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Systematic review of bone turnover Biochemical markers in diabetes mellitus (DM)

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Abstract: **In diabetics with low bone mass, histomorphometry research studies recommended that osteopenia was because of reduced bone development rate . Hyperglycemia has actually been linked in the pathogenesis of diabetic bone illness and, reduced activity of osteoblasts under diabetic conditions has actually been reported in both animal designs and humans. The aim of this systematic review study was to examine Biochemical bone turnover markers between patients with T1D and T2D and evaluate the effect of glucose on bone turnover, and to evaluate the evidence based which involved the discussion of BTMs in diabetes mellitus.**
A systematic literature search was conducted in September 2016. 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 more than 250 potential studies limited to human studies.
Biochemical markers of bone resorption and bone formation were lower in patients with type 2 diabetes compared to patients with type 1 diabetes. Bone turnover markers were negatively associated with p-glucose. In conclusion, some BTMs may yield the potential to predict fractures in diabetes patients.

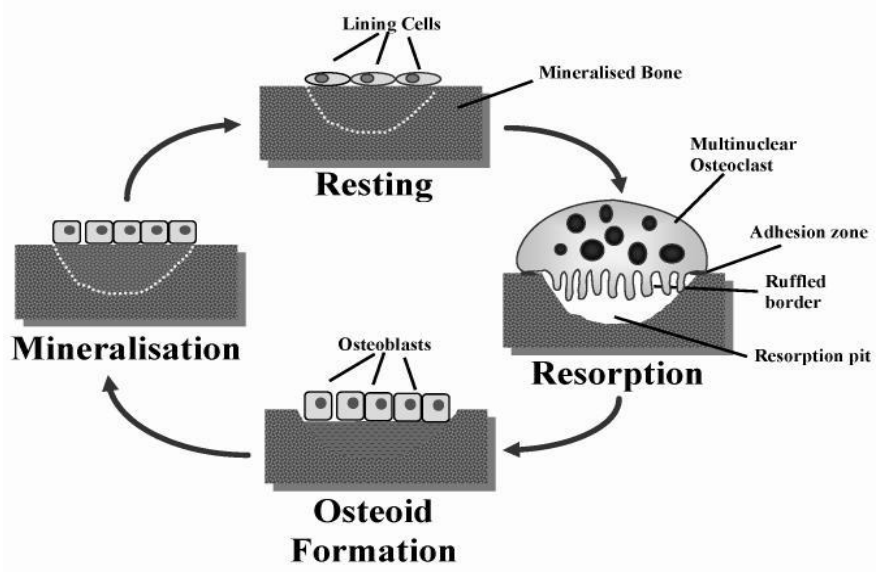
Keywords: **bone turnover, diabetes mellitus.**

1. INTRODUCTION

Diabetes is a team of metabolic conditions defined by hyperglycemia arising from flaws in insulin secretion, insulin activity, or both. The persistent hyperglycemia of diabetes is connected with long-lasting damages, disorder, and also failing of other body organs, specifically the eyes, kidneys, nerves, heart, as well as capillary [1,2].

According to American Diabetes Organization [1] Numerous pathogenic procedures are associated with the advancement of diabetes. These variation from autoimmune damage of the β-cells of the pancreatic with following insulin shortage to problems that lead to resistance to insulin activity [1]. Diabetes remains in 2010 turned into one of the leading problems worldwide, getting to an approximated 300 million people by[1]. Diabetes is related to issues [2,3] such as altered bone metabolism that may lead to osteopenia, increased risk of fracture and osteoporosis [4,5,6]. The causal relationship in between diabetes and bone loss has actually been questionable and the bone illness that establishes in type 1 and type 2 diabetes might change. In type 1 diabetic clients, bone mineral density is lowered by higher than 10% compared with nondiabetics and associates with the period of diabetes, whereas in type 2 diabetes bone density is more frequently increased [7,8]. In diabetics with low bone mass, histomorphometry research studies recommended that osteopenia was because of reduced bone development rate [9]. Hyperglycemia has actually been linked in the pathogenesis of diabetic bone illness and, reduced activity of osteoblasts under diabetic conditions has actually been reported in both animal designs and humans[10,11].

Bone is a metabolically active tissue that goes through constant renovation by 2 neutralizing procedures, particularly bone development and bone resorption. These procedures depend on the activity of osteoclasts (resorption), osteoblasts (development) and osteocytes (upkeep). Under typical conditions, bone resorption and development are securely paired to each other, so that the quantity of bone gotten rid of is constantly equivalent to the quantity of recently formed bone. (**Figure 1**)[21].



Figur 1: The bone remodelling cycle [21].

Bone turnover markers (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 [12]. 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) [12]. 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 [13], 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[13]. Furthermore, it is unknown whether the differences observed between OGTT and IVGTT were related to the administration form or dose of glucose [13]. Healthy obese subjects have reduced BTM compared to controls [14]. Following OGTT the BTM decreased in both obese and controls, however the decrease in osteocalcin (OC) was significantly more pronounced in controls [14,15] **(figure2).**

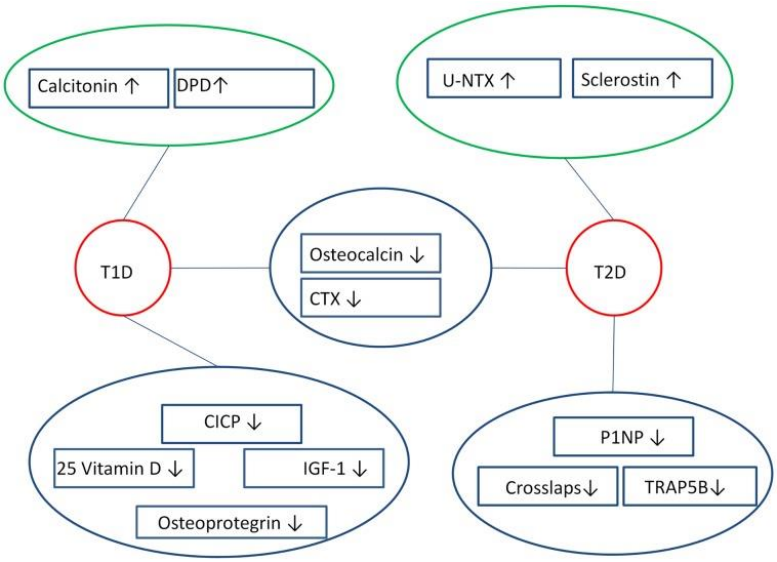


Figure2: Overview of bone markers that are likely to differ in diabetics (T1D, T2D) compared to controls

Objectives

The aim of this systematic review study was to examine Biochemical bone turnover markers between patients with T1D and T2D and evaluate the effect of glucose on bone turnover, and to evaluate the evidence based which involved the discussion of BTMs in diabetes mellitus.

2. METHODOLOGY

2.1 Study Design

2.1.1 Systematic review study

2.1.1.1 Search strategy:

A systematic literature search was conducted in September 2016. 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 more than 250 potential studies limited to human studies. The eligibility criteria for the studies were to assess bone turnover markers in either type, reports were screened so they are of a cross-sectional, retrospective, case-control, or prospective design. The eligibility criteria to the studies are; that they shall examine bone turnover markers in relationship to diabetics with or without a control group. Type 1 diabetes (T1D) or Type 2 diabetes (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 were not included in the study, as the meta-analysis itself was included.

3. RESULTS AND DISCUSSION

We identified a recent 2014 meta-analysis study by Starup-Linde et al, [16] evaluating BTMs in both T1D and T2D based on 22 studies reported increased levels of alkaline phosphate in diabetes patients and decreased OC, CTX, and 25 OHD levels compared to controls [16]. Neither P1NP, NTX, calcium, DPD, CICP, BAP nor PTH differed statistically significantly from controls, but in general the BTM levels tended to be decreased in diabetes patients with the exception of urinary NTX (u-NTX) [16]. Heterogeneity between the studies such as patient characteristics and the use of different assays to measure BTMs may have influenced the results[17]. Inflammatory processes in diabetes may also contribute to bone alterations as few studies have addressed. Berberoglu et al.[18] showed a significant negative correlation between BAP and TNF-α, whereas correlations between OC and inflammation markers all were insignificantly negative [18]. Another study yielded contradictive results; OC was negatively correlated with the inflammatory markers interleukin-6 and high-sensitivity CRP (hs-CRP) [19].

In contrast,[21] markers of bone formation are either by-products of collagen neosynthesis (e.g. propeptides of type I collagen), or osteoblast-related proteins such as osteocalcin (OC) and alkaline phosphatase (AP). For clinical purposes, therefore, markers of bone formation are distinguished from indices of bone resorption, the BTMs summerized in **Table1[21].**

Table 1: Markers of bone turnover[21].

Marker	Tissue of Origin	Specimen	Analytical Method	Remarks
Markers of bone formation				
Bone-specific alkaline phosphatase (BAP, bone ALP)	Bone	Serum	Electrophoresis, Precipitation, IRMA, EIA	Specific product of osteoblasts. Some assays show up to 20% cross-reactivity with the liver isoenzyme (LAP)
Osteocalcin (OC)	Bone,	Serum	RIA, IRMA,	Specific product of osteoblasts;

Marker	Tissue of Origin	Specimen	Analytical Method	Remarks
	platelets		ELISA	many immunoreactive forms in blood; some may be derived from bone resorption.
C-terminal propeptide of type I procollagen (PICP)	Bone, soft tissue, skin	Serum	RIA, ELISA	Specific product of proliferating osteoblasts and fibroblasts.
N-terminal propeptide of type I procollagen (PINP)	Bone, soft tissue, skin	Serum	RIA, ELISA	Specific product of proliferating osteoblast and fibroblasts; partly incorporated into bone extracellular matrix.
Markers of bone resorption				
Collagen-related markers				
Hydroxyproline, total and dialysable (Hyp)	Bone, cartilage, soft tissue, skin	Urine	Colorimetry HPLC	Present in all fibrillar collagens and partly collagenous proteins, including C1q and elastin. Present in newly synthesised and mature collagen, i.e. both collagen synthesis and tissue breakdown contribute to urinary hydroxyproline.
Hydroxylysine-glycosides	Bone, soft tissue, skin, serum complement	Urine (serum)	HPLC ELISA	Hydroxylysine in collagen is glycosylated to varying degrees, depending on tissue type. Glycosylgalactosyl-OHLys in high proportion in collagens of soft tissues, and C1q; Galyctosyl-OHLys in high proportion in skeletal collagens.
Pyridinoline (PYD)	Bone, cartilage, tendon, blood vessels	Urine Serum	HPLC ELISA	Collagens, with highest concentrations in cartilage and bone; absent from skin; present in mature collagen only.
Deoxypyridinoline(DPD)	Bone, Dentin	Urine Serum	HPLC ELISA	Collagens, with highest concentration in bone; absent from cartilage or skin; present in mature collagen only.
Carboxyterminal cross-linked telopeptide of type I collagen (ICTP, CTX-MMP)	Bone, Skin	Serum	RIA	Collagen type I, with highest contribution probably from bone; may be derived from newly synthesised collagen.
Carboxyterminal cross-linked telopeptide of type I collagen (CTX-I)	All tissues containing type I collagen	Urine (a-/β) Serum (β only)	ELISA RIA	Collagen type I, with highest contribution probably from bone. Isomerisation of aspartyl to β-aspartyl occurs with ageing of collagen molecule.
Aminoterminal cross-linked telopeptide of type I collagen (NTX-I)	All tissues containing type I collagen	Urine Serum	ELISA CLIA RIA	Collagen type I, with highest contribution from bone.
Collagen I alpha 1 helicoidal peptide (HELP)	All tissues containing	Urine	ELISA	Degradation fragment derived from the helical part of type I

Marker	Tissue of Origin	Specimen	Analytical Method	Remarks
	type I collagen			collagen (alpha-1 chain, AA 620-633). Correlates highly with other markers of collagen degradation, no specific advantage or difference in regards to clinical outcomes.
Non-Collagenous Proteins				
Bone Sialoprotein (BSP)	Bone, Dentin, hypertrophic cartilage	Serum	RIA ELISA	Acidic, phosphorylated glycoprotein, synthesised by osteoblasts and osteoclastic- like cells, laid down in bone extracellular matrix. Appears to be associated with osteoclast function.
Osteocalcin fragments(ufOC, U-Mid-OC, U-LongOC)	Bone	Urine	ELISA	Certain age-modified OC fragments are released during osteoclastic bone resorption and may be considered an index of bone resorption.
Osteoclast Enzymes				
Tartrate-resistant acid phosphatase (TRAcP)	Bone Blood	Plasma Serum	Colorimetry RIA ELISA	Six isoenzymes found in human tissues (osteoclasts, platelets, erythrocytes). Band 5b predominant in bone (osteoclasts).
Cathepsins (e.g. K, L)	K: Primarily in osteoclasts L: Macrophage, Osteoclasts	Plasma, Serum	ELISA	Cathepsin K, a cysteine protease, plays an essential role in osteoclast-mediated bone matrix degradation by cleaving helical and telopeptide regions of collagen type I. Cathepsin K and L cleave the loop domain of TRAP and activate the latent enzyme. Cathepsin L has a similar function in macrophages. Tests for measurement of Cathepsins in blood are presently under evaluation.

Bone Turnover Markers (BTM) in type 1 diabetes (T1D):

The meta-analysis [16] reported previously decreased OC levels in T1D compared to controls, whereas other specific formation or resorption markers were not available in sufficient numbers for detailed analysis [16]. Recent studies add to this, as OC and TRAP levels were lower and CTX seemed to be lower at onset of T1D, but all markers normalized after 3 months.

Jehle et al study [20] showed that T1D patients tend to have lower IGF-1 levels than T2D, therefore the mechanism of the lower bone turnover may be mediated by IGF-1 deficiency in T1D. Even so, T1D and T2D do not seem to differ in regard to BTMs, as neither 25 OHD, carboxy-terminal propeptide of type I procollagen (PICP), type I collagen cross-linked carboxy-terminal telopeptide (ICTP), BAP, nor OC was different between the groups [20]. T1D seems to have decreased bone turnover when evaluated by BTM, however a human histomorphometric study showed no difference in bone metabolism in T1D compared to non-diabetics [29]. Thus, evidence is conflicting. Low bone turnover in T1D may be related to different diabetes stages, complications, and metabolic regulation or to a specific age group, gender, or treatment.

Bone Turnover Markers (BTM) in type 2 diabetes (T2D):

The meta-analysis[16]found borderline significantly decreased OC levels (P = 0.06) and increased levels of alkaline phosphate in T2D compared to non-diabetics [16]. we identified newer studies that suggested BTMs to be decreased, as CTX, OC, P1NP, TRAP, u-NTX, and PTH were lower in T2D than controls [19,22,23,24,25,26,27,28,29,30,31]. Also, IGF-1, sclerostin, osteocalcin, u-NTX, and BAP were all decreased in T2D [29,30]. Results are still conflicting, as studies have reported no differences in the BTMs or even increased levels in T2D. P1NP [28,32], OC, TRAP, alkaline phosphatase, OC, DPD, and HP were not different when comparing T2D with controls [18,24,33].

A longitudinal study Hamilton et al [34] found no differences in OC after 5 years, but an increase in CTX in T2D [34]. The differences between studies may be explained by differences in metabolic status, diabetes duration, and medication at the time of the measurement. OPG levels have been found to be higher in T2D than controls [31,35]. Thus OPG/RANKL signaling may be involved in the disturbed bone turnover in T2D. However, RANKL did not differ between T2D and controls [31]. In this context it should be noted that RANKL may be difficult to measure [36]. The effect on BTMs may be caused by alterations in WNT-signaling as sclerostin levels were elevated in T2D compared to controls in several studies [29,32], but not in T1D [37]. Furthermore, sclerostin was found to be positively correlated with BMD [38], which may explain previously found differences in BMD between T1D and T2D [31]

4. CONCLUSION

BTMs have been widely investigated in diabetes patients. BTMs seem to be lower in diabetes patients, but with large heterogeneity between studies. Markers of bone resorption and formation seem to be lower whereas BAP, an enzyme of mineralization, is normal to increased, and suggests that the matrix becomes hypermineralized in diabetes patients. This may explain the paradox of low bone strength and increased BMD. Biochemical markers of bone resorption and bone formation were lower in patients with type 2 diabetes compared to patients with type 1 diabetes. Bone turnover markers were negatively associated with p-glucose. In conclusion, some BTMs may yield the potential to predict fractures in diabetes patients. However, little is known of the mechanisms affecting bone. Further investigation of the effect of glucose on bone in diabetes patients is needed.

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