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Review

Biochemical bone turnover markers in diabetes mellitus — A systematic review

Jakob Starup-Linde [a,b,*], Peter Vestergaard [b,c]

[a] Department of Endocrinology and Internal Medicine, Aarhus University Hospital THG, Aarhus, Denmark
[b] Department of Clinical Medicine, Aalborg University Hospital, Aalborg, Denmark
[c] Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark

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ABSTRACT

Background: Diabetes mellitus is associated with an increased risk of fractures, which is not explained by bone mineral density. Other markers as bone turnover markers (BTMs) may be useful.
Aim: To assess the relationship between BTMs, diabetes, and fractures.
Methods: A systematic literature search was conducted in August 2014. The databases searched were Medline at Pubmed and Embase. Medline at Pubmed was searched by "Diabetes Mellitus" (MESH) and "bone turnover markers" and Embase was searched using the Emtree by "Diabetes Mellitus" and "bone turnover", resulting in 611 studies. The eligibility criteria for the studies were to assess BTM in either type 1 diabetes (T1D) or type 2 diabetes (T2D) patients.
Results: Of the 611 eligible studies, removal of duplicates and screening by title and abstract lead to 114 potential studies for full-text review. All these studies were full-text screened for eligibility and 45 studies were included. Two additional studies were added from other sources. Among the 47 studies included there were 1 meta-analysis, 29 cross-sectional studies, 13 randomized controlled trials, and 4 longitudinal studies. Both T1D and T2D were studied. Most studies reported fasting BTM and excluded renal disease.
Conclusion: Markers of bone resorption and formation seem to be lower in diabetes patients. Bone specific alkaline phosphatase is normal or increased, which suggests that the matrix becomes hypermineralized in diabetes patients. The BTMs: C-terminal cross-link of collagen, insulin-like growth factor-1, and sclerostin may potentially predict fractures, but longitudinal trials are needed. This article is part of a Special Issue entitled Bone and diabetes.

Contents

Abbreviations: 25 OHD, 25 hydroxy vitamin D; BMD, bone mineral density; BAP, bone specific alkaline phosphatase; BTM, bone turnover marker; PICP, carboxy-terminal propeptide of type I procollagen; CICP, collagen type 1C propeptide; CTX, C-terminal cross-link of collagen; DPD, deoxypyridinoline; HP, hydroxyproline; IDDM, insulin dependent diabetes mellitus; IGF-1, insulin-like growth factor-1; IVGTT, intravenous glucose tolerance test; NTX, N-terminal propeptide type 1 collagen; OGTT, oral glucose tolerance test; OC, osteocalcin; OPG, osteoprotegerin; P1NP, procollagen type 1 N-terminal propeptide; RANKL, Receptor Activator of Nuclear factor Kappa beta Ligand; TRAP, tartrate resistant acid phosphatase; ICTP, type I collagen cross-linked carboxy-terminal telopeptide; T1D, type 1 diabetes; T2D, type 2 diabetes.

* Corresponding author at: Department of Endocrinology and Internal Medicine (MEA), Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark. Fax: +45 78467684.
E-mail address: jakolind@rm.dk (J. Starup-Linde).

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1. Introduction

Diabetes mellitus is associated with an increased risk of fractures, which is not explained by bone mineral density (BMD) — at least measured by Dual energy X-ray absorptiometry (DXA) [1]. Furthermore, in the Fracture Risk Assessment Tool (FRAX) model, common risk factors and BMD underestimated the fracture risk in type 2 diabetes patients [2]. Although, many studies have investigated biochemical bone turnover markers (BTMs) in diabetes patients, no definite inferences can be made [3]. A meta-analysis reported significant heterogeneity among the biochemical markers of bone turnover as well as a dissociative pattern in formative and resorptive markers [4].

BTMs are chemical compounds whose presence can be detected in serum, plasma, or urine, and who ideally reflect bone turnover, i.e. resorption, formation or combinations of both [5].

These compounds may reflect 1) the mineralized matrix (hydroxyapatite, i.e. calcium and phosphate), 2) the non-mineralized matrix (collagen, osteocalcin (OC), matrix metalloproteinases, osteopontin, osteonectin etc.), and 3) the cellular matrix (osteoclasts, osteoblasts, and osteocytes).

The compounds may either be a part of the matrix (OC, osteonectin, and osteopontin), precursors or degradation products of the matrix (pro-collagen or cross-links of collagen), enzymes (alkaline phosphatase, tartrate resistant acid phosphatase (TRAP)), or signaling substances (OC, sclerostin).

Some compounds may have several roles (OC is a part of the unmineralized matrix, but also a signaling compound i.e. has hormonal properties, alkaline phosphatase is both an enzyme which initializes mineralization, and a marker of osteoblast function). Some compounds may thus both represent cellular function (alkaline phosphatase) and be an enzyme in the matrix.

In diabetes patients, bone and bone markers may be affected through different pathways. The marker C-terminal cross-link of collagen (CTX) was decreased by food intake [6], however the mechanism was unknown. Both an oral glucose tolerance test (OGTT) and intravenous glucose tolerance test (IVGTT) decreased CTX and OC in healthy postmenopausal women; however the OGTT induced a significantly larger decrease in CTX than the IVGTT [6]. Furthermore, it is unknown whether the differences observed between OGTT and IVGTT were related to the administration form or dose of glucose [6]. Healthy obese subjects have reduced BTM compared to controls [7]. Following OGTT the BTM decreased in both obese and controls, however the decrease in osteocalcin (OC) was significantly more pronounced in controls [7]. Different and changing medication use may also affect bone in diabetes patients and glitazones were related to an increased fracture risk in women with type 2 diabetes (T2D) [8]. The growth factors; growth hormone and insulin-like growth factor-1 (IGF-1) may be altered in diabetes and were both related to bone turnover [9]. Furthermore, comorbidities and complications to diabetes may alter BTM and modulate fracture risk.

To further explore BTM in diabetes we conducted a systematic literature search.

2. Material and methods

We used the PRISMA guidelines [10].

2.1. Data sources, searches, and eligibility criteria

A systematic literature search was conducted in August 2014. The databases searched were Medline at Pubmed and Embase. Medline at Pubmed was searched by using the key words “Diabetes Mellitus” (MESH) and “bone turnover markers” leading to 378 potential studies. Embase was searched using the Emtree with the key words “Diabetes Mellitus” and “bone turnover” limited to human studies revealing 233 potential studies. In total 611 studies were gathered. Additionally two papers [11,12], were too recently published to be indexed at the time of the literature search, but the authors found these papers by hand-searching in their respective journals. The eligibility criteria for the studies were to assess bone turnover markers in either type 1 diabetes (T1D) or T2D patients. The following BTMs were included: CTX, N-terminal propeptide type 1 collagen (NTX), TRAP, deoxypyridinoline (DPD), hydroxyproline (HP), OC, 25 hydroxy vitamin D (25 OHD), procollagen type 1 N-terminal propeptide (P1NP), collagen type 1C propeptide (CICP), bone specific alkaline phosphatase (BAP), parathyroid hormone (PTH), sclerostin, osteoprotegerin (OPG), Receptor Activator of Nuclear factor Kappa beta Ligand (RANKL), IGF-1, inflammatory markers, and pentosidine. If several studies used the same population and BTM, the studies rated as poorest were excluded. Studies included in the recent meta-analysis [4] were not included in the study, as the meta-analysis itself was included.

2.2. Data extraction and quality assessment

The data extracted from the studies were study design, randomization and intervention (if applicable), HbA1c, duration of the study (if applicable), number of participants, diabetes type, how diabetes was determined, which BTMs were measured, fasting status of the time of blood sample collection, and if the participants had renal disease. Study quality was not rated due to differences in design ranging from meta-analysis, randomized controlled trials, cohort studies, to cross-sectional studies. All the different study types had their own strengths and limitations, and were not found comparable by the authors.

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