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Diabetic Bone Disease

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Diabetes mellitus is associated with an extensive list of late complications involving nearly every tissue. Diabetic bone disease was already recognized at the beginning of this century [1] and described as a retardation of bone development and bone atrophy in children with long-standing diabetes. Albright and Reifenstein [2] and Berney et al. [3] also described the coexistence of diabetes and osteoporosis. Since then, diabetic bone and mineral homeostasis have been studied in both humans and experimental animals and the confusing and frequently contradictory data are now gradually evolving into a more logical picture of events.

In human diabetes, a clear distinction needs to be made between insulin-dependent diabetes mellitus (IDDM) associated with (near) total lack of insulin in usually young lean persons and noninsulin-dependent diabetes mellitus (NIDDM) which develops gradually in later life, usually in obese subjects. As age and obesity have marked effects on the frequency and severity of osteoporosis, the two common types of diabetes could have different effects on the occurrence and/or severity of diabetic bone diseases.

In IDDM, a decreased bone mass has frequently been observed [4–17] when measured by X-ray radiogrammetry and single or dual photon absorptiometry (Table 1). However, the decrease in bone mass is usually small (about 10% decrease or 1 SD below the mean of age-matched control). Therefore, the bone loss is not necessarily associated with a decrease below the fracture threshold unless age- and menopause-associated bone loss would or will be superimposed. This might explain the difference between the frequency of decreased bone mineral content (BMC) and the frequency of osteoporotic bone fractures in long-standing diabetes.

The situation in NIDDM is more confusing as both decreased [4, 18–22] and increased bone mass have been observed. As obesity is associated with an increased bone mass and a reduced incidence of osteoporosis [23, 24], an appropriate control group for the obese diabetics is necessary, but this was usually not done in the few studies on bone mass in NIDDM.

The incidence of bone fractures in diabetics is clearly increased when all reports [25, 27–35] are pooled (Table 2), with an approximately twofold increased risk. However, such studies are case control studies and could have been confounded by diabetes complications that predispose to falls or bone fractures such as neuropathy, hypoglycemia, or vascular disease [25].

The relationship between osteopenia and diabetes duration or control is not obvious. Indeed, when diabetic children are studied, a retardation in bone maturity (bone age) and osteopenia usually develops within the first few years of diabetes, and, except in one study [12], the bone loss did not increase further with increasing duration of diabetes [6–8, 10, 13–14]. Similar observations have been made in adult-onset IDDM [12]. Moreover, bone mass measured by radiogrammetry and single and dual photon absorptiometry [15] in long-standing IDDM (mean disease duration 18 years) was not more decreased than in most other studies involving diabetics with a much shorter duration of diabetes (Table 1). This resembles the picture of menopause-associated bone loss when estrogen deficiency temporarily accelerates bone loss until a new steady state is achieved. The relationship between osteopenia and diabetes control has not been evaluated in most studies but poor metabolic control was associated with higher bone loss in one study [9]. It would be useful to compare bone loss with parameters of very long-term diabetes control (e.g., collagen cross-linking) [26].

The decrease in bone mass observed in diabetes is not necessarily due to insulin deficiency itself as diabetes is frequently associated with other risk factors for osteoporosis such as negative protein balance, reduced physical activity, or impaired gonadal function. Animal diabetes studies are therefore more appropriate for evaluating possible pathogenic mechanisms.

Mechanisms of Bone Loss in Animal Diabetes

Several hypotheses have previously been proposed as possible pathogenic mechanisms of diabetic osteopenia including primary disturbances in calcium or vitamin D metabolism [34–37], chronic malnutrition [38], or chronic vascular disease of bone [31]. Insulin deficiency itself could also influence bone cells either directly or through its effects on other bone growth factors.

Abnormalities in calcium absorption and excretion are well documented. Hypercalciuria is frequent in both human and experimental diabetes [34] and can be partially explained by osmotic diuresis and renal hemodynamic changes induced by prostaglandin excess [35].

Duodenal calcium malabsorption is also well documented in diabetic animals [36, 39, 40] and is associated with a decrease in duodenal calbindin D-9K concentration despite general hypertrophy of the intestinal mucosa [40, 41]. The active duodenal calcium transport was almost completely abolished in diabetic BB rats but the passive intestinal calcium absorption was increased due to increased food (and calcium) intake; this has been explained by increased hypothalamic concentrations of neuropeptide Y [42]. Calcium intake-matched nondiabetic rats also had decreased duodenal calbindin D-9K concentrations but their active intestinal calcium absorption was not totally suppressed [40].

Abnormalities in vitamin D metabolism have also been repeatedly observed in diabetic animals. 25-Hydroxyvitamin D concentrations remained normal in most reports [40, 43] but serum 1,25-dihydroxyvitamin D concentrations were

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Table 1. Insulin-dependent diabetes mellitus and bone mass

Author	Method of evaluation	Patients			Results	
		N	Age (mean and/or range)	Diabetes duration (years)	BMC vs controls	Frequency of BMC <10% of controls
[4]	SPA[a] of forearm	36	9–57	0.3–43	−6% (cort. bone) −13% (trab. bone)	54% (M/F)
[5]	SPA of forearm	57	33	19	−4% (F) −5% (M)	31% (F) 48% (M)
[6]	SPA of forearm	196	6–26	NM	−8% (F) −5% (M)	48% (F) 29% (M)
[7]	Radiogrammetry	107	12 (4–18)	5 (0.4–13)	NM	41% (M)[b] 13% (F)[b]
[17] [8]	SPA of forearm	86	7–25	10	−14%	70% (M/F)
[22] [9]	SPA of forearm	60	23–64	6	−9%	NM
[18] [10]	Radiogrammetry of second metacarpal	45	12 (7–18)	5 (0.5–14)	−1 SD[c]	NM
[11]	SPA of forearm	51	12	4	−13%	NM
[12]	SPA of forearm	78	15 (8–25)	7 (1–18)	−1.24 SD ($P < 0.001$)	NM
	Radiogrammetry of second metacarpal				−0.25 SD ($P < 0.05$)	NM
[13]	SPA of forearm	60	15 (8–25)	6 (1–4)	−0.9 SD ($P < 0.01$)	NM
	Radiogrammetry of second metacarpal				−0.7 SD ($P < 0.01$)	NM
[14]	Radiogrammetry	206	7–20	6	NM	−22%
[15]	SPA (forearm) 8 cm 3 cm DPA (lumbar spine) Radiogrammetry	31	41	18	NM NM NM NM	35% 54% 38% 38%
[16]	SPA of forearm	54[d]	41 (17–74)	16	NS	NM
[17]	Radiogrammetry	87	11 (2–21)	NM	NM	−9.5%

[a] SPA and DPA: single and dual photon absorptiometry.
F: females, M: males; NM: not mentioned or studied; NS: not significant
[b] Calculated as below the 5th percentile for age-adjusted normal values
[c] Z score
[d] "Insulin-requiring diabetes" from diagnosis onwards

usually depressed. The most marked decreases were found in male diabetic rats, either spontaneously diabetic BB rats [40] or in streptozotocin-induced diabetes [43–46]. Less marked decreases have been observed in female diabetic rats [44], alloxan-diabetic rabbits, and human IDDM. In human diabetes, decreased concentrations of $1,25(OH)_2D$ were only observed in children and adolescents during poor diabetes control or ketoacidosis whereas reasonable diabetes treatment normalized serum $1,25(OH)_2D$ concentrations [47].

Low levels of $1,25(OH)_2D$ can partly be explained by decreased concentrations of the serum vitamin D-binding protein (DBP) due to impaired liver synthesis of this protein [40, 44]. Decreased renal synthesis of $1,25(OH)_2D$ may also be involved as both insulin and IGF_1 are known to stimulate renal 1α-hydroxylase activity [48, 49]. The *in vivo* conversion of 25OHD into $1,25(OH)_2D$ is also decreased in diabetic rats whereas the metabolic clearance of the vitamin D hormone remains normal [37]. When free concentrations of $1,25(OH)_2D$ were calculated, no decreased but normal or even increased concentrations were found [40, 41, 44, 50] suggesting peripheral vitamin D resistance rather than deficiency of active vitamin D hormone. The concentration of vitamin D receptors has been found to be markedly decreased in the duodenal mucosa of diabetic rats [40, 51].

Parathyroid hormone concentrations in diabetic rats were initially reported to be increased [52] but when better rat PTH assays were used, low or undetectable PTH levels were observed [45, 46].

However, the abnormalities of calcium homeostasis as just described (hypercalciuria, decreased intestinal calcium

Table 2. Incidence of osteoporotic fractures associated with diabetes[a]

Author	Total no. fractures studied	No. of diabetic patients		
		Observed	Expected	Relative risk
[27]	M: 202 F: 808	M: 5 F: 44	3 17	
	1010	49	20	2.44
[28]	340	75	50	1.5
[29]	157	22	18	1.2
[30]	NM	35	30	1.2
[31]	935	239	70	3.4
[32]	986	167	228	0.7
[33]	83	8	3	3.3 (risk adjusted)
[25]	125	23	5	4.6

[a] The type of diabetes (type 1 or 2), its duration or association with obesity or other diabetes complications is usually not studied or mentioned. The use of insulin was also not mentioned except in ref. [27] (21 patients), ref. [28] (27 patients), and ref. [31] (30 patients).

absorption, and decreased total $1,25(OH)_2D$ concentrations) can hardly explain the observed bone abnormalities. Indeed, no signs of secondary hyperparathyroidism or vitamin D deficiency were observed on bone histology. On the contrary, a decreased bone turnover is the hallmark of diabetic bones. Dynamic bone histology studies in human IDDM are scanty, but older studies already indicated decreased bone formation [53, 54] and more recent studies in diabetic patients with renal insufficiency have confirmed these data [55, 56]. Diabetic rats have been better studied and decreased osteoblast number, osteoid formation [41, 45, 46, 50, 57], and bone mineral apposition rate [50, 58] were the rule. Bone resorption, as judged from the number of osteoclasts, seems to be less decreased than bone formation [50, 58] and osteopenia should, therefore, be the endpoint. However, most rat studies have not revealed a clear decrease in total bone calcium unless the diabetes duration exceeded 2 months [50, 59]. The decreased osteoblast number/function is also documented by the very low serum concentration of a biochemical osteoblast marker, osteocalcin, or bone GLA protein, in diabetic rats [50, 58–60] and human diabetics [61].

Although the remaining osteoblasts of diabetic animals could not increase their osteocalcin secretion in response to exogenous $1,25(OH)_2D$ [58], the decreased bone formation can be largely explained by a simple decrease in osteoblast number. The relative osteoid surface, mineral apposition rate, and serum osteocalcin concentrations were all depressed to about the same extent as the number of osteoblasts in short- and long-term diabetic BB rats [50, 58], indicating that individual osteoblast function might be reasonably conserved. Decreased osteoblast recruitment then could either be directly dependent on deficiency of insulin or could be due to deficiency of insulin-dependent growth factors. IGF_1 concentrations were clearly depressed in diabetic animals and osteocalcin concentrations showed a significant correlation ($r = 0.89$) with circulating IGF_1 concentrations in long-term diabetic BB rats [62]. Osteoblastic cells contain receptors for both insulin and IGF_1, and insulin as well as IGF_1 promote osteoblast replication and function [63, 64]. The effect of insulin deficiency on bone growth is well documented: the growth plate thickness is decreased and longitudinal growth is depressed. Both parameters were corrected by IGF_1 infusion [65]. The decreased bone growth, however, is no explanation for the decreased bone mass as the bone length and diameter are much less decreased than total bone mass in long-term diabetic BB rats [50]; however, other growth factors (e.g., IGF_2 or skeletal growth factor) may also be deficient. Androgen deficiency, associated with androgen resistance, is frequent in diabetic male animals [58, 62] and could contribute to the low bone formation. Growth hormone levels are also low in diabetic animals, in contrast to the usually increased growth hormone concentrations in diabetic humans [66].

The decreased body weight of diabetic animals raised the suspicion that malnutrition and weight loss might be responsible for the decreased bone formation and osteopenia of diabetic animals. Indeed, malnutrition was reported to depress bone turnover [38]. However, the bone histology and serum biochemistry of weight-matched nondiabetic BB rats were different from that of diabetic BB rats, excluding malnutrition as the major reason for diabetic osteopenia [40, 58].

The effect of diabetic osteopenia on bone strength has been evaluated in both streptozotocin and BB rats and a severe deficiency in all biomechanical properties has been observed [50, 62]. The fragility of the bone seems to exceed the mineral deficiency and this might be explained by collagen abnormalities. Diabetes is not only associated with decreased collagen synthesis in several tissues such as bone and cartilage, but also with a decreased collagen strength [26] probably related to abnormal collagen glycosylation and cross-linking.

Although a complete picture of the pathogenesis of diabetic bone disease is still difficult to draw, it has become clear that no single mechanism can explain all observed phenomena (Fig. 1). The most prominent effect of insulin deficiency on bone structure is probably a decreased osteoblast recruitment, either directly or in concert with abnormal production of other hormones or growth factors. This results in a decreased bone formation and turnover and, if the diabetes is long standing and/or under poor control, in true osteoporosis. Chronic hyperglycemia also increases collagen glycosylation, contributing to the brittleness of diabetic bone. Abnormalities in vitamin D metabolism are partly due to the insulin effect on DBP synthesis, renal 25OHD-1α-hydroxylation, and vitamin D receptor concentration, all contributing to the decreased synthesis of vitamin D-

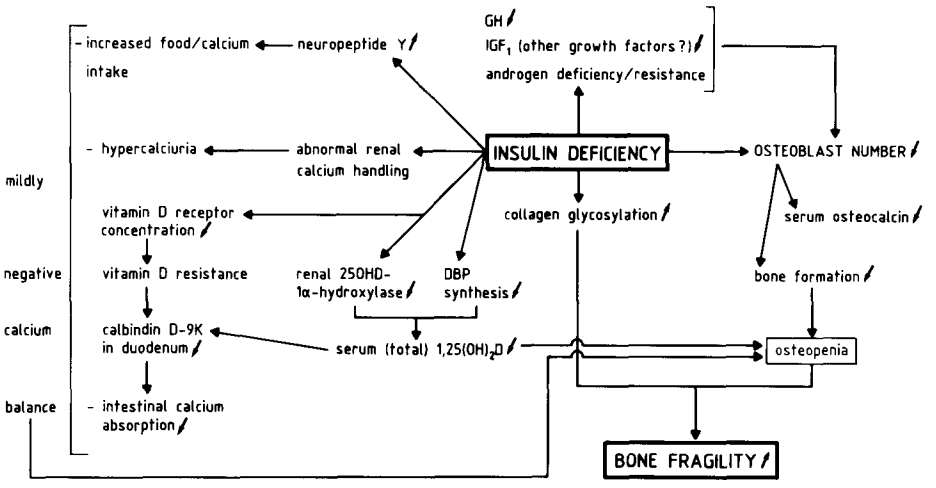

Fig. 1. Schematic integration of the effects of insulin deficiency on mineral and bone metabolism in insulin-deficient diabetes mellitus.

dependent proteins (calbindin D-9K and osteocalcin). The picture is further complicated by the increased food (and thus calcium) intake of diabetic rats and by abnormal renal calcium handling, resulting in hypercalciuria.

The osteoporosis of diabetic animals may be relevant for human IDDM. Although the bone repercussions of diabetes alone might be comparable to the effect of estrogen deficiency, the combination of both may be more serious than previously suspected, especially in view of the increasing long-term survival of IDDM patients. Secondly, the retardation of bone formation in diabetic animals is more pronounced than in other models of osteoporosis induced by hormone deficiencies or corticosteroid excess. Thirdly, as insulin itself of insulin-dependent growth factors is able to stimulate bone formation, high insulin levels as observed in obesity might contribute to the increased BMC in this disorder. Finally, the study of several biosynthetic insulin or insulin-dependent growth factors in diabetic animals might well become relevant for their evaluation as potential bone growth factors *in vivo*.

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