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Lower bone turnover markers in metabolic syndrome and diabetes: The population-based Study of Health in Pomerania

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Abstract *Background and aims:* Accumulating evidence demonstrates an important interaction between bone and energy metabolism. We aimed to study the associations of three bone turnover markers (BTM: osteocalcin, beta-crosslaps, procollagen type 1 N-terminal propeptide) as well as of 25-hydroxyvitamin D and parathyroid hormone with metabolic syndrome (MetS) or type 2 diabetes mellitus (T2DM) in a large population-based cohort.
Methods and results: This cross-sectional study comprised 2671 adult men and women participating in the first follow-up of the population-based Study of Health in Pomerania (SHIP-1). Multivariable logistic regression analyses were performed to assess sex-specific associations between the BTMs, 25-hydroxyvitamin D or parathyroid hormone and metabolic disease. All models were adjusted for age, body mass index, smoking status, physical activity, estimated glomerular filtration rate and month of blood sampling. The models for women were further adjusted for menopausal status. Higher BTM or 25-hydroxyvitamin D concentrations were associated with significantly lower odds for metabolic disease, while there was no association between parathyroid hormone and MetS or T2DM.
Conclusion: Our results contribute to the accumulating evidence of a cross-sectional association between high BTM or 25-hydroxyvitamin D concentrations and a lower prevalence of MetS or T2DM. Further research is necessary to evaluate the mechanisms underlying these results.

Introduction

There is accumulating evidence showing an important interaction between bone and energy metabolism [1]. On the one hand, it was suggested that adipose tissue-derived hormones such as leptin control bone mass [1]. On the other hand, there is an endocrine regulation of energy metabolism by the skeleton mediated via hormones such as osteocalcin (OC) [2]. An increasing number of studies report associations of low OC concentrations with obesity as well as with type 2 diabetes mellitus (T2DM) [1]. Next to OC, also vitamin D has been suggested as important factor in the pathogenesis of metabolic syndrome (MetS) and T2DM [3]. While there is a relatively large body of evidence showing an important role of OC as well as vitamin D in the development of MetS and T2DM [1,4], the role of other bone turnover markers (BTM) such as beta-

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crosslaps (CTX) or procollagen type 1 N-terminal propeptide (PINP) is less well studied. Lower bone remodelling has, however, been proposed as a factor contributing to the impaired bone quality observed in MetS [5].

So far, there is no large population-based study, covering all relevant age groups, that investigates the association of CTX or PINP with MetS or T2DM. Previous studies [5–12] addressing this association were mainly based on small study samples, included only older men or postmenopausal women, and revealed conflicting results. Some studies reported that CTX and PINP concentrations are lower in patients with MetS [5,7,8]. Other studies demonstrated that bone resorption is enhanced in T2DM [9] and that a reduction in blood glucose concentrations in diabetic subjects is associated with a decrease in CTX concentrations [11]. Further studies failed to detect independent associations of CTX or PINP with MetS [6,12] or T2DM [10].

In view of these previous inconsistent results and the lack of evidence from population-based studies including younger subjects, we aimed to study the cross-sectional associations of three BTMs (OC, CTX, PINP) as well as 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH) with MetS or T2DM in a large population-based cohort.

Methods

Study population

The Study of Health in Pomerania (SHIP) is a population-based study in northeast Germany [13]. For the baseline study (SHIP-0) a representative sample of 7008 men and women aged 20–79 years was drawn and 4308 individuals underwent the examinations. The first follow-up examination (SHIP-1) was conducted with 3300 subjects, aged 25–88 years. Serum BTM, 25(OH)D and PTH concentrations were measured in SHIP-1 but not in SHIP-0, thus the present study was restricted to cross-sectional analyses in SHIP-1. All participants provided written informed consent. The study conformed to the principles of the Declaration of Helsinki as reflected by an a priori approval of the Ethics Committee of the University of Greifswald.

Interview and physical examinations

All SHIP-1 participants underwent standardized medical examinations including measurements of height, weight, and waist circumference. Current smoking status (yes/no) and physical activity (yes/no) were defined according to self-report.

Non-fasting blood samples were taken from the cubital vein of subjects in the supine position between 8 a.m. and 8 p.m. Serum OC, CTX, PINP, 25(OH)D and PTH concentrations were determined on the IDS-iSYS Multi-Discipline Automated Analyser (Immunodiagnostic Systems Limited, Frankfurt am Main, Germany). Further laboratory methods are described in Supplemental Table 1. Systolic and diastolic blood pressures were measured using an oscillometric digital blood pressure monitor (HEM-705CP, OMRON Corporation, Tokyo, Japan). Women younger than 40 years of age as well as women between 40 and 60 years of age, who reported menstrual cycling, were defined as premenopausal, all other women as postmenopausal. Intake of medication was classified using the anatomical therapeutic chemical classification system (ATC). The following substances were defined as influencing bone metabolism: bisphosphonates, selective estrogen receptor modulators, parathyroid hormone, vitamin D, calcium, steroids, testosterone, oral contraceptives and postmenopausal hormone therapy. Antihypertensive treatment was defined based on self-reported and ATC code C02, antidiabetic treatment as intake of oral antidiabetic drugs or insulin, lipid-lowering treatment as intake of fibrates or nicotinic acids.

Definition of MetS and T2DM

MetS was defined when at least three of five diagnostic criteria were fulfilled: waist circumference $\geq$94 cm (men) or $\geq$80 cm (women); non-fasting glucose $\geq$8 mmol/l or antidiabetic treatment; HDL-cholesterol $<$1.0 mmol/l (men) or $<$1.3 mmol/l (women), or lipid-lowering treatment; non-fasting triglycerides $\geq$2.3 mmol/l or lipid-lowering treatment; blood pressure $\geq$130/85 mmHg or antihypertensive treatment. This definition is based on the criteria by Alberti et al. [14] but adapted to compensate for the non-fasting blood sampling conditions. T2DM was defined when subjects reported either a respective physician's diagnosis, antidiabetic treatment, had non-fasting glucose levels $\geq$11.1 mmol/l or HbA1c $\geq$ 6.5% and had no type 1 diabetes mellitus (T1DM).

Exclusions

For the present analyses we excluded 104 participants with missing information in outcome or exposure. Moreover, 96 subjects with missing information in confounders or renal function, renal insufficiency [estimated glomerular filtration rate (eGFR) $<$ 30 ml/min/1.73 m^2], missing information on, or history of, liver disease were excluded. Furthermore, 41 subjects with T1DM, PTH $>$120 pg/ml, alcohol consumption $>$400 g/day, pregnant women and 388 subjects using medication that influences bone metabolism were excluded. This resulted in a final study population of 2671 subjects (1449 men and 1222 women).

Statistical analyses

Continuous data are expressed as median (1st–3rd quartile), categorical data as proportions. Proportions of MetS or T2DM were reported for quintiles of BTMs, 25(OH)D and PTH. Group comparisons were performed using Kruskal–Wallis (continuous data) or χ^2-squared (categorical data) tests. Due to marked sex differences in BTMs and significant interactions between sex and OC or CTX, sex-specific analyses were performed. Further, the risk for metabolic disease strongly increases with aging and BTMs