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LATE BREAKING CLINICAL TRIALS

Calcification Propensity –Test: Prediction of Survival after Kidney Transplantation

One of the consequences of CKD (chronic kidney disease) is that the kidney loses its ability to eliminate excess phosphate, resulting in serum phosphate concentrations rising above the normal range. The permanent increase in phosphate concentrations, in particular in combination with calcium concentrations that are also elevated, results in a high general propensity for calcification in many organs, and soft tissues. The vessels are particularly affected by this. This vascular calcification that is associated with a stiffening of the vascular walls has long been known to be one of the main causes of high mortality in patients with severe renal failure [1]. Even though therapeutic attempts are made to lower elevated phosphate levels by the restriction of the dietary phosphate intake and the administration of oral phosphate-binding agents, damage to the vessels can hardly ever be fully prevented due to the complexity of the disease processes. It is also unclear why some patients are clearly at greater risk to develop calcifications than others.

In the past, it was assumed that calcification was a passive process that occurred as soon as the calcium-phosphate product was exceeded, while we now know that different regulators promote or inhibit the process in vivo. Crystal growth occurs as soon as the body can no longer keep the protein-mineral complexes (calciprotein-particles, CPPs) that are present in solution. A new test (nanoparticle-based overall calcification propensity assay) can determine the overall calcification propensity through investigation of the so-called CPP maturation in the serum [2]. This involves measuring the time (T50) to spontaneous formation of secondary (ellipsoid elongated, crystalline) CPPs from primary (spherical colloidal) CPPs.

This test has already been used to demonstrate that the overall calcification propensity is a predictor for mortality in pre-dialysis patients [3]. The study that is now being presented in LBCT investigated the association between overall calcification propensity, mortality and transplant failure in kidney transplant patients. Increased serum calcification propensity, i.e. reduced serum T50, was strongly associated with an increased risk of all-cause mortality and graft failure in these patients.

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[1] Block GA, Hulbert-Shearon TE, Levin NW et al. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis 1998; 31: 607-17

[2] Pasch A, Farese S, Gräber S et al. Nanoparticle-based test measures overall propensity for calcification in serum. J Am Soc Nephrol 2012; 23(10): 1744-52

[3] Smith ER, Ford ML, Tomlinson LA et al. Serum calcification propensity predicts all-cause mortality in predialysis CKD. J Am Soc Nephrol 2014; 25(2): 339-48

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ABSTRACT 4064

High Serum Calcification Propensity Is Associated With Mortality And Graft Failure In Renal Transplant Recipients

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INTRODUCTION AND AIMS: Vascular calcification is highly prevalent in renal transplant recipients (RTR) and strongly predicts all-cause mortality. Renal allograft calcification may contribute to graft failure. Recently, a blood test was developed that provides an overall measure of calcification propensity by monitoring the maturation time (T50) of calciprotein particles. We prospectively investigated the hypothesis that serum T50 is associated with mortality and graft failure in stable RTR.

METHODS: Serum calcification propensity was quantified in a cohort of stable outpatient RTR with a functioning graft for ≥1 year between 2008 and 2011. The cohort consisted of 699 RTR (57% male, 53±13 years) with baseline measurements at 5.4 [1.9-12.1] (median[IQR]) years after kidney transplantation. Determinants of serum T50 were evaluated using multivariate linear regression models. Associations between T50 and the risk of all-cause mortality or death-censored graft failure were assessed using multivariable Cox regression analyses.The predictive value of T50 for mortality was compared with Framingham risk factors (smoking, BMI, diabetes mellitus, systolic blood pressure and LDL cholesterol) using C-statistic, integrated discrimination improvement (IDI), and net reclassification index (NRI).

RESULTS: Mean serum T50 was 286±62 minutes. Serum magnesium, albumin, PTH and bicarbonate were positively associated with T50. Serum phosphate, Hb, and the use of a vitamin K antagonist or calcineurin inhibitor were inversely associated with T50. Altogether, these parameters explained 41% of the variation in T50. During follow-up for 3.1 [2.7-3.9] years, 81 (12%) patients died and 45 (6%) patients developed graft failure. T50 was inversely associated with the risk of mortality (hazard ratio 0.59 [95% CI 0.48-0.73] and graft failure (HR 0.38 [0.29-0.52], both P<0.001 per SD increase), independent of known risk factors and T50 determinants. T50 had predictive value for mortality in a model adjusted for age, gender, and eGFR (IDI 0.016, P=0.03; NRI 0.14, P=0.002), whereas Framingham risk factors did not (IDI 0.008, P=0.28; NRI -0.02, P=0.70).

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CONCLUSIONS: Increased serum calcification propensity, i.e. reduced serum T50, is strongly associated with an increased risk of all-cause mortality and graft failure in stable RTR. T50 improves mortality prognostication among stable RTR. Further studies are needed to clarify whether targeting of serum T50 improves long-term outcomes after kidney transplantation.

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