High serum calcification propensity is associated with mortality and graft failure in renal transplant recipients

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Introduction

Vascular calcification is highly prevalent in renal transplant recipients and strongly predicts all-cause mortality. Recently, a blood test was developed that provides an overall measure of calcification propensity by monitoring the maturation time (T_{50}) of calciprotein particles (CPPs).

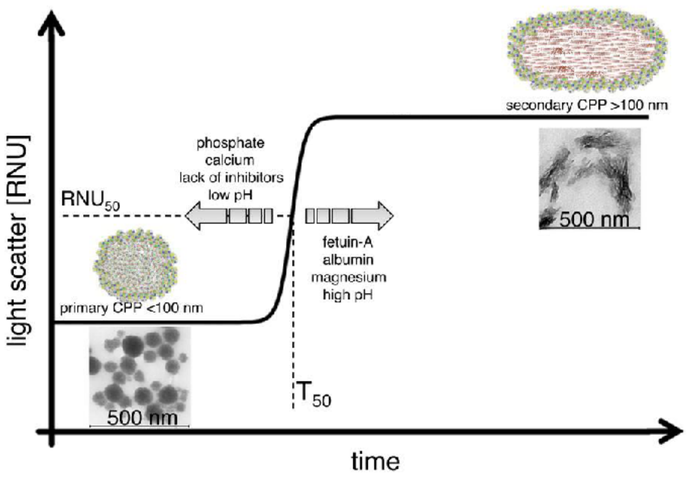

Figure 1. Illustration of test principle. The addition supersaturated calcium and phosphate to serum triggers formation of primary CPPs. Serum T_{50} depends on all calcification-promoting and inhibiting factors present in serum.

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Aim

We prospectively investigated the hypothesis that serum T_{50} is associated with all-cause mortality and graft failure after kidney transplantation (KTx).

Methods

Serum calcification propensity was quantified in a cohort of 699 stable outpatient renal transplant recipients with a function graft for ≥ 1 year.
Correlates of serum T_{50} were evaluated using linear regression models, associations between T_{50} and the risk of mortality or death-censored graft failure with Cox regression analyses. The predictive value of T_{50} for mortality was compared with Framingham risk factors using C-statistic, integrated discrimination improvement (IDI), and net reclassification improvement (NRI).

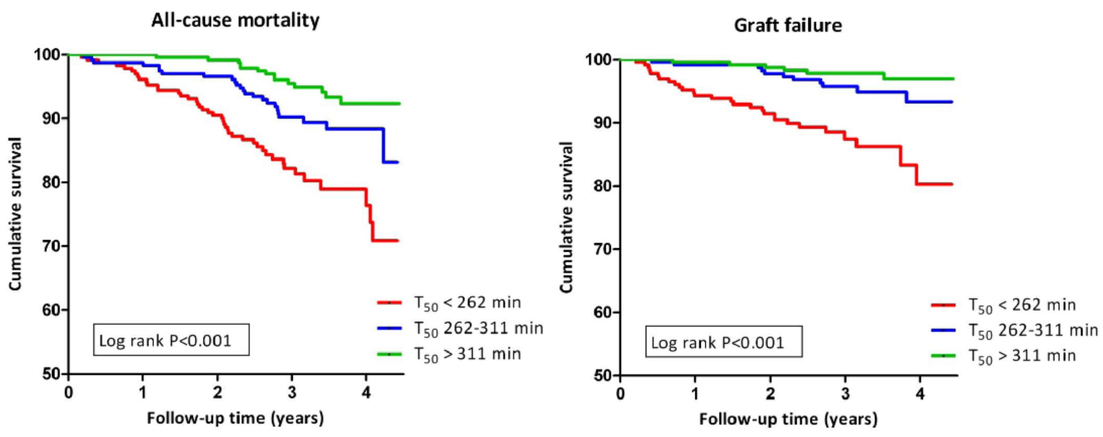
Results

Table 1. Patient baseline characteristics.

	Tertiles of serum T_{50}			
	Tertile 1 N = 231	**Tertile 2 N = 233**	**Tertile 3 N =235**	***P*-value**
T_{50}, min.	<262	262-311	>311	<0.001
Age, years	54±13	54±13	52±13	0.2
Male gender, n (%)	135 (58)	128 (55)	135 (57)	0.7
BMI, kg/m²	26.9±5.1	26.8±4.6	26.2±4.6	0.1
Systolic BP, mmHg	137±18	136±17	135±18	0.4
Post KTx, years	6.1[1.7-12.8]	5.3[2.0-12.3]	5.2[1.8-10.1]	0.5
Living donor, n (%)	61 (27)	77 (34)	98 (42)	0.002
eGFR, mL/min/1.73m²	46.6±20.3	53.3±19.3	56.7±19.5	<0.001
Albuminuria, mg/24h	82[16-300]	36[9-133]	25[9-112]	<0.001
Hb, mmol/L	8.0±1.1	8.3±1.1	8.4±1.0	<0.001
Calcium, mmol/L	2.37±0.14	2.40±0.14	2.45±0.15	<0.001
Phosphate, mmol/L	1.07±0.24	0.95±0.17	0.87±0.18	<0.001
Bicarbonate, mmol/L	23.6±3.6	24.5±2.6	25.8±2.6	<0.001
Magnesium, mmol/L	0.93±0.13	0.95±0.11	0.98±0.11	<0.001
Mortality, n (%)	43 (19)	24 (10)	14 (6)	<0.001
Graft failure, n (%)	28 (12)	11 (5)	6 (3)	<0.001

Serum T_{50} was normally distributed and mean SD was 286 62 minutes. Serum magnesium, albumin, PTH, and bicarbonate were positively and serum phosphate, Hb, and the use of vitamin K antagonist or calcineurin inhibitor were inversely associated with T_{50}. Altogether, explaining 41% of the variation in serum T_{50}.

Figure 2. Kaplan-Meier curve for all-cause mortality and graft failure.



During follow-up for 3.1 [2.7-3.9] years, 81 patients died and 45 patients developed graft failure. Reduced T_{50} was associated with increased mortality (HR 1.69 [1.37-2.09]) and graft failure risk (HR 2.61 [1.94-3.50], both *P*<0.001 per SD decrease), independent of known risk factors and T_{50} determinants.

Table 2. Additive value of serum T_{50} for prediction risk of mortality.

Model	**C-statistics (95% CI)**	**IDI (%)**	***P*-value**
Age, gender, eGFR	0.72 (0.66-0.78)	-	-
Age, gender, eGFR plus *Ca x Pi product*	0.72 (0.66-0.78)	0.2	0.42
Age, gender, eGFR plus *Framingham factors*	0.73 (0.67-0.79)	0.8	0.28
Age, gender, eGFR plus *Ca x Pi product and Framingham factors*	0.73 (0.67-0.79)	0.9	0.23
Age, gender, eGFR plus *serum T_{50}*	0.75 (0.70-0.80)	1.6	0.03

Framingham risk factors included current smoking status, diabetes mellitus, BMI, systolic BP and LDL cholesterol.

Table 3. NRI based on addition of serum T_{50}.was 14%.

	With serum T_{50}			
Without serum T_{50}	**<5%**	**5-10%**	**>10%**	**Total (n)**
Patients with all-cause mortality				
<5%	4	4		8
5-10%		9	4	13
>10%		3	57	60
Total	4	16	61	81
Patients without all-cause mortality				
<5%	176	17		193
5-10%	43	90	22	155
>10%	3	40	225	268
Total	222	147	247	616

Multivariable model: recipient age and gender, and eGFR (CKD-EPI). *P*=0.002.
1 out of 7 patients had improved classification with addition of serum T_{50}.

Conclusion

Increased serum calcification propensity, i.e. reduced serum T_{50}, is strongly associated with an increased risk of mortality and graft failure in stable renal transplant recipients. Serum T_{50} improves mortality prognostication post KTx. Further studies are needed to clarify whether therapeutic targeting of serum T_{50} improves outcome after KTx.

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