Serum calcification propensity (T_{50}) is a strong predictor of cardiac and all-cause mortality in kidney transplant recipients

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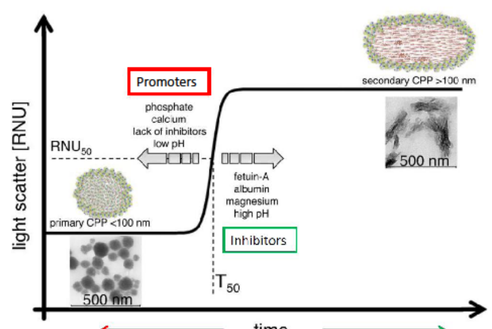
INTRODUCTION

Calcification of the vasculature is associated with cardiovascular disease and death in kidney transplant recipients (KTRs)[1,2]. Without the presence of endogenous inhibitors, calcium and phosphate would precipitate in vivo. A novel functional blood test measures the calcification inhibition time by detecting the time point of transformation (T_{50}) from primary (~50 nm) to larger secondary (~100 nm) calciprotein particles[3] (Figure 1). Accelerated T_{50} indicates a diminished ability of serum to resist calcification, and is associated with morality in chronic kidney disease[4] and maintenance KTRs[5]. We hypothesized that T_{50} measured early after transplant was associated with all-cause and cardiac mortality, and that T_{50} was associated with progression in aortic stiffness.

PATIENTS AND METHODS

All kidney transplantations in Norway are performed at Oslo University Hospital which serves a population of 5 million people and annually performs 250-300 transplantations. Most patients attend our outpatient clinic until week 8-10, at which time serum has been biobanked since year 2000. Since 2009, aortic stiffness has been measured by pulse wave velocity (PWV) and repeated after 1 year. Here we included patients with a long follow up time (year 2000-2003) and patients with repeated PWV (year 2009-2012). The Calcification Inhibition Time T_{50} was measured in biobanked serum by nephelometry (Figure 1, adapted from ref. 3). PWV progression was defined as an increase > 1 m/s during the first year. Mortality data was collected from the Norwegian Renal Registry. The clinical correlates of T_{50} at baseline (week 8-10) were determined by linear regression with backward elimination (p>0.10 for exclusion). The association with PWV progression was assessed with logistic regression. The association with mortality was determined by Cox regression adjusting for prognostic risk factors from a previously validated prognostic model[6]. The relative contribution of risk factors was assessed by scaling continuous risk factors to the interquartile range (IQR).

Figure 1. Transformation time T_{50}



adapted from ref. 3

Clinical correlates of T_{50}

	Beta (95% CI)	Adj. R^2	*P* value
Phosphate, per 0.20 mmol/L	-38 (-41 to -35)	0.25	<0.001
Albumin, per g/L	5 (4 to 6)	0.37	<0.001
Prednisolone dose ≥ 12.5 mg	-30 (-38 to -21)	0.41	<0.001
Deceased donor	-15 (-21 to -9)	0.42	<0.001
Diabetes	-11 (-17 to -4)	0.43	0.001
High CNI trough levels*	-10 (-17 to -3)	0.43	0.01
First tx	-13 (-21 to -4)	0.43	0.01
Rejection	-12 (-20 to -3)	0.43	0.01
First era (2000-03 vs. 2009-12)	-7 (-14 to 0)	0.44	0.05

*CsA > 220 ng/mL or TAC > 8.5 ng/mL.

RESULTS

1435 of 1886 (76%) KTRs transplanted in the relevant periods attended the visit in week 8-10 and had serum biobanked for measurement of T_{50}. From year 2009-2012 589 of 770 (77%) KTRs had repeated aortic stiffness (PWV) measurements. Median (IQR) T_{50} was 188 (110) minutes, age 53.4 (21.5) years, male 66%, diabetes 29.1%. The clinical correlates are shown in the Table, with serum phosphate being the most influential determinant of T_{50}. During the first year, 156 of 589 (24%) KTRs progressed in aortic stiffness (PWV increase > 1 m/s), but mean PWV did not change, and there was no association between T_{50} and PWV progression (data not shown).

After a median follow-up of 5.1 years, 283 patients had died, 70 from a cardiac cause. Cardiac death was attributed to sudden death, myocardial infarction and cardiac failure in 43, 21 and 6 patients, respectively. An IQR decrease in T_{50} of 110 minutes was associated with mortality (HR 1.39 [1.13-1.71], p=0.002) and cardiac mortality (HR 1.88 [1.20-2.93], p=0.01). Of note, this was of similar magnitude as the risk associated with diabetes or coronary heart disease (Figure 2).

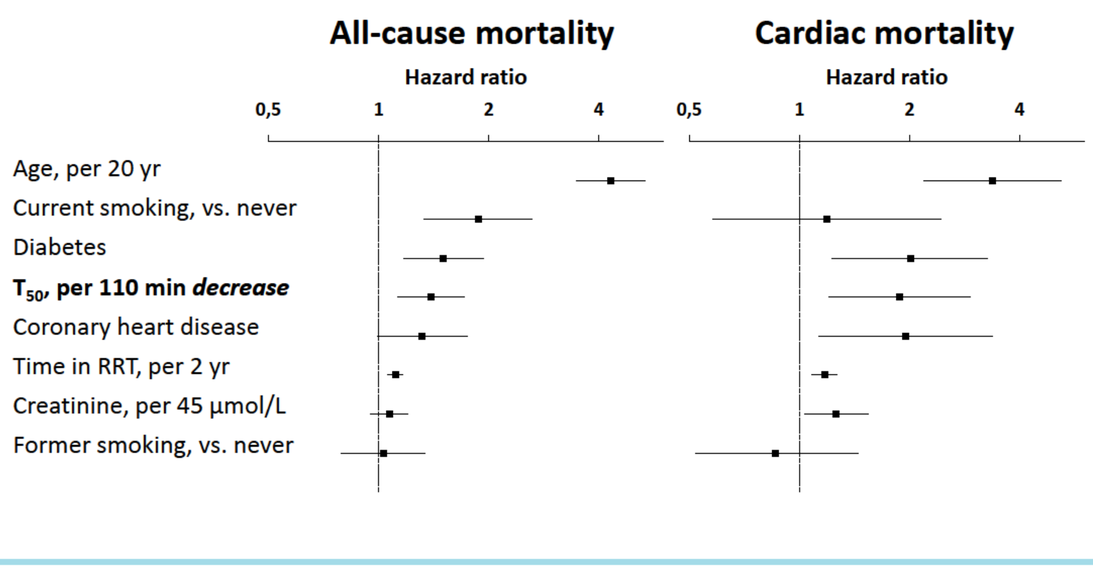


Figure 2. Risk factors for mortality. Continuous risk factors were scaled to the interquartile range.

CONCLUSIONS

1. Serum calcification propensity T_{50} is associated with all-cause and cardiac mortality in kidney transplant recipients.
2. Serum phosphate is the most influential determinant of T_{50} in our cohort.
3. We found no association between T_{50} and progression in aortic stiffness during the first year of follow-up.

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