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The association between insulin use and volumetric bone mineral density, bone micro-architecture and bone strength of the distal radius in patients with type 2 diabetes – The Maastricht study

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ABSTRACT

Type 2 diabetes mellitus (T2DM) has been associated with an increased risk of fractures, despite normal to increased bone mineral density (BMD). Insulin use is one of the factors linked to this increased fracture risk. However, direct negative effects of insulin on bone quality are not expected since insulin is thought to be anabolic to bone. In this cross-sectional study the association between insulin use and volumetric BMD (vBMD), bone micro-architecture and bone strength of the distal radius, as measured with HR-pQCT, was examined. Data from 50 participants with T2DM of The Maastricht Study (mean age 62 ± 7.5 years, 44% women) was used. Participants were classified as insulin user (n = 13) or non-insulin user (n = 37) based on prescription data. Linear regression analysis was used to estimate the association between current insulin use and HR-pQCT derived parameters. After adjustment for age, sex, body mass index, glycated hemoglobin A1c and T2DM duration, insulin use was associated with lower total vBMD (standardized beta (β): −0.56 (95% CI: −0.89 to −0.24)), trabecular vBMD (β: −0.58 (95% CI: −0.87 to −0.30)), trabecular thickness (β: −0.55 (95% CI: −0.87 to −0.23)), cortical thickness (β: −0.41 (95% CI: −0.74 to −0.08)), log cortical pore volume (β: −0.43 (95% CI: −0.73 to −0.13)), bone stiffness (β: −0.39 (95% CI: −0.62 to −0.17)) and failure load (β: −0.39 (95% CI: −0.60 to −0.17)) when compared to the non-insulin users. Insulin use was not associated with cortical vBMD, trabecular number, trabecular separation, cortical porosity and cortical pore diameter. This study indicates that insulin use is negatively associated

Abbreviations: aBMD, areal bone mineral density; AGE, advanced glycation end product; ATC, anatomical therapeutical chemical; β, standardized beta; BMD, bone mineral density; CI, confidence interval; HbA1c, glycated hemoglobin A1c; HR-pQCT, high resolution peripheral quantitative tomography; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; vBMD, volumetric bone mineral density.

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with bone density, bone micro-architectural and bone strength parameters. These findings may partly explain the previously observed increased fracture risk in insulin users, although there may be residual confounding by other factors related to disease severity in insulin users.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic disease leading to complications such as neuropathy, retinopathy and nephropathy [1]. More recently, T2DM has been associated with an increased risk of fractures, despite a normal to increased bone mineral density (BMD) [2,3]. The mechanisms leading to this increased fracture risk are not completely elucidated, but both an increased falling frequency and bone fragility are thought to contribute to the increased fracture risk [4,5]. Bone fragility can be the result of various factors, and in patients with T2DM, among others, unfavorable changes in micro- and macro-architecture of the bone, accumulation of advanced glycation end products (AGEs) in bone collagen and a low bone turnover have been reported [4,5].

The use of antihyperglycemic drugs may also contribute to the increased fracture risk. Except for thiazolidinediones, oral antihyperglycemic drugs are not associated with an increased fracture risk [6,7] However, insulin has been associated with an increased fracture risk [7]. Since previous studies showed that insulin may be anabolic to bone [8] it has been hypothesized that the increased fracture risk in insulin users is not caused by the drug itself. It is rather due to an increased falling frequency and to the long-term negative effects of hyperglycemia on bone quality, as insulin is most often used in patients with long disease duration.

The association between hyperinsulinemia and areal BMD (aBMD) in nondiabetic participants, as measured with DXA, has been examined in several studies that demonstrated a positive association between hyperinsulinemia and aBMD [9–11]. However, only two small studies have examined the association between insulin therapy and aBMD in patients with T2DM. Both showed a positive correlation between insulin dose and aBMD [12,13].

High resolution peripheral quantitative computed tomography (HR-pQCT) is a relatively new technique which can be used to measure volumetric BMD (vBMD), micro-architecture and bone strength [14,15]. The association between insulin use and bone parameters measured by HR-pQCT has not been studied before [7]. Therefore, the aim of this study was to examine the association between insulin use and vBMD, bone micro-architecture and bone strength in participants with T2DM. It is hypothesized that insulin use will be positively associated with HR-pQCT derived parameters when compared to non-insulin use.

2. Materials and methods

2.1. Source population

Data from The Maastricht Study, an ongoing observational prospective population-based cohort study, was used in the present study. The rationale and methodology have been described previously [16]. In brief, the study focuses on the etiology, pathophysiology, complications and comorbidities of T2DM and is characterized by an extensive phenotyping approach. Eligible participants were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns as well as from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency.

To determine glucose metabolism status, all participants, except those who used insulin, underwent a standardized 2-h 75 g oral glucose tolerance test (OGTT) after an overnight fast. For safety reasons, participants with a fasting glucose level > 11.0 mmol/l (>200.0 mg/dl), as determined by a capillary blood glucose measurement, did not undergo the OGTT. Fasting glucose level, 2-h plasma glucose level and information about diabetes medication were used to determine glucose metabolism status. Participants were classified as having T2DM when they had a fasting plasma glucose level ≥ 7.0 mmol/l (≥126 mg/dl) or a two hour plasma glucose level ≥ 11.1 mmol/l (≥200 mg/dl) as specified by the World Health Organization guidelines [17] or if they used antihyperglycemic drugs at baseline. Individuals without type 1 diabetes who used antihyperglycemic drugs were classified as having T2DM. Participants who were not classified as T2DM, but did use an antihyperglycemic drug in the six months prior to the date of the HR-pQCT scan (based on their pharmacy data) were also included.

The present study includes cross-sectional data from participants with T2DM who completed the baseline survey between November 2010 and September 2013 and returned to the research center between March 2015 and February 2016 for the HR-pQCT scan of the distal radius. Dispensing records were collected at the pharmacy for all participants who gave written informed consent for the collection of their drug dispensing history. Dispensing data was available from January 1st 1991 through the date of the HR-pQCT scan and contained the product name, the anatomical therapeutical chemical (ATC) code [18], the dispensed quantity, the dispensing date and the prescribed daily dose [19]. When a participant had a prescription for insulin (ATC code A10A) in the six months before the date of the HR-pQCT scan, the participant was classified as current insulin user. All other T2DM participants were classified as non-insulin users. The mean time since first prescription of insulin was calculated from the prescription data.

The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131,088-105,234-PG). All participants gave written informed consent.

2.2. HR-pQCT imaging

The non-dominant radius was scanned on an HR-pQCT scanner (Xtreme-CT; Scanco Medical AG, Brüttisellen, Switzerland) using the standard in vivo protocol as described in literature [20,21]. If the patient has previously sustained a distal radius fracture at the non-dominant site, the dominant site was scanned. The forearm was placed into a carbon fiber cast. An anteroposterior scout projection of the scan site was acquired for positioning of the tomographic acquisition. A reference line was placed on the radial joint surface. The scan volume spanned 9.02 mm in length and started 9.5 mm from the reference line in the proximal direction. Images were reconstructed using an isotropic voxelsize of 82 μm, resulting in 110 consecutive slices. Total scan time was 2.8 min, with each acquisition resulting in an effective dose of approximately 3 μSv. All scans were graded with regard to motion, and scans with quality 4 or 5 were repeated once [22]. Only scans with quality 1 to 3 were used for subsequent image analysis [23].

2.3. Image analysis of HR-pQCT scans

All scans were evaluated using the standard patient evaluation protocol that was provided by the manufacturer and that has been described previously in detail [24–26]. First, the periosteal contour was automatically derived and manually modified when contours visually deviated from the periosteal boundary [27]. The images were