Diabetes and Bone
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Abstract
Diabetes – both type 1 (T1D) and type 2 (T2D) has profound effects on the skeleton. Bone turnover is reduced, i.e. bone biopsies show a reduced bone formation with reduced mineralisation, and a reduced number of bone cells. Biochemical markers of bone turnover show a reduction in both formation and resorption. Bone mineral density (BMD) is reduced in T1D, whereas an increased BMD is seen in T2D. Despite this, an increased risk of hip fractures is seen in both T1D and T2D, the increase in risk of fractures being more pronounced in T1D than in T2D. This discrepancy between BMD and fracture risk along with evidence from animal studies of a reduced bone biomechanical competence in diabetes suggest that the bone tissue is weakened in patients with diabetes. This weakening may be related to glycation of collagen and formation of advanced glycation end-products (AGE), which together with their receptor (RAGE) lead to a decreased activity of the bone cells and thus a reduced turnover and a reduced de-novo formation of bone. The reduced competence despite normal BMD makes the diagnosis of osteoporosis difficult as standard bone scans (DXA) may not truly reflect bone strength. Regarding anti-diabetic treatment, most such drugs improve glucose control and thus reduce the detrimental effects of diabetes on the skeleton. However, the thiazolidinediones (rosiglitazone and pioglitazone) are associated with a decreased BMD and an increased fracture risk through an effect on the stem cells in the bone marrow leading to formation of adipocytes rather than osteoblasts. Anti-resorptive treatment for osteoporosis seem equally effective in diabetes patients as in non-diabetics despite the reduced bone turnover in diabetes.

In conclusion diabetes has many effects on bone and bone-turnover, and more research is needed.

Keywords: Diabetes; Osteoporosis; Fracture; Type 1 diabetes; Type 2 diabetes

Introduction
Diabetes and osteoporosis are both frequent endocrine disorders. However, they seem to be interconnected in several ways as demonstrated by recent studies, who have shown an increased risk of fractures [1], a decreased bone mineral density (BMD) in patients with type 1 diabetes (T1D) [2], an increased BMD in patients with type 2 diabetes (T2D) [2], evidence of an impaired bone biomechanical competence [3], and evidence of disrupted bone turnover with a low bone turnover [4,5].

Material and Methods
The following presents a narrative review of the effects of diabetes on the skeleton.

Review
Bone turnover: Bone is constantly being formed through the action of osteoblasts and degraded through the action of osteoclasts [6]. Usually formation and resorption (degradation) are tightly coupled. Bone turnover may be assessed through biopsies of bone [7], but may also be assessed more practically through sampling of blood and urine [8]. Patients with diabetes in general have a reduced bone turnover expressed by decreased levels of biochemical markers of bone turnover [4,5].

Formative biochemical markers of bone turnover: Formative markers of bone turnover include osteocalcin, which is a peptide embedded in bone matrix during formation, and alkaline phosphatase, which is an enzyme secreted by the osteoblasts as part of the formation of mineral matrix. PINP is the N-terminal peptide of procollagen type 1, which is embedded in bone matrix and thus is a formative marker.

Many studies have shown decreases in osteocalcin level of 7% to 22% [4,9-12]. However, osteocalcin may also be a marker of beta-cell function and not just a marker of bone turnover [13]. For alkaline phosphatase, no study has reported a significant decrease in diabetics compared to controls. One study reported a 7% nonsignificant decrease in both total alkaline phosphatase and bone-specific alkaline phosphatase [9], while two other studies [11,12] reported small nonsignificant decreases in total alkaline phosphatase of 2% and 4%, respectively. One study actually reported increased levels of alkaline phosphatase in young adult T1D patients indicative of impaired osteoblast differentiation and maturation, which down-regulated later stages of matrix mineralization [14].

It is remarkable that total alkaline phosphatase was not different since 25-hydroxyvitamin D tended to be significantly lower in patients with diabetes than in controls [12]. In general low vitamin D may lead to osteomalacia with an increased level of alkaline phosphatase reflecting increased deposition of unmineralised bone. Vitamin D may thus counter high alkaline phosphatase levels [15]. However, it may be that the diabetes countered the effect of the lower vitamin D to increase alkaline phosphatase by lowering bone turnover and thus alkaline phosphatase per se.

Biochemical markers of bone resorption: Bone resorption may among others be assessed through measurements of N-terminal

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cross links of collagen (NTx) and C-terminal markers of cross-links of collagen (CTX). These cross-links along with urine pyridinoline represents degraded collagen.

Urinary NTx has been reported to be markedly and statistically significantly decreased by 66% in diabetes [11]. A smaller, but still significant, decrease of 14% has been observed for urine deoxypyridinoline [12]. Regarding CTX, a nonsignificant decrease of around 26% has been reported in one study [4], while another study reported a significant 31% decrease in CTX in patients with diabetes [12].

Effects of the changes in bone turnover: It thus seems that bone formation may be decreased ranging from small decreases of 2-7% for alkaline phosphatase to 7-22% for osteocalcin. The resorptive markers show an even larger reduction of 14-66%. The larger reduction for resorption as expressed by biochemical markers of bone turnover is in line with the results from a study in healthy college students where an oral glucose load of 75 g was associated with a 5-10% reduction in the formative marker P1NP, whereas the resorptive marker CTX decreased by 40-50% [16]. In theory this imbalance should lead to accumulation of bone and thus an increase in bone mineral density. This accumulation of BMD is actually seen in patients with type 2 diabetes (T2D) [2], whereas patients with type 1 diabetes (T1D) have a decreased BMD [2]. However, in contrast to non-diabetics, where an increase in BMD is associated with a decrease in the risk of fractures [17], a reduction is not seen in patients with diabetes [1,2].

Causes of the decrease in biochemical markers of bone turnover: The decrease in bone turnover may be related to the hyperglycemia since acute ingestion of glucose in healthy non-diabetic subjects leads to a decrease in CTX of around 40-50% and in P1NP of 5% after two hours [16]. However, it may be questioned if such a rapid decrease really reflects changes in bone turnover, but rather may reflect extraskeletal alterations in e.g. degradation and excretion of the markers in question. Food intake including ingestion of glucose affects reflect extraskeletal alterations in e.g. degradation and excretion of the markers in question. Food intake including ingestion of glucose affects extraskeletal alterations in e.g. degradation and excretion of the markers in question. Food intake including ingestion of glucose affects.

Effects on bone turnover assessed by bone biopsies and animal experimental data: Few data are available on histomorphometry in humans with diabetes [5,21]. In general the number of osteoblasts and osteoclasts are reduced in both human [5,21] and animal studies [22-25]. The animal models have included spontaneously diabetic rats [22,23], and streptozotocin-induced diabetic rats [24,25].

In streptozotocin-induced diabetes in rats, a study of mandibular bone, showed that the number of osteoclasts were reduced [26] in accordance with the observations of reduced bone resorption from studies of biochemical markers [11]. In Spontaneously diabetic BB/OK (F60/61) rats, mineralization lag time may be prolonged from around 1 day to around 15 days and mineralization surfaces may decrease from 32% to 9% in poorly controlled diabetic rats [22]. Upon administration of insulin, these changes are reversed [22]. This decrease in mineralization and thus bone formation is far greater than what should be expected from the bone formative biochemical markers [4,9-12]. The quality of the newly formed bone may also be questionable [27]. In addition to the changes described above, a recent study on alveolar bone in streptozotocin-induced diabetes in Wistar rats showed that bone quality was significantly deteriorated as evaluated by micro CT [26]. A study on osteocalcin function using a mice model of streptozotocin-induced diabetes showed impaired osteocalcin function [28]. This study concluded that the delayed bone formation in the diabetic mice may have resulted from an impairment of cartilage resorption. The study reported that 80% of the osteoclasts in the callus of the experimental fractures were derived from bone marrow and that the sizes of the osteoclasts as well as the resorption pits formed were significantly smaller in the diabetic mice than in non-diabetic mice [28]. Transcripts analyses using RNA isolated by laser capture microdissection showed that the expression of DC-STAMP, a putative pivotal gene for osteoclast fusion, was decreased in osteoclasts from diabetic mice [28]. Since the sustainability of osteocalcin function depends on the controlled renewal of multinuclear osteoclasts, impaired osteocalcin function in diabetes may contribute to decreased cartilage resorption and delayed endochondral ossification [28].

Osteocalcin, diabetes, and bone

Animal experimental studies have revealed a link between the bone turnover marker osteocalcin and type 2 diabetes [13]. Mice lacking osteocalcin have decreased insulin levels and increased blood glucose levels [13]. This may however not directly be translated into clinical practice, as patients with diabetes have a number of other metabolic disturbances as previously mentioned, and these bone metabolic disturbances may per se affect osteocalcin levels. The lower insulin levels in the knock-out mice mimic a state which is intermediate to T1D (absolute insulinopenia) and T2D (insufficient insulin secretion for the requirements) [13]. It may thus both mimic early stages of T1D where insulin secretion is declining and late stages of T2D where the initial increase in insulin secretion is followed by a decrease resulting from declining beta-cell function. Although osteocalcin may affect insulin secretion [29] it is not entirely clear if the opposite is the case. In streptozotocin induced diabetes in rats, serum osteocalcin decreases, and histomorphometry shows decreased bone remodeling [24].

In patients with diabetes a cross sectional study has shown decreased levels of osteocalcin in patients with T1D and increased levels in patients with T2D irrespective of whether these were treated with oral hypoglycemic agents or insulin compared to control subjects [30]. However, this could not be confirmed in another study, who reported normal levels of osteocalcin in patients with T1D and decreased levels in T2D compared with normal controls [31]. A further study in male patients with T2D also showed reduced osteocalcin levels, whereas no differences between patients and controls were evident for sex steroid status and CTX levels [4]. The findings of the latter two studies [4,31] are more in line with what should be expected from histomorphometric findings of a decreased bone formation [21]. Upon correction of poorly regulated blood glucose levels, serum osteocalcin has been shown to increase [32].

In patients with T1D serum osteocalcin levels have been shown to be lower in patients with complications (retinopathy and/or proteinuria) than in patients with diabetes without complications [31,33]. In newborns to mothers with diabetes, umbilical cord osteocalcin levels have been shown to be decreased [34].

Due to the usually close coupling between bone formation and resorption, other markers of bone formation such as P1NP and resorption such as CTX are also decreased [16].
Advanced glycation end products (AGE) and their receptor (RAGE)

Besides the direct effects on bone turnover and bone density, bone biomechanical competence may also be altered in diabetes through glycation of other proteins besides haemoglobin (examplified by HbA1C). The glycation may alter the strength of the bone matrix thus leading to an increased brittleness of bone that is not directly reflected in BMD.

The prime glycation end product is pentosidine [35], but a number of other advanced glycation end products (AGE) and their receptor (RAGE) may be involved in the development of arteriosclerosis and diabetic microangiopathy [36]. The AGE-RAGE interaction activates nuclear factor kB (NF-kB), which interacts with cytokines, growth factors and adhesion molecules, all of which may contribute to osteoporosis. Glycation may reduce cross-linking in collagen and thus reduce mineralisation and bone biomechanical competence [35]. It also interacts with osteoblast functioning thus reducing bone formation [37]. This may also affect processes vital to bone turnover such as glycosylation of skeletal collagen leading to decreased strength of the collagen [38] and thus of the bone and abnormal resorption and formation of bone [35,37,39-42]. AGE may decrease osteoclast activity [43], and decreased osteoclast activity would lead to less bone resorption. Thus, the net effect is not fully understood. Osteoblastic cells from rats, who were cultured on AGE-modified type 1 collagen, showed a reduced secretion of alkaline phosphatase (ALP) and osteocalcin. Also formation of bone nodules was reduced [44,45].

Furthermore, AGE may affect osteoblastic function by stimulating osteoblast apoptosis via the MAP kinase and cytosolic apoptotic pathways as demonstrated in a study using cell culture and mice [46]. This was further supported and expanded by a study using cell cultures that reported that AGE significantly decreased osteoblast proliferation, alkaline phosphatase activity and type 1 collagen production, while increasing osteoblastic apoptosis and reactive oxygen species production [47]. These effects were completely reverted by low doses of bisphosphonates [47] lending support to a positive effect of these drugs despite a low bone turnover 1 diabetes. These studies are thus in line with the observations of a decrease in formative bone markers. Bone collagen from rats with streptozotocin-induced diabetes had a higher accumulation of AGE, which was associated with a reduced BMD [44]. This may thus explain the reduced BMD in T1D but not the increased BMD in T2D.

Patients with T1D are insulinopenic and patients with T2D may have increased levels of insulin. In general serum insulin levels are positively correlated with BMD [48], and this may explain why BMD in general is higher in T1D than in T2D [2]. The increased insulin levels in T2D may also be associated with increased levels of insulin-like growth factor (IGF), which may also be bone anabolic [5].

Negative calcium balance

Early studies pointed at an increased calcium excretion in the urine from calcicuric effects of the high blood sugar [49]. This leads to a loss of calcium from the skeleton with a decrease in the bone mineral density (BMD) [49] and an increased risk of fractures [2]. A direct correlation has been shown between the blood sugar levels and the excretion of calcium in the urine [49,50], and the loss of calcium from the forearm may amount to as much as 10% within the first 5 years after the diagnosis of diabetes [49].

Besides the effects of high blood glucose on calcium excretion in the urine, the blood pressure also has effects on urine calcium excretion. The higher the blood pressure, the greater the loss of calcium is in the urine [51]. This may represent a hitherto somewhat overlooked risk factor for osteoporosis as hypertension is also associated with a decreased BMD, and thus an increased risk of fractures [51]. In diabetes, hypertension may thus contribute further to the negative calcium balance [52].

Bone mineral density

BMD is reduced by approximately 0.2 Z-scores in the hip and spine in T1D, while it is increased by approximately 0.3-0.4 Z-scores in the hip and spine in T2D [2]. In theory this should translate into an increase in hip fractures of RR=1.4 in T1D and a decrease RR=0.8 of in T2D [2]. This is in stark contrast to the observed RR for hip fractures of 6.2 in T1D and 1.7 T2D [2] pointing at a weakening of bone biomechanical competence in diabetes [3]. In diabetes [2] as well as in non-diabetics [53] a positive relationship exists between body mass index (BMI) and BMD, to some extent explaining the differences between the often normal to underweight T1D patients and the obese T2D patients [2]. No differences in BMD seemed present between T1D and T2D after adjustment for body weight [2]. It thus seems that the effect of the underlying diabetic condition may be the same and probably linked to glucose levels.

Fracture risk

In T1D an increased risk of hip fractures was seen [2]. However, for other fracture types the number of studies was too scarce for a meta-analysis [2] although most studies revealed a trend towards an increase [2]. In T2D an increased risk of hip, foot, and perhaps overall risk of fractures was seen [1,2], while no increase in spine, forearm, or ankle fractures was seen [1,2]. It thus seems that the hip is the fracture site with the most consistent increase in fracture risk in both T1D and T2D. However, little is known for other skeletal sites.

From one study it seems that the increase in risk of fractures in T2D is seen early after diagnosis followed by a decline to the same levels as in the background population [54]. The reasons for this are not known but may signal an effect of the increased calcium loss in the urine with high blood glucose levels as it is in line with early studies suggesting a marked negative calcium balance that is corrected once better metabolic control is obtained, which also reflected in an increase in forearm bone mineral content [49,50]. However, an effect on bone biomechanical competence cannot be excluded with better control of blood glucose levels.

The increase in risk of fractures did not to any mior degree seem linked to complications to the diabetes, i.e. was not the result of falls from impaired eye-sight [54], decreased proprioception from neuropathy [54], or falls related to accidents stemming from hypoglycemia [55]. It may thus be the effects of the underlying alterations in bone competence that were responsible for the increase in risk of fractures.

The overweight and obesity seen in patients with T2D may thus merely protect against the loss of bone [2] and to some degree ameliorate the increase in risk of fractures as also seen in non-diabetics [53].

Effects of treatment

Effects of drugs against diabetes: In animal models, improvement of diabetes control has resulted in reversal of the histomorphometric changes induced by diabetes [22]. Observational studies have pointed at a reversal of e.g. the loss of calcium in the urine and an improvement of BMD when blood glucose levels are better controlled.
In general drugs against diabetes improve metabolic control, and should thus be expected to be able to prevent osteoporosis. Insulin, the sulphonylureas, and metformin seem associated with a decrease in the risk of fractures or a trend towards a decrease [55] probably related to better metabolic control of diabetes. Metformin has also been shown to have positive effects on bone turnover by improving metabolic control [56]. Recently published results from rodent models suggest a positive effect of exenatide on bone, but there are no clinical studies [57].

Thiazolidinediones (TZD): TZDs act by improving insulin sensitivity through activation of the nuclear receptor, peroxisome proliferator-activated receptor γ (PPAR-γ) [58]. The TZDs affect the differentiation of mesenchymal stem cells [59]. Normally the common mesenchymal progenitor stem cell can differentiate into among others osteoblasts and bone marrow adipocytes [60]. TZDs increase adipogenesis at the expense of osteoblasts, leading to bone loss [61,62]. Other effects by PPARγ agonists include decreased circulating IGF-1 concentrations [63], and a decrease in oestrogens levels, as treatment has been shown to affect the synthesis of sex steroids by inhibiting the aromatase pathway which is the main source for oestrogen in postmenopausal women [64].

Mice treated with troglitazone show an increased marrow concentration of adipocytes [59], whereas the ratio of osteoblasts to osteoclasts decreases causing bone loss in mice treated with rosiglitazone [62]. Similarly, treatment with rosiglitazone has been shown to decrease BMD in mice [65-67]. Concomitantly with decreased BMD, treatment may change bone morphology, as a decreased trabecular number and an increase in trabecular spacing has been reported [67]. In human cell models [68] the effect of rosiglitazone on adipogenesis has also been confirmed. Besides the effects on osteoblasts, TZDs may also have an effect on the osteoclasts [69] with an increased osteoclast differentiation due to the PPAR agonistic effect of rosiglitazone. The clinical effects of this are not completely understood.

Two randomised controlled trial (RCT) have shown decreased levels of biochemical markers of bone formation in humans treated with rosiglitazone, indicating a decreased activity of osteoblastic cells [9]. In a group of 82 postmenopausal women, 12 weeks of treatment with rosiglitazone 4 mg/d caused a 21% decrease in plasma levels of bone-specific alkaline phosphatase, compared with placebo (p<0.05) [9]. Similarly, in a RCT including 50 postmenopausal women without diabetes or osteoporosis, 14 weeks of treatment with rosiglitazone 8 mg/d caused an approximately 10% (p<0.05) decrease in biochemical markers of bone formation (osteocalcin and procollagen type 1 N-terminal propeptide), while markers of bone resorption did not change in response to treatment [70]. Moreover, compared with placebo, rosiglitazone caused a 1.7% (95% CI 0.6 to 2.7, p <0.01) decrease in BMD at the total hip. BMD at the lumbar spine decreased as well but did not differ significantly between groups (1.0%, 95% CI -0.2 to 2.3, p=0.13) at the end of treatment [70]. The findings from the RCTs are in line with the results from a previous cohort study showing that treatment with glitazones is associated with approximately 50% increased annualized rate of bone loss in elderly diabetic women, whereas no effects were found in men [71]. However, in elderly men with T2DM significantly higher annualized bone loss rates have been found in those treated with glitazones (–1.22 ± 1.3%, n=32) compared with those who were not (–0.20 ± 1.25%, n=128) [72]. The fact that bone turnover is often increased in elderly women compared with elderly men may augment the consequences of reduced osteoblastic activity in response to treatment with TZDs, which may explain that the effects of TZDs on BMD is more consistently present in women than in men.

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Most important, treatment with TZDs seems to increase fracture risk. According to the results from the ADOPT study, risk of fracture is approximately doubled in users of rosiglitazone compared with risk of fracture in users of either metformin or glyburide [73]. In the ADOPT trial, 4,360 (42% women) participants with a mean age of 57 years were followed for a median of 4 years. The study was a RCT designed to evaluate rosiglitazone, metformin, and glyburide as initial treatment for recently diagnosed T2DM. The primary outcome was time to monotherapy failure as determined by fasting glucose. Review of adverse event reports revealed that the proportion of women reporting a fracture was 9.3% for rosiglitazone, 5.1% for metformin, and 3.5% for glyburide, corresponding to an approximate relative risk (RR) of 2.3 (95% CI 1.6–3.4) for rosiglitazone versus the other treatments combined. However, although fractures were similarly distributed across treatment groups in male participants, the increase in risk of fracture did not reach statistical significance (RR 1.2; 95% CI, 0.8–1.8 for rosiglitazone versus the other treatments combined). Similar to treatment with rosiglitazone, treatment with pioglitazone has been reported to increase risk of fracture [74], and the increase in risk of fractures was similar for rosiglitazone and pioglitazone [74].

In terms of fracture risk it is an important finding that TZDs as the only class of drugs against diabetes seems associated with an increased risk of fractures, whereas all other classes of drugs seem either are not associated with risk of fractures or are associated with a small decrease in risk of fractures probably linked to the glucose-lowering effect and thus improvement of the otherwise negative effects on bone of hyperglycaemia [55].

Regarding bone density measurements in patients being started or currently managed with TZD, no consensus exists. Also no consensus exists as to the best way to manage patients with decreased BMD receiving TZDs. At present care should be taken not to prescribe TZDs to patients at high risk of fractures, i.e. patients with osteoporosis (T-score <-2.5 at any site) and significant risk factors for fractures. The potential benefit of TZDs in terms of improved diabetes control (and thus also indirectly potentially better bone turnover) should be carefully weighed against the risk of fractures, as the risk of fractures seems increased even in the presence of improved diabetes control [73].

In patients which have a low a priori risk of fractures (men and women below the age of approximately 50 years), BMD measurements by DXA may not be particularly indicated if no other risk factors are present, whereas in postmenopausal women and men above the age of 65 years, the prevalence of osteoporosis is so high that DXA scanning may be indicated [75]. Depending on the level of bone density, DXA scans may be repeated after 2-3 years [75]. However, this may represent a rather large cost in comparison with the gains obtained. TZD therapy thus needs to be carefully considered in patients at high risk of fractures and osteoporosis.

Serum and urine markers of bone turnover are very variable and do thus not have a place in the considerations regarding risk of osteoporosis [76].
Weight loss: A special feature is that weight loss is encouraged in obese patients with T2D. A randomised controlled trial in overweight patients with T2D showed that weight loss was associated with a decrease in BMD (0.9% decrease in total body BMD over 12 month with non-significant decreases in spine and femur BMD) [77], and that exercise training seemed to prevent the loss of BMD [77]. In patients treated by gastric by-pass, which is used for weight reduction in morbidly obese patients with T2D, a decrease is seen in BMD [78].

Conventional treatment of osteoporosis with anti-resorptive drugs

Antiresorptive drugs: These include the bisphosphonates and the selective estrogen receptor modulators (SERMs) [79]. In theory these may present a special problem as bone turnover is low in diabetes. Two studies have shown improvements in BMD with the bisphosphonate alendronate over placebo [80,81]. The paper by Keegan et al. was a post hoc analysis of a randomized trial [81]. The paper by Dagdelen et al. was an observational study without a placebo group [80]. In this study, the authors found that diabetic patients on alendronate lost bone compared to non-diabetic patients on alendronate. The study is difficult to interpret since we do not know how much bone the diabetic patients would have lost on placebo [80]. However, no fracture data are available. It may thus be concluded that the decrease in bone turnover does not lead to decreases in BMD, however, it is not possible to deduce if the quality of the newly formed bone is adequate. An observational study suggested that anti-resorptive drugs including the bisphosphonates were equally effective in patients with diabetes as in patients without [82]. However, it may be that the diabetes in these subjects was well-controlled. What happens in patients with poorly controlled diabetes is not known. Further studies are thus needed.

A post hoc analysis of a raloxifene trial identified reduced vertebral fracture risk compared to placebo in participants with diabetes [83]. However, this study only included patients with T2D and the number of patients was very limited [83]. Strontium ranelate is also effective against osteoporosis [84], however, for this compound no specific studies on the effects in patients with diabetes are available.

Anabolic drugs: This class of drugs include parathyroid hormone and analogues [85,86]. In theory these drugs may pose an advantage due to the decreased bone turnover in patients with diabetes, but no clinical studies are available. However, one study have indicated that teriparatide may perhaps have a limited actue adverse effect on insulin resistance [87]. Further studies are thus needed.

Conclusion

In conclusion bone mineral density is decreased and hip fracture risk increased in patients with T1D, while in patients with T2D hip fracture risk is increased although to a lesser degree than in T1D. However, in T2D patients bone mineral density is increased. This points at a decreased bone quality in patients with diabetes. Patients with diabetes should be treated against osteoporosis when indicated. It is important to be aware that patients with diabetes do seem to tolerate anti-resorptive drugs including the bisphosphonates despite having biochemical signs of reduced bone turnover.

References


