The profound effects of thyroid hormones on bone metabolism were first described in detail by von Recklinghausen in 1891 (1).

For the past decade it has been known that osteoblasts possess nuclear receptors for tri-iodothyronine (T3); however, so far receptors have not been demonstrated in osteoclasts. These findings are in agreement with several organ- and cell-culture studies. In human osteoblast-like cell culture it has been shown by Kassem et al. (2) that T3 stimulates cell proliferation and production of alkaline phosphatase. T3 was found to be unable to stimulate resorption in monocultures of osteoclasts, whereas in co-cultures of osteoclasts and osteoblasts or osteosarcoma cells both T3 and thyroxine stimulated osteoclastic resorption on cortical bone slides, and both the number and the area of the resorption pits were increased (3, 4). It therefore appears that osteoblasts play an important role in mediating the thyroid hormone stimulation of osteoclastic resorption. It is still not clear whether this effect is a direct effect or if mediators are involved; insulin-like growth factor-I has been suggested as a candidate.

After the first recognition by von Recklinghausen of the effects of thyroid hormone on bone turnover, many clinical investigations have been performed to further elucidate the mechanisms behind the stimulatory effects. In hyperthyroid patients, calcium kinetic studies have demonstrated a 25% increase in intake of calcium, but a reduction in intestinal absorption by 66%. Furthermore, fecal calcium loss and dermal calcium loss were increased by 50 and 70%. The overall calcium balance was therefore more negative than in normals: −7.9 mmol/day versus −2.1 mmol/day. The bone resorption rate was increased by 170% and the bone mineralization rate by 140% compared with normals (5).

Early histomorphometric studies of trabecular bone revealed decreased trabecular bone volume, and increased osteoclastic activity and calcification rate (6). Reconstruction of the remodelling sequence by Eriksen et al. (7) revealed an increase in activation frequency from once every 3 years to once every 1.4 years. The duration of the total remodelling sequence was reduced from 151 days to 109 days. The outcome of the completed remodelling sequence, i.e. the balance between resorption and formation, was negative (−10 μm versus 0 μm in the normals). The negative balance in combination with the increased activation frequency resulted in bone loss; trabecular bone volume was reduced by 15–30%. The resorption rate was increased by 250% and the resorption period correspondingly reduced by 70%, but the final resorption depth was unchanged. The formation period was decreased by 30% and bone formation rate was increased 40–60%. But most importantly, the completed wall thickness was reduced by 13%. Thus, the bone loss was mainly caused by impaired osteoblast function.

The effects seen in both the calcium kinetic and histomorphometric studies were the results of cellular exposure to thyroid hormones for extended periods of time. The acute effect of thyroid hormones on bone metabolism has also been investigated. In humans this has been done using biochemical markers of bone turnover. In younger normal volunteers it has been demonstrated that both ongoing resorption and formation were stimulated and that new remodelling units were initiated by stimulation with T3 (8). The same response to thyroid hormone stimulation has been demonstrated in perimenopausal women (9), elderly women, women on hormone replacement therapy, and osteoporotic women (10).

As demonstrated by Bollerslev et al. in this issue of the journal (11) this is also the case in patients with osteopetrosis. Osteopetrosis is an autosomal dominant disease causing defective bone resorption due to defective osteoclast function. From this study, the authors conclude that new remodelling units can be stimulated by thyroid hormones to the same extent in osteopetrotic patients as in normal controls. However, the authors also point out that when looking at the figures showing the progress in the formative markers over time, one could get the impression that the increase during the later phase is less pronounced, if present at all, in the osteopetrotic patients. However, no statistically significant differences could be demonstrated between patients and normal controls. The set-up is however very interesting and certainly warrants more studies on activation of remodelling in diseases.
characterised by defective osteoclast function. Such models may offer new insights into the elusive coupling mechanism.

References


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