact of phosphate and calcium levels and calcium and phosphate metabolism and is highly prevalent in chronic kidney disease (CKD) and end stage renal disease (ESRD) [9, 10]. Vascular calcification in CKD is thought to be due to hyperphosphataemia and hypocalcaemia [13, 14]. Following renal transplantation, there can be rapid shifts in these molecules leading to hypophosphataemia and hypercalcicaemia post-transplant [15, 16].

A number of studies have assessed the effect of post-operative serum phosphate and calcium levels on long-term outcomes and mortality in kidney transplant recipients. However, results have been conflicting, with some studies showing that higher serum phosphate may predict higher mortality in kidney transplant recipients and others reporting no effect on mortality while still others report a U-shaped association with graft and recipient survival [17–19]. However, the clinical implications of post-transplant calcium and phosphate levels remain unclear, and hypophosphataemia may simply reflect good graft function. Our aim was to assess the impact of derangement of calcium and phosphate metabolism in the first 90 days post-transplant on allograft and recipient outcomes.

We included all individuals who received a first, single, living or deceased kidney transplant between 1 January 1999 and 31 December 2015. We excluded all those aged <18 years, those who did not receive standard immunosuppression and those who did not have functioning graft 1-year post-transplantation. All renal transplants were performed at Beaumont Hospital, Dublin, Ireland. All were ABO compatible and had a negative complement-dependent cytotoxicity assay, flow cross-match or virtual cross-match assay. Follow-up was weekly immediately post-transplant, monthly in the first year and 3 monthly thereafter. Outcome data were censored on 31 December 2017.

Standard immunosuppression consisted of tacrolimus and mycophenolate with or without prednisolone. The initial tacrolimus trough level was 8–10 ng/mL for the first month, followed by a trough of 4–8 ng/mL in the low-risk group and 8–10 ng/mL in the high-risk group.

Each participant’s serum calcium and phosphate levels were recorded as part of routine care immediately pre-transplant and at regular intervals post-transplant. Management of calcium and phosphate metabolism was at the treating nephrologist’s discretion and was not subject to a formal treatment protocol. Phosphate supplementation was given in the form of potassium phosphate or sodium phosphate. The general practice was to commence phosphate supplementation if the patient was symptomatic with low levels.

Renal function was estimated using the creatinine (Cr) based CKD Epidemiology Collaboration formula, using serum creatinine obtained on the same day as the lowest serum phosphate.

Hypophosphataemia was said to be present if levels fell <0.7 mmol/L at any point. Severe hypophosphataemia was present if serum phosphate levels fell <0.5 mmol/L. Hypercalcemia was considered to be present if serum calcium rose >2.6 mmol/L.

The primary outcome was death-censored graft failure and recipient survival. Delayed graft function (DGF) was defined as dialysis required in the post-transplant period. Acute rejection was diagnosed on the basis of a transplant renal biopsy that demonstrated evidence of acute cellular or humoral rejection on histologic analysis by an experienced renal pathologist and was graded according to the Banff classification.

Statistical analysis

The study population was classified into tertiles, each containing equal numbers of patients based on the lowest phosphate level and the highest calcium level recorded in the 90-day post-transplant. The tertiles for phosphate were serum phosphate <0.46 mmol/L, 0.46–0.57 mmol/L and >0.57 mmol/L. The tertiles for calcium levels were: serum calcium <2.47 mmol/L, 2.47–2.60 mmol/L and >2.60 mmol/L.

Kaplan–Meier methods were used to estimate survivor functions and to present graft loss and patient survival based on the above-described tertiles. The log-rank test was used to determine whether there were significant differences between the phosphate and calcium tertile categories.

Univariate and multivariate Cox proportional hazard models were then used to test for association between calcium and phosphate levels and composite endpoints. The final Cox models were constructed by means of a backwards stepwise selection process to identify the most parsimonious summary model for each outcome in question.

The covariates included in the regression models were selected among baseline variables and compared in a bivariable
model, with patient outcomes and phosphate and calcium levels. We selected variables to be included in the regression models if P-value was <0.20. History of diabetes, smoking history, weight, cytomegalovirus and panel reactive antigen (PRA) status was initially discarded from the models due to lack of significance. We settled upon four main models: Model 1: univariate test with either phosphate or calcium level; Model 2: Model 1 + recipient age + sex; Model 3: Model 2 + log of Cr at 3-month post-transplant; Model 4: Model 3 + acute rejection in the first year post-transplant + number of Human leukocyte antigen (HLA) mismatches + cold-ischaemia time (CIT) + donor age + donor sex + DGF + time on dialysis.

To better represent the shape of the association between the levels of serum phosphate and calcium and the hazard ratio (HR), spline curves were modelled using restricted cubic spline curves. Analyses were performed using Stata SE (version 13, College Station, TX, USA). Probability of a Type 1 error of <5% (P < 0.05) was considered significant.

RESULTS

Our initial cohort was 1705 patients; we excluded 117 patients that were <18 years, 59 that had graft failure during the first year and 4 patients that had incomplete data, so that finally, we analysed 1525 patients. The median follow-up beyond the first year was 8.1 years (range 0.02–18.9). The baseline characteristics of the patients per tertile of calcium and phosphate can be seen in Table 1.

The transplant recipients in the lowest tertile of serum phosphate (<0.46 mmol/L) were significantly younger, had lower weights, spent less time on dialysis, and had lower PRA, lower incidence of DGF and higher estimated glomerular filtration rate (eGFR). They were more likely to be female, had a younger donor age and were less likely to receive a pre-emptive transplant. The recipients in the highest calcium tertile (>2.6 mmol/L) were significantly younger, heavier, more likely to be male and had spent more time on dialysis. Their eGFR was higher and they had a reduced incidence of DGF, they were less likely to receive a pre-emptive transplant but more likely to receive a living transplant and they were more likely to have a male donor and CIT was likely to be shorter.

Hypophosphataemia occurred in 86.3% of cases, severe hypophosphataemia in 46.3% and hypercalcaemia in 36.1% of cases. Lowest serum phosphate levels were recorded at a mean [standard deviation (SD)] of 16.5 (17.7) days post-transplant, and the highest calcium level was longer, occurring at 38.5 (26.9) days post-transplant. The mean (SD) minimum serum phosphate recorded was 0.53 (0.15) mmol/L, while the mean (SD) peak serum calcium was 2.55 (0.19) mmol/L.

During the follow-up period, 211 recipients (13.8%) died and 331 (21.7%) lost their graft. The most common causes of death were cardiovascular (31.3%), infection (13.3%) and malignancy (23.7%). Other causes accounted for 16 deaths (7.6%), and the cause of 51 deaths (24.2%) was not known.

Using univariate analysis, the graft failure occurred less frequently in recipients with the lowest phosphate (P = 0.03), but there was no difference as per calcium levels. Likewise, there was no statistically significant difference between the rate of death for calcium levels, but those in the lowest level of phosphate were less likely to die (P = 0.001) (Tables 2 and 3). The significance was lost after multivariate analysis.

Kaplan–Meier analysis revealed that the lowest levels of phosphate were significantly related to better outcomes in terms of graft survival (P = 0.02) and mortality (P = 0.001) in the post-transplant period, while calcium tertiles were not significantly related to graft failure or mortality (Figure 1).

Table 1. General characteristics as per tertiles of phosphate and calcium levels during the first 90 days

| Variables                        | Phosphate, mmol/L | Calcium, mmol/L |
|----------------------------------|-------------------|-----------------|
|                                  | First             | Second          | Third            | P-value |
| Recipient age, mean (SD), years  | 45.0 (14.3)       | 48.3 (14.0)     | 50.5 (14.0)     | 0.001   |
| Donor age, mean (SD), years      | 39.2 (14.7)       | 42.8 (14.4)     | 45.0 (14.1)     | 0.001   |
| Donor men, n (%)                 | 300 (57.7)        | 283 (55.9)      | 291 (59.1)      | 0.59    |
| Recipient men, n (%)             | 295 (56.3)        | 316 (62.1)      | 341 (69.3)      | 0.001   |
| Current smoker, n (%)            | 41 (7.9)          | 30 (5.9)        | 25 (5.1)        | 0.19    |
| NODAT, n (%)                     | 50 (10.8)         | 50 (11.3)       | 44 (10.5)       | 0.93    |
| Weight, mean (SD), kg            | 72.2 (15.0)       | 73.6 (15.4)     | 75.7 (13.4)     | 0.005   |
| Dialysis vintage, mean (SD), months | 30.3 (21.9)       | 31.6 (20.5)     | 36.2 (45.7)     | 0.01    |
| Living donor                     | 52 (9.9)          | 39 (7.7)        | 46 (9.4)        | 0.41    |
| Deceased donor                   | 472 (90.1)        | 470 (92.3)      | 445 (90.6)      | 0.001   |
| Pre-empted                       | 24 (4.6)          | 48 (9.6)        | 69 (14.1)       | 0.001   |
| Peritoneal dialysis              | 182 (34.9)        | 154 (30.7)      | 136 (27.8)      | 0.001   |
| Haemodialysis                    | 315 (60.5)        | 300 (59.8)      | 285 (58.2)      | 0.001   |
| Donor CMV+                       | 172 (33.1)        | 178 (35.6)      | 168 (34.8)      | 0.70    |
| Recipient CMV+                   | 184 (36.0)        | 178 (35.5)      | 178 (36.8)      | 0.92    |
| HLA mismatch, mean (SD)          | 3.3 (1.4)         | 3.4 (1.5)       | 3.4 (1.5)       | 0.57    |
| GPT, mean (SD), h                | 16.4 (5.2)        | 16.0 (4.4)      | 16.6 (4.8)      | 0.19    |
| PRA, mean (SD), %                | 9.8 (29.8)        | 12.2 (22.9)     | 14.2 (21.1)     | 0.009   |
| DGF, n (%)                       | 48 (9.3)          | 61 (12.1)       | 111 (22.7)      | 0.001   |
| TBAR, n (%)                      | 60 (11.6)         | 57 (11.3)       | 64 (13.3)       | 0.60    |
| Cr, mean (SD), mmol/L            | 120 (35.4)        | 131.0 (36.7)    | 153.8 (57.4)    | 0.001   |
| eGFR, mean (SD)                  | 61.0 (18.9)       | 54.2 (16.5)     | 47.1 (17.0)     | 0.001   |
| Phosphate/calcium, mean (SD), mmol/L | 0.38 (0.05)       | 0.51 (0.03)     | 0.71 (0.12)     | 0.005   |
| Time to value, mean (SD), days   | 19.5 (18.6)       | 16.2 (16.8)     | 13.7 (17.2)     | 0.001   |

NODAT, new-onset of diabetes after transplant; CMV, cytomegalovirus; TBAR, transplant biopsy acute rejection; eGFR at the time of lowest phosphate.
Results of different models of Cox regression analysis are summarized in Table 4. In univariate analysis, the lowest phosphate tertile group had better death-censored graft survival and lower mortality than the highest tertile (HR 1.23, 95% confidence interval (CI) 1.02–1.49 and HR 1.36, 95% CI 1.15–1.60, respectively). However, when we undertook a full multivariable model to take account of differences in baseline differences between the different tertiles, we were unable to identify any independent effect of post-transplant hypophosphataemia or post-transplant hypercalcaemia on either patient or graft survival.

We constructed spline curves to show the association between calcium and phosphate and death-censored graft failure and all-cause mortality (Figure 2). A phosphate level of 0.46 mmol/L representing hypophosphataemia and calcium 2.60 mmol/L representing hypercalcaemia were defined as the reference values. The spline curves represent the association of serum phosphorus and calcium concentrations as a continuous variable with death-censored graft failure and mortality, and as a restricted cubic spline curve; we observe a trend for increased risk of death-censored graft failure and mortality with the higher levels of phosphate, and no effect with the lowest levels. On the contrary, there is a tendency to decrease the risk of death-censored graft failure with the higher levels of calcium levels, and a bidirectional or U-shape association between the calcium levels and mortality. However, phosphate and calcium serum levels were not statistically associated.

DISCUSSION

We evaluated the association of early post-transplantation biochemical values (during the first 90 days) with death-censored graft failure and mortality as derangements in calcium and phosphate are greatest during the early post-transplant period. A successful graft will more likely to improve the previously deranged calcium and phosphate metabolism, but this improvement is slow, mechanistically incomplete and variable. Rapid effects of renal transplantation include reduced serum PTH levels (even where serum calcium levels are stable), increased calcium production and decreased serum phosphate levels [20]. To our knowledge, this is the first study that analyses and reports the association between graft survival and mortality with calcium levels in the first 90 days post-transplantation.

The post-transplantation hypercalcaemia occurred in 36.1% of recipients, consistent with previously published reports (9–66%) [17, 21–24]. Furthermore, the incidence of hypophosphataemia (<0.7 mmol/L) was 86.3% at 90 days, also consistent with previous reports (47.0–77.3% [24–26]). When the levels were reported
FIGURE 1: Survival curves for renal transplant recipients stratified by serum phosphate and calcium as per tertiles. (A and B) Death-censored graft failure and mortality according to phosphate levels. (C and D) Death-censored graft failure and mortality according to calcium levels.

Table 4. Multivariable Cox regression models to assess the association between phosphate and calcium levels with graft failure and mortality

|                | Phosphate tertiles, mmol/L |            | Calcium tertiles, mmol/L |            |
|----------------|-----------------------------|------------|--------------------------|------------|
|                | HR (95% CI)                 | P-value    | HR (95% CI)              | P-value    |
| Graft failurea |                             |            |                          |            |
| Model 1        | 1.23 (1.02–1.49)            | 0.03       | 0.99 (0.82–1.20)         | 0.90       |
| Model 2        | 1.31 (1.08–1.91)            | 0.01       | 0.98 (0.80–1.18)         | 0.80       |
| Model 3        | 1.16 (0.94–1.43)            | 0.16       | 1.00 (0.83–1.22)         | 0.98       |
| Model 4        | 1.14 (0.92–1.41)            | 0.25       | 0.98 (0.80–1.20)         | 0.86       |
| Mortality      |                             |            |                          |            |
| Model 1        | 1.36 (1.15–1.60)            | 0.001      | 0.92 (0.78–1.09)         | 0.31       |
| Model 2        | 1.16 (0.98–1.37)            | 0.10       | 0.96 (0.81–1.12)         | 0.58       |
| Model 3        | 1.14 (0.95–1.36)            | 0.16       | 0.96 (0.82–1.13)         | 0.63       |
| Model 4        | 1.10 (0.91–1.32)            | 0.33       | 0.96 (0.81–1.13)         | 0.60       |

aFailure censored for death with a functioning graft.
during the first year post-transplant, the incidence decreased to 4.1 from 51.9% [17, 19, 23, 27, 28]. Also, 46.3% had severe hypophosphataemia (<0.5 mmol/L) similar to that reported by van Londen et al. [25] who reported hypophosphataemia in 43.6%. However, the time to the lowest phosphate was 16.5 days, earlier than 33 days reported by the same group [25]. Therefore, the presence of hypophosphataemia and hypercalcaemia are frequent in the post-transplant period [20], especially during the first month; this should be noted for the possible implications and clinical involvement that it represents.

There are conflicting results in the literature about the effect of the serum phosphate and calcium levels on graft function and mortality. While some studies suggest that there is a positive effect of the low levels of phosphate [19, 25], or the high levels of calcium in the post-transplant period [17], our results suggest that there is no independent association between the levels of the lowest serum phosphate or the highest serum calcium during the first 90 days post-transplant, when adequate account is made for baseline differences between groups, similar to other reports [23, 24, 28]. Patients with hypophosphataemia in general receive younger better functioning kidneys, which explains most of the difference in long-term graft outcome for patients who develop hypophosphataemia. On the contrary, the high levels of phosphate have a more consistent positive association [17, 19, 29, 30]. In our report, the incidence of hyperphosphataemia was very low at 90 days.

Because of the retrospective nature of our study, FGF-23 was not available and PTH data were incomplete, which may have resulted in some degree of bias and residual confounding. However, previous analysis about PTH, using multiple imputation to account for missing data, did not materially change the association [25]. Also, our patient population mainly consisted of whites (Irish population), with an age different from other reports and with an immunosuppressive regimen limited to tacrolimus, mycophenolate and steroids, which may limit the generalizability of our findings. However, strengths of our study include the design, a large number of intra-individual measurements, the high external validity due to the use of real-life data, and the complete and long-term follow-up.

The management of biochemical abnormalities after kidney transplantation can vary between clinicians or institutions. However, our general practice is to start supplementation if symptomatic with very low levels of phosphate, given that these changes are transitory. A possibility of selection

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**FIGURE 2**: Spline curves illustrating the association between the serum phosphate levels and the risk of (A) death-censored graft failure, (B) all-cause mortality; the serum calcium levels and the risk of (C) death-censored graft failure and (D) all-cause mortality. Models are on the basis of a cubic spline term (restricted cubic spline) with three knots, with a serum phosphate level of 0.46 mmol/L and calcium level of 2.6 mmol/L, as the reference value. The solid lines represent the fully adjusted HRs (Cox regression Model 4) with their 95% CIs.
bias may exist as we chose to exclude kidney transplant recipients who had graft failure or mortality before 1 year after transplantation. We decided to exclude these patients because the most frequent reason to lose the allograft function is more related to other causes and less likely to be associated with calcium and phosphate derangements.

CONCLUSIONS
In summary, post-transplantation hypercalcaemia and hypophosphataemia are common complications after kidney transplantation, especially in younger patients, with short time in dialysis and with a better kidney function post-transplant. We did not find a relation between the serum phosphate and serum calcium at 90 days post-transplant and the risk of death-censored graft failure and all-cause mortality.

Further studies are needed to assess whether evaluation and management of phosphate and calcium derangements in the post-transplant period will improve outcomes.

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AUTHORS’ CONTRIBUTIONS
J.C., D.J.S. and P.J.C. were involved in conception and design. J.C., P.O. and P.J.C. were involved in analysis and interpretation of data. J.C., D.J.S., P.J.C., S.J.M., C.E.A., F.O., Y.E.W., C.M.O. and D.M.L. were involved in drafting the article, revising it and in final approval of the manuscript.

CONFLICT OF INTEREST STATEMENT
The authors declare that there is no conflict of interest.

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