14. BONE REMODELLING IN DIABETES MELLITUS

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1.1. Introduction

There is some controversy about the effects of diabetes mellitus on bone remodelling and bone mineral density (BMD). The question whether diabetes mellitus is a risk factor for osteopathy (i.e. osteoporosis) and osteopathy is a complication of diabetes mellitus remains to be answered. Increases in osteoporotic fractures were observed only in some studies and no general trends for fracturing of bones were found in diabetics. However, there are strong indications that bone metabolism is influenced differently by type 1 (IDDM) and type 2 (NIDDM) diabetes mellitus. The factors present in diabetes mellitus, which may influence bone remodelling, will be reviewed.

1.2. Bone remodelling

Bone remodelling comprises the process of bone resorption, which is always followed by bone formation and provides a mechanism for bone self-repair. It represents simultaneous action of bone destroying (resorption) cells, osteoclasts, and bone forming cells, osteoblasts, which take place on the specific bone surface termed bone remodelling units (BRU).

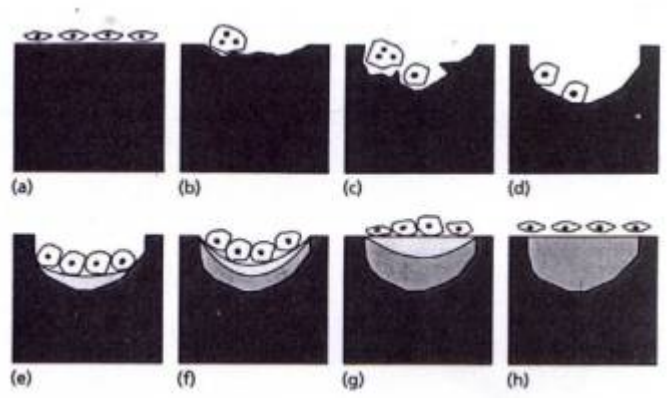

Figure 1. Bone remodelling

a) Quiescent bone surface; b) Attraction of multinucleated osteoclasts; c) Creation of resorption cavity; d) Smoothing of erosion cavity by mononuclear cells; e) Deposition of cement substance and attraction of osteoblasts (coupling); f) Bone matrix synthesis; g) Osteoid mineralization; h) End of bone remodelling – bone surface is covered by lining cells (inactive osteoblasts). (from Kanis JA. Osteoporosis: Blackwell HC Ltd., 1997, p.26).

The bone-remodelling process includes five stages: BRU activation, bone resorption, 'coupling', bone formation and mineralization of newly formed bone matrix.

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1. The attraction of osteoclasts to the bone surface is called activation of BRU. The term refers to the event and not to activity of osteoclasts themselves. PTH, TH and calcitriol (1,25(OH)2 vit.D) increase the frequency of BRU activation i.e. number of BRU. In healthy subjects, BRU activation occurs every 10 sec and 35 million BRU are active in the whole skeleton at the same time.
2. During bone resorption the bone mass is being resorbed by osteoclasts. Giant multinucleated cells, osteoclasts, excavate the erosion cavity (Howership lacunae) under themselves in an acid medium by excretion of proteolytic enzymes: cathepsin K, collagenase and phosphatase. The erosion cavity is normally of 40-60 µm depth. Bone resorption takes from 4-12 days. Thereafter osteoclasts are replaced by mononuclear cells to smooth off the cavity. Over the next 7-10 days the layer of cement substance (rich in proteoglycans, glycoproteins, but poor in collagen.) is deposited into the cavity.
3. After the cement substance synthesis is complete, the step named coupling attracts osteoblasts to eroded surface.
4. In the step of bone formation the osteoblasts form a sheet of cells within erosion cavity and start to synthesise an osteoid matrix.
5. Mineralization. Osteoid undergoes mineralisation few days later. It is a slow process and it could take from one to two months.

Table 1. Systemic and local factors, which control bone remodelling

HORMONE	FORMATION	RESORPTION	**LOCAL FACTORS**	FORMATION	RESORPTION
Estrogens	increase	decrease	TGFβ	increase	
PTH	increase	increase	IGF	increase	
Calcitiol	increase	increase	BMP	increase	
Insulin	increase	no influence	PDGF	increase	
Growth hormones	increase	no influence	FGF	increase	
			PGE2	increase	increase
Thyroxin	no influence	increase	IL-1	decrease	increase
Calcitonin	no influence	decrease	IL-6, 11		increase
Glucocorticoids	decrease	decrease	TNFα, β		increase
			CSF		increase
			INFγ		decrease
			IL-4		decrease

The stages in the bone-remodelling process are well co-ordinated by many systemic and locally acting bone factors (Table 1).

Formation of the bone mass is slower and takes several months when compared with bone resorption which is completed within 7-14 days.

10 % of the bone surface is involved in the remodelling process at any one time. In healthy mature adult (25–35 years) the net activity of osteoclasts equals the net activity of osteoblasts. Therefore skeletal size neither increases nor decreases although bone tissue is

continuously being turned over. In younger subjects bone formation normally exceeds bone resorption and, in elder subjects, bone resorption is higher than bone formation.

1.3. Bone diseases

The bone status could be assessed by measurement of bone mineral density (BMD). Biochemical markers of bone turnover, like osteocalcin, bone specific alkaline phosphatase (as bone resorption markers) and deoxypyridinoline, collagen 1α1 telopeptides (as bone resorption markers) are mainly used for follow up of treatment.

Osteoporosis is a common bone disease that affects one in three women after menopause. According to WHO, osteoporosis is a systemic bone disease, where BMD is more than 2·5 SD lower than the maximal BMD achieved in young adult life. Arising changes in the microstructure of the bone tissue result in an increased risk of bone fractures. Bone fractures for example of hip or spine may appear even at normal daily work and pneumonia as one of fracture healing complication is a common cause of death in osteoporotic patients.

Development of osteoporosis is stimulated by low levels of oestrogens and by other risk factors. BMD can be decreased by endocrine, metabolic, drugs, dietary, physical activity and genetic factors.

Sex hormones are required to maintain the balance between resorption and bone formation as well as to control the intensity of them in the process of bone remodelling. By advancing age, the concentration of oestrogens decrease in both genders, what is particularly evident in women after menopause. This, on the one hand, increase the frequency of BRU activation (by 2-3 times), while on the other, it slows down the activity of osteoblasts and formation of new bone. The final result is enhanced bone resorption, which is followed by inadequate increase in bone formation. Owing to this, insufficient quantity of new bone mass is synthesized into each erosion cavity, what leads to progressive bone mass loss. The time when BMD will reach the critical limit of - 2.5 SD depends on the peak (maximal) BMD achieved between 25 and 40 years of age and speed of bone loss in the old age.

1.4. Factors influencing bone remodelling in diabetes mellitus

1.4.1. Hyperglycaemia

Advanced glycated end-products (AGE), rising in hyperglycaemia, increase activity of osteoclasts. Hyperglycaemia in rats shows also disrupted vitamin D metabolism and calcium absorption in the small intestine as well as severe suppression of osteoblast activity.

1.4.2. Insulin

The lack of insulin, as in patients with type 1 diabetes, may be disadvantageous for osteoblast number and activity and collagen formation. On the contrary, hyperinsulinaemia can be a cause of positive effects on bone mass or even increased osteogenesis in the spine in elderly patients with type 2 diabetes. In both cases a stimulating effect of insulin on bone can be confirmed.

Table 2. Factors which may influence bone metabolism in diabetes mellitus

POSITIVE EFECTS	NEGATIVE EFFECTS
Hyperglycaemia	Inflammation
Hyperinsulinaemia	Hypoinsulinism
Excess of GH (IGF)	Lack of GH
Obesity	Hypogonadism
Medical care	Hyperparathyrioidism
	Reduced mobility
	Diabetic complications

1.4.3. IGF1

IGF as growth factor and androgens have a strong anabolic effect on bone mass. IGF-1 co-operates with calcitriol (1,25-dyhydroxyvitamin D) in stimulating collagen synthesis and osteoid mineralization.

1.4.4. Inflammation

Inflammation that is a part of type 1 DM pathogenesis could lead to bone loss in the so-called 'inflammation-mediated osteopenia' and the peak of bone mass achieved in the young adult may be reduced by such process.

1.4.5. Obesity

Obesity is itself negatively correlated with osteopenia. Furthermore it could have additional favourable effect by yielding metabolically active steroid hormones and the storing of sex hormones.

1.4.6. Hypogonadism

Poor diabetic control or some autoimmune endocrine disorder could cause amenorrhea in women with diabetes. Decreased level of oestrogenic hormones increase bone resorption and cause bone loss by an action which is common in postmenopausal osteoporosis, the most frequent bone disease. In addition, delayed puberty in boys and acquired testosterone deficiency in adult men have also been closely linked to low bone mass. However, the mechanism of maintaining of bone mass by androgens is not completely understood.

1.4.7. Hyperparathyroidism

PTH activates osteoclasts in order to prevent hypocalcaemia and it is one of potential causes of secondary osteoporosis. However the incidence of primary hyperparathyroidism in diabetic patients is not very high (0.82%). In contrast, hypoparathyroidism decreases bone formation via depression of IGF transcription in osteoblasts.

1.4.8. Hyperthyroidism

Hyperthyroidism is an established cause of osteoporosis because frequency of BRU activation is increased. The prevalence of hypothyroidism is increased in both type of diabetes because of an autoimmune thyroiditis. If these patients are treated with extensively high doses of thyroxin, the possibility for increased bone loss emerges.

1.4.9. Medical care

In diagnosed patients medical care may be profitable with respect of prophylaxis of other diseases.

1.4.10. Diabetic complication

Complications like retinopathy, neuropathy and anginopathy may influence the fracture event independently from bone mass. Patients with blindness, postural hypertension, limb amputation, etc. have reduced physical activity and stability; this could increase the risk of falls and bone fractures. This increased risk of falling may be as important in terms of fracture risk for older patients as any reduction in BMD.

In diabetic patients fracture repair is prolonged. One of possible reason could be the accelerated bone collagen ageing in diabetes mellitus.

Decreased BMD in diabetes mellitus type 1, i.e. diabetic patients of higher risk for osteopathy, is mainly caused by presence of:

- decreased IGF and insulin levels
- an autoimmune process accompanied with inflammation reaction
- decreased testosterone,
- decreased body weight

1.5. Conclusion

In order to show the role of diabetes mellitus in osteopenia, it seems essential to distinguish between type 1 and type 2 diabetes mellitus, because of their different pathogenesis and consequently their influence on bone metabolism is different. Therefore adult patients with type 1 diabetes, which is characterised by insulin deficiency, normal weight and an autoimmune process, show a reduced BMD. It is unknown if this results from reduced peak bone mass or from increased bone loss. In contrast, patients with type 2 diabetes mellitus, which is characterized by insulin resistance and hyperinsulinaemia in overweight person, have a normal (or even increased) BMD. Because specific causes of low BMD in type 1 diabetes are unknown, these patients should be evaluated for known determinants of osteoporosis and offered appropriate measures to prevent and treat osteopororsis with the ultimate goal to preventing bone fractures.

Recommended literature:

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