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The association between plasma homocysteine levels and bone quality and bone mineral density parameters in older persons

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ABSTRACT

Introduction: High plasma homocysteine levels have been associated with incident osteoporotic fractures, but the mechanisms underlying this association are still unknown. It has been hypothesized that homocysteine might interfere with collagen cross-linking in bone, thereby weakening bone structure. Therefore, we wanted to investigate whether plasma homocysteine levels are associated with bone quality parameters, rather than with bone mineral density.

Methods: Cross-sectional data of the B-PROOF study (n = 1227) and of two cohorts of the Rotterdam Study (RS-I (n = 2850) and RS-II (n = 2023)) were used. Data on bone mineral density of the femoral neck and lumbar spine were obtained in these participants using dual-energy X-ray assessment (DXA). In addition, participants of B-PROOF and RS-I underwent quantitative ultrasound measurement of the calcaneus, as a marker for bone quality. Multiple linear regression analysis was used to investigate the associations between natural-log transformed plasma levels of homocysteine and bone mineral density or ultrasound parameters.

Results: Natural-log transformed homocysteine levels were inversely associated with femoral neck bone mineral density in the two cohorts of the Rotterdam Study (B = −0.025, p = 0.004 and B = −0.024, p = 0.024). In B-PROOF, no association was found. Pooled data analysis showed significant associations between homocysteine and bone mineral density at both femoral neck (B = −0.032, p = 0.010) and lumbar spine (B = −0.098, p = 0.021). Higher natural-log transformed homocysteine levels associated significantly with lower bone ultrasound attenuation in B-PROOF (B = −3.7, p = 0.009) and speed of sound in both B-PROOF (B = −8.9, p = 0.001) and RS-I (B = −14.5, p = 0.003), indicating lower bone quality. Pooled analysis confirmed the association between homocysteine and SOS (B = −13.1, p = 0.016). Results from ANCOVA-analysis indicate that differences in SOS and BUA between participants having a plasma homocysteine level above or below median correspond to 0.14 and 0.09 SD, respectively.

Discussion: In this study, plasma levels of homocysteine were significantly inversely associated with both bone ultrasound parameters and with bone mineral density. However, the size of the associations seems to be of limited clinical relevance and may therefore not explain the previously observed association between plasma homocysteine and osteoporotic fracture incidence.

Introduction

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and increased fracture risk [1]. Osteoporotic fractures are a major health care problem, since they lead to a significant increase in morbidity and mortality [2]. For example, excess mortality rates in the first year after a hip fracture vary from 12% to 35% [3]. Due to a continuing rise in life expectancy and aging of the population, the economic burden of osteoporotic fractures in Europe is expected to increase substantially in the coming decades; from €36.3 billion in 2000 to €76.8 billion in 2050 [4].

Moderately elevated plasma homocysteine (Hcy) levels have been associated with osteoporotic fracture incidence [5–7]. However, the mechanisms underlying the association between Hcy and osteoporotic

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fractures have not yet been unraveled. In literature, conflicting results concerning the association between Hcy and bone mineral density (BMD) exist; inverse [8,9], mixed [10] and no associations [7,11,12] have been reported. A recent meta-analysis in women showed no significant association between Hcy and BMD [13]. A meta-analysis in men was not possible. It therefore remains not fully certain whether the major pathway underlying the association between Hcy and osteoporotic fractures includes BMD. It has also been hypothesized that Hcy may interfere with the collagen cross-linking in the bone, thereby weakening bone structure [14]. Since the bone structure and micro-architecture are not completely captured by BMD, which measures the amount of mineralized bone in an area, it has been suggested that quantitative ultrasound (QUS) measurement might be more suitable for determining bone quality [15]. Bone micro-architecture has been shown to be a determinant of QUS-parameters, independent of BMD [16]. In addition, QUS has been proven to predict fracture risk to a similar degree as does BMD measured using dual-energy X-ray assessment (DXA) [17,18]. More importantly, both QUS and DXA predict fracture incidence partly independently of each other [19], as was recently confirmed in an updated meta-analysis [27]. Two studies investigating the association between Hcy and QUS parameters have been published [9,20], showing an inverse association in women only.

Thus, data concerning the association between Hcy and bone quality are relatively scarce, and the association between Hcy and BMD remains inconsistent. We therefore analyzed cross-sectional data from three large Dutch studies to investigate the association between Hcy and BMD. In one of these studies, associations between Hcy and QUS parameters were studied as well.

Methods

Design and study population

In this study, data of three studies (B-PROOF, Rotterdam Study-I and Rotterdam Study-II) were analyzed, both per cohort and pooled where applicable.

B-vitamins in the PRevention Of Osteoporotic Fractures (B-PROOF)

In the current study, baseline data of a subsample of the B-PROOF-study with data on bone parameters available were used. The B-PROOF-study is a multicenter, double-blind, randomized, placebo-controlled trial investigating the effect of a 2-year daily oral supplementation with 500 μg of vitamin B_{12} and 400 μg of folic acid on fracture incidence. The study population consists of 2919 Dutch men and women aged 65 years and over who have elevated plasma levels of Hcy (12–50 μmol/l) and normal serum creatinine levels (<150 μmol/l). Details on the B-PROOF study design and population have been described elsewhere [21]. QUS-measurements were performed in a random subsample of persons who were screened for participation, and of whom levels of Hcy were not available yet (n = 2185). DXA-measurements were done in a subsample of included participants (Hcy ≥ 12 μmol/l) who were able to visit one of the study centers. In total, of the participants having Hcy ≥ 12 μmol/l 627 participants underwent both DXA and QUS-measurements, while 600 underwent DXA only and 618 underwent QUS-measurement only (Fig. 1). In addition, QUS-measurements were performed in 940 participants who turned out to be excluded from further participation in the B-PROOF-trial based on the exclusion criterion of a plasma Hcy-level < 12 μmol/l. The Wageningen University Medical Ethics Committee approved the study protocol, and the Medical Ethics committees of Erasmus MC and VUmc gave approval for local feasibility. All participants, including those who were not eligible for the trial, gave written informed consent.

Rotterdam Study (RS-I and RS-II)

The Rotterdam Study is an ongoing, population-based cohort study among people aged 55 years or over, who reside in the Ommoord district of the city of Rotterdam in the Netherlands. The Rotterdam Study was designed to investigate chronic, disabling diseases. Its rationale and design have been described previously [22]. The participants in the current study are part of either the Rotterdam Study-I (RS-I) or the RS-II cohort. Baseline measurements in the RS-I cohort were performed between 1990 and 1993 (RS-I-1). This cohorts' second follow-up visit after baseline took place between 1997 and 1999 (RS-I-3). Measurements and blood drawing performed at this second visit are used for cross-sectional analysis in the current study. Enrollment to the RS-II cohort started in 2000 and baseline data (RS-II-1) collected at that visit are used in the current study. From the RS-I and RS-II cohorts, 2859 and 2023 participants who underwent DXA were included in the analyses, respectively. In addition, QUS-parameters were available in 744 persons from the RS-I cohort.

The Rotterdam Study was conducted according to the Declaration of Helsinki and approved by the medical ethics committee of Erasmus MC. All participants gave written informed consent.

Measurements

Bone mineral density (B-PROOF and Rotterdam Study)

In the B-PROOF-study, BMD-measurements were performed at two study centers (VUmc or Erasmus MC). DXA was used to measure femoral neck (FN) and lumbar spine (LS) BMD (g/cm^2) under standard protocols

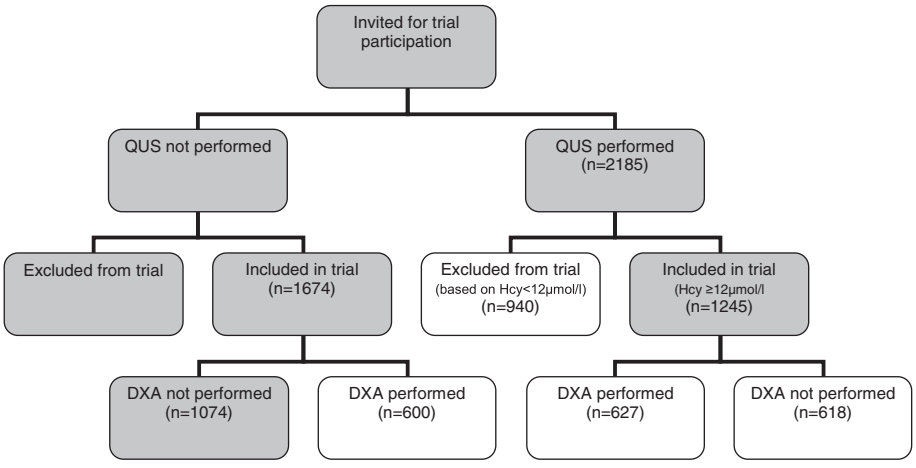

Fig. 1. Flow-chart describing number of B-PROOF-participants with data on DXA and/or QUS. (White blocks represent participants with QUS and/or DXA measured at baseline included in the current, cross-sectional analyses.)