CALCIFICATION MEDICINE
CPP/T50 NEWSLETTER
JUNE 2023

Yet unidentified factor(s) protect the fetus from accelerated calcification

Calcium and phosphate levels are comparatively high in cord blood (~ 2.65 mmol/L and ~ 1.75 mmol/L, respectively), while the main calcification inhibitor fetuin-A is not elevated (~0.35 g/L). This unfavourable combination should theoretically result in increased calcification propensity, i.e. low T50 values.

In contrast, and thus quite unexpectedly, Prof. Smith and his team* from Melbourne, Australia, found a low calcification propensity in the cord blood from 20 newborns with T50 values as high as ~454 min. For comparison: normal adults ~298 min., dialysis patients ~218 min.

These high T50 values could not be explained even upon extensive seach for increased concentrations of other calcification inhibitors (magnesium, pyrophosphate, albumin and others).

It was thus concluded by the authors that «the ability of cord blood serum to strongly resist de novo crystallisation [...], is consistent with the presence of unidentified, possibly infant-specific, inhibitory substances retarding CPP transformation.»

Commentary by Prof. Andreas Pasch:
This is a nice example of how mother nature controls high mineralization pressure to avoid calcification. Fetuses need mineral, i.e. calcium and phosphate to build bone. Before birth, mineral enters the fetus via cord blood, after birth via mother's milk. Understanding how exactly newborns handle and control this high mineral pressure may even be helpful for the development of drugs directed against accelerated calcification in adults. Understanding the physiology and pathophysiology of the CPP/T50 mineral buffer system (Figure) will be decisive in this regard.

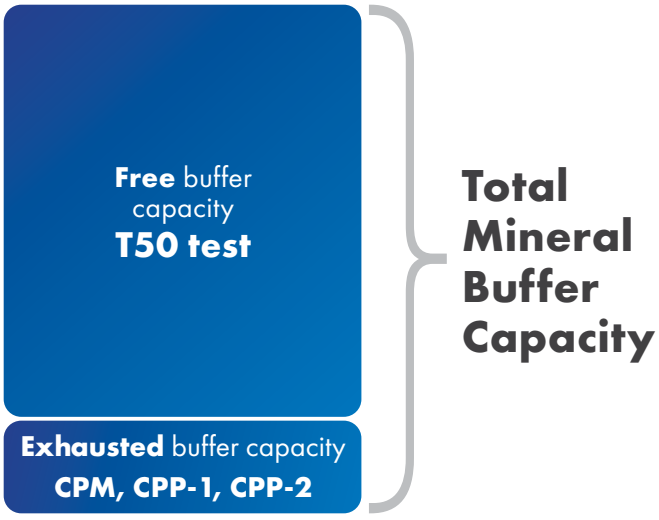
***Cord blood effectively resists mineralization through mechanisms that stabilize calciprotein particles.** Smith, ER, Champion de Crespigny, PJ, Vally, F, Toussaint, ND, Cade, TJ, Holt, SG. Kidney Int. 2023, 103(4):782-786.

Editorial Commentary: Solving the insoluble: calciprotein particles mediate bulk mineral transport. Jahnen-Dechent, W, Pasch, A. Kidney Int. 2023, 103(4):663-665.

The *Mineral Buffer System* in blood controls mineralization pressure. The free buffer capacity can be measured by the T50 test. In contrast, particles containing calcium phosphate mineral represent the already used, „exhaused buffer capacity". The physiological and pathophysiological significance of this system is subject to intensive research. This also became evident at a recent Gordon Research Conference on *The Cellular Effects and Regulation of Phosphate Homeostasis* in Galveston, TX, February 12 - 17, 2023.

Please note, that the proportions shown here are not drawn to scale.

CPM: Calciprotein Monomers
CPP: Calciprotein Particles



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SHORT OVERVIEW:
T50, CALCIPROTEIN PARTICLES (CPP) AND MINERAL BUFFER SYSTEM

Calciprotein particles (CPP, Fig. 1) are naturally occurring circulating nanoparticles. They consist of calcium, phosphate and specific proteins, mainly fetuin-A, and other bioactive molecules. CPP are a part of the body's recently discovered **mineral buffer system**, i.e. the physiological system to control precipitation and to facilitate the transportation and excretion of calcium phosphate mineral. The mineral buffer system is fundamental for cardiovascular health and healthy aging.

CPP2 induce *oxidative stress, inflammation and calcification*. In contrast, CPP1 are regarded as relatively non-toxic. This dichotomous CPP system resembles the cholesterol system of LDL ("bad cholesterol") and HDL ("good cholesterol").

T50 is a unique diagnostic blood test that measures the transformation from CPP1 to CPP2 *in vitro* (Fig. 1). The result is given in minutes (Fig. 2). A rapid transformation time (low T50) is associated with poor prognosis (all-cause mortality, cardiovascular mortality, calcification progression and others) (Fig. 3). Consequently, T50-guided treatments are expected to considerably improve patient prognosis.

Research interest in CPP and T50 continues to grow, indicating the establishment of the new and highly relevant medical field of *Calcification Medicine* (Fig. 4). Given their close association with prognosis, T50 and CPP may also become important novel targets for drug development.

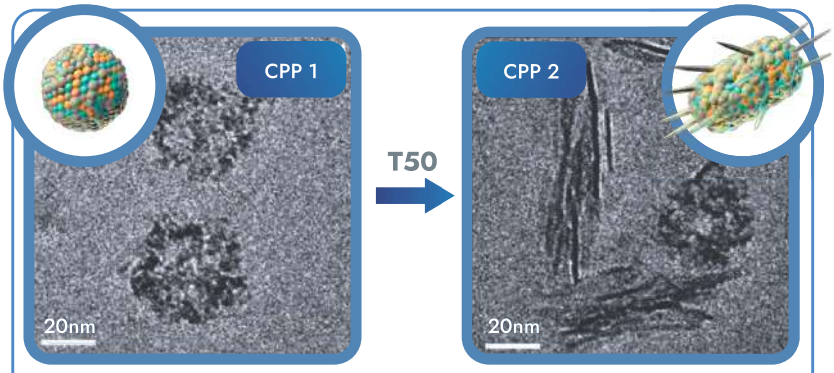

Figure 1: Electron microscopy of CPP 1 and CPP 2. T50 measures the transformation from CPP 1 to CPP 2 *in vitro*.

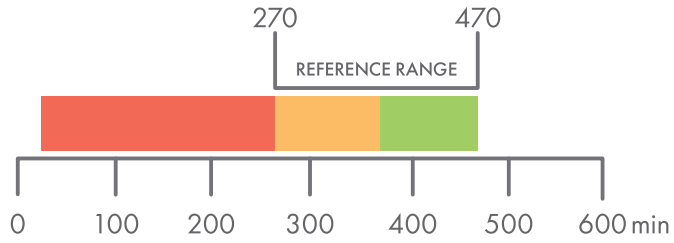

Figure 2: T50 reference range. Colors are for illustration purposes only.

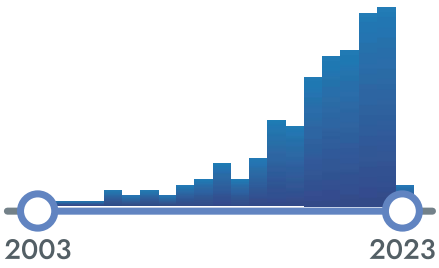

Figure 4: Pubmed listed publications on "calcification propensity" and/or "calciprotein particles" as of early 2023 (202 results).

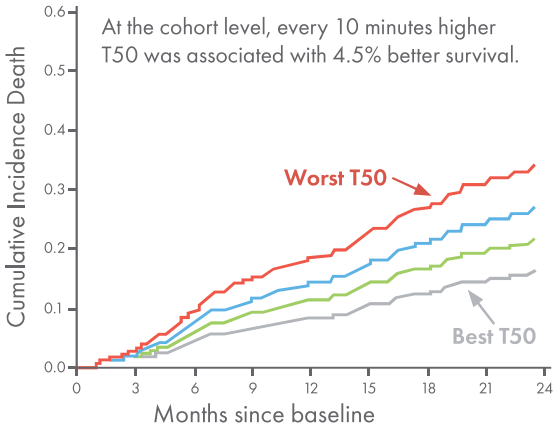

Figure 3: Kaplan-Meier survival plot of ~800 prevalent dialysis patients by T50 value. Lowest (= worst) T50 is associated with highest mortality rate.

References for the statements made here are provided upon request.

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If you want to know more, or want to have T50 or CPP measured in your research samples, please contact:
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