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Associations between calcium-phosphate metabolism and coronary artery calcification; a cross sectional study of a middle-aged general population

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ABSTRACT

Background and aims: High serum calcium-phosphate levels are associated with increased risk of cardiovascular disease (CVD) in patients with chronic kidney disease. Recent studies have demonstrated this relationship also in subjects with normal kidney function. Our aim was to examine whether calcium-phosphate metabolism is associated with the presence and extent of coronary artery calcification (CAC) in asymptomatic and apparently healthy individuals.

Methods: Serum samples from 1088 randomly recruited middle-aged men and women without known CVD and diabetes (DM), from the general population, were analysed for total calcium, phosphate, parathyroid hormone (PTH) and 25-hydroxyvitamin D (25(OH)D). CAC was measured by a non-contrast cardiac CT scan and categorised into four groups: 0, 1–99, 100–399, ≥400 Agatston units. The association of calcium-phosphate metabolism with CAC was evaluated by a multiple ordered logistic regression model. All the multiple regression analyses were performed in the entire cohort as well as in men and women separately.

Results: In the study population, 96% of the serum calcium values, 93% of the PTH values, 90% of the phosphate values, and only 64% of the 25(OH)D values were placed within the normal range.
In men, the odds of being in a higher CAC category, i.e. having more severe CAC, increased by 30% when serum calcium concentration increased by 0.1 mmol/l (95% CI: 1.04–1.61, $p = 0.019$), independently of traditional cardiovascular risk factors. In women, no significant association between serum calcium and CAC was identified (OR 0.99, 95% CI: 0.81–1.21, $p = 0.91$). Neither phosphate, PTH nor 25(OH)D was significantly associated with CAC in men, in women or when performed in the entire cohort.

Conclusions: Serum calcium, even with values within normal range and independent of traditional risk factors, was significantly associated with CAC in asymptomatic and apparently healthy middle-aged men, but not in women.

1. Introduction

Despite improved primary prevention and treatment over the

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last decades, cardiovascular disease (CVD) still remains the major cause of death, globally [1]. Risk stratification and modification are based on the traditional cardiovascular risk factors e.g. Systematic Coronary Risk Evaluation (SCORE) [2] and the Framingham Risk Score [3]. However, the general rather than individual approach of these methods has been criticised for some time [4,5]. Therefore, new non-traditional cardiovascular risk factors linked to early stages of the atherosclerotic process have been extensively investigated in an attempt to provide individualized risk assessment, and hereby further improve residual risk reduction.

The calcium-phosphate homeostasis is a complex system involving several hormones including parathyroid hormone (PTH), fibroblast growth factor 23 and vitamin D. Serum calcium and phosphate levels are strictly regulated within a narrow range and are involved in multiple physiological processes, including signal transduction, membrane transport, energy production, bone mineralization and vascular function [6]. Imbalance in the calcium-phosphate homeostasis has for a considerable time been known to be a major non-traditional cardiovascular risk factor in individuals with chronic kidney disease [7,8]. Recent studies suggest that serum calcium and phosphate might also be related to subclinical CVD in individuals with preserved renal function [9–11]. Data addressing potential relationships between calcium-phosphate metabolism and subclinical CVD in a healthy Caucasian general population are limited.

For this reason we aimed for this study to investigate whether calcium-phosphate metabolism was associated with the presence and extent of coronary artery calcifications (CAC) detected by cardiac computed tomography, as a marker of subclinical CVD, in an asymptomatic and apparently healthy cohort of middle-aged men and women from the general population.

2. Materials and methods

2.1. Study design and participants

The Danrisk Study is a prospective multicentre cohort study designed to study the relationship between traditional cardiovascular risk factors and subclinical CVD (measured by CAC) in a middle-aged asymptomatic general population free of known CVD and/or diabetes.

The Danrisk study has previously been described in detail [12]. Briefly, the cohort was established in 2009–2010 based on random retrieval from the Danish national civil registry (N = 1825). Initially, distribution of gender, area of residence and year of birth (1949 or 1959) were equal. A total of 1257 subjects (69%) accepted the invitation to undergo cardiovascular risk evaluation and were examined in one of four regional centres (Odense, Esbjerg, Svendborg or Vejle). Participants with diabetes (defined as fasting blood glucose ≥7.1 mmol/l on two different days or postprandial plasma glucose ≥11.1 mmol/l or treatment with antidiabetic agents) or known CVD (such as MI, revascularisation and stroke) were excluded (n = 100).

In this cross sectional study of the DanRisk cohort we further excluded participants with missing or insufficient biobank material (n = 57), as well as participants with eGFR<60 ml/min/1.73m2 (n = 12). As a result, in total 1088 subjects with normal kidney function, free of CVD and diabetes remained to be included in this study (Fig. 1).

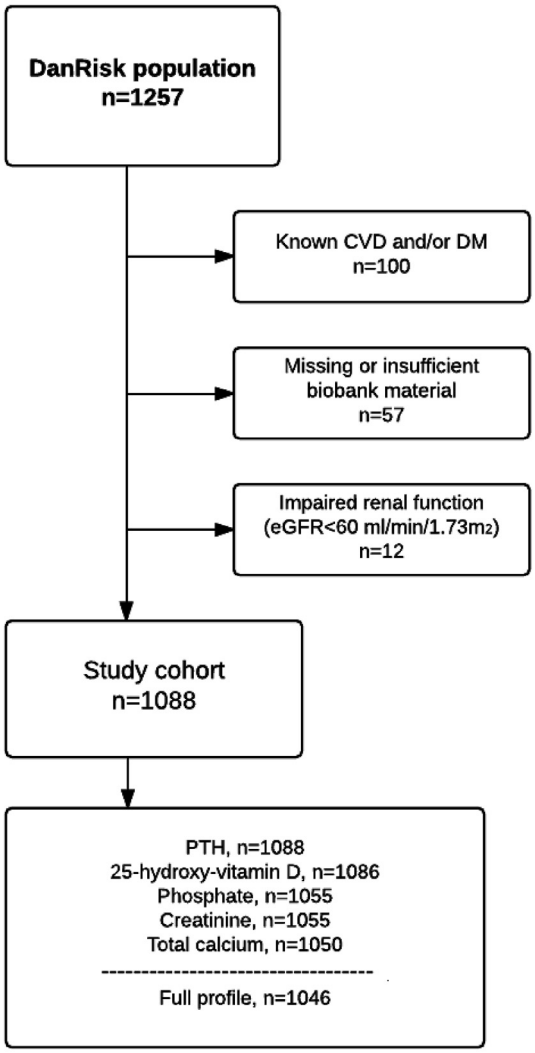

Fig. 1. Study population flowchart.

2.2. Cardiovascular risk factors

At baseline, all participants completed a questionnaire regarding their use of medication, previous diseases, smoking status and family history of CVD. Study personnel completed the medical history, and measured weight, height, waist circumference as well as blood pressure. In addition, blood samples were drawn and analysed, and a biobank was established. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or treatment with calcium channel blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor antagonist, β-blocker and/or thiazides (n = 515). Hypercholesterolemia was defined as total cholesterol ≥5.0 mmol/l, LDL-cholesterol ≥3.0 mmol/l or treatment with statins (n = 822). Antiplatelet treatment was defined as the use of platelet aggregation inhibitors excluding heparin.

A non-contrast cardiac CT-scan was performed to evaluate CAC. CAC was assessed by summing the scores from all foci in the coronary arteries and expressed in Agatston units (AU) [13]. Diederichsen et al. [12] have previously reported the CT-scan specifications and technical settings.

2.3. Biochemical analyses

Levels of vitamin D, calcium, phosphate, PTH and creatinine