Norma Christine Grandi
Dr. sc. hum.

Markers of Bone Metabolism as Prognostic Factors for Cardiovascular Disease

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Dr. med. H. Brenner

25-Hydroxyvitamin D (25-OH-D), parathyroid hormone (PTH), calcium and phosphate, for long known to be key parameters in bone metabolism, have recently been linked to cardiovascular diseases (CVD), as well. Since longitudinal studies in healthy populations and populations with pre-existing coronary heart disease are still sparse and CVD account for more deaths worldwide than any other disease, it would be desirable to elucidate possible associations of bone markers with prognosis in order to explore further potential for prevention.
The objective of the present work was therefore to conduct a systematic review and meta-analysis in order to summarize current evidence on prospective studies reporting on the association of 25-OH-D levels with primary or secondary cardiovascular event incidence and mortality in healthy populations and populations with pre-existing coronary heart disease. Furthermore, the prognostic value of baseline 25-OH-D, PTH, calcium and phosphate (and their product) and of 25-OH-D levels measured after one year of follow-up for secondary cardiovascular event incidence and all-cause mortality should be analyzed in a population with stable coronary heart disease after an acute event and rehabilitation (KAROLA study).
For the review, a systematic literature search in EMBASE and Pubmed-Medline databases was performed until November 2009. Prospective studies published in English were selected reporting estimates for the association of 25-OH-D with primary or secondary cardiovascular event incidence or mortality in the general population or subjects with prevalent CVD. Pooled risk estimators were derived by meta-analysis using a random effects model approach.
For the analyses of prognosis, serum-25-OH-D, PTH, calcium and phosphate-levels were measured in a cohort of initially 1206 CHD-patients from two German clinics undergoing a 3-week rehabilitation programme after an acute cardiovascular event and participants were followed for up to 8 years. Multivariate Cox-regression analysis was employed to obtain risk estimates for cardiovascular event incidence and all-cause mortality according to different marker levels (continuous levels or different categories).
Four incidence and five independent mortality studies were included in the systematic review. Two incidence and three mortality studies reported a two- to five-fold risk increase for both outcomes in subjects with lower 25-OH-D, while the others did not detect a significant association. Meta-analysis supported the existence of an inverse association. As to analyses in the KAROLA population, unadjusted partially significant associations of the lowest vs. highest category of 25-OH-D with both outcomes were attenuated in the case of 25-OH-D levels measured at one-year follow-up (cardiovascular event incidence: hazard ratio (HR) [95% confidence interval] $HR_{<15ng/ml}$=1.55 [0.82-2.95]; mortality: $HR_{<15ng/ml}$=1.38 [0.70-2.71)), and entirely disappeared in the case of 25-OH-D levels measured at baseline (cardiovascular event incidence: $HR_{<15ng/ml}$=0.90 [0.41–1.96]; mortality: $HR_{<15ng/ml}$=0.93 [0.39–2.21]) after adjustment for cardiovascular risk factors. By contrast, age- and sex-adjusted Cox-regression analysis yielded statistically significant positive associations of PTH with both cardiovascular event incidence and all-cause mortality (HR per standard deviation increase: 1.35 [1.21-1.51] and 1.25 [1.11-1.42], respectively). Associations remained essentially unchanged after additional adjustment for multiple cardiovascular risk factors.

However, strong risk elevation was mostly confined to above-normal levels of PTH. Concerning calcium, phosphate and their product, no significant risk elevations were observed for secondary cardiovascular event incidence. High calcium levels and the calcium/albumin ratio, however, were strongly predictive for mortality risk in adjusted models ($HR_{Q4vs.Q1}$=2.39 [1.22-4.66]; ($HR_{Q4vs.Q1}$=2.66 [1.35-5.22]), respectively).

Unlike summarized data from previous investigations, results in the KAROLA population did not statistically confirm an independent inverse association of 25-OH-D levels for with any outcome. Likewise a predictive value of PTH for the prognosis in patients with stable coronary heart disease was restricted to abnormal marker levels, highlighting possible differences between previously described healthy populations and this diseased cohort. Finally, calcium and the ratio of calcium with albumin, its major binding protein, were highly predictive for all-cause mortality among patients with coronary heart disease which was not previously reported. However, given the small number of longitudinal studies, more research is needed to evaluate a potential prognostic value of markers of bone metabolism for CVD incidence and mortality and to elucidate the underlying mechanisms and the clinical implications of the associations found.