

## Summary

Circadian rhythm of parathyroid hormone (PTH) is well documented, but its physiological role is not fully understood. In healthy individuals, biochemical markers of bone remodeling follow a similar circadian rhythm to PTH with a nocturnal rise in bone resorption and formation. The loss of PTH diurnal variation was observed not only in primary hyperparathyroidism, but also in patients with postmenopausal osteoporosis. Continuously elevated concentrations of PTH lead to excessive stimulation of bone resorption, whereas intermittent PTH administration has a strong osteoanabolic effect in patients with osteoporosis. It has not been examined whether the skeletal sensitivity to PTH action depends also on the time of its application.

The aim of our study was to verify the hypothesis that the application of teriparatide (TPTD, recombinant human PTH [1-34]) at different times of the day in the context of its diurnal variability affects the physiological circadian rhythm of bone remodeling and also the bone mineral density (BMD) after the long-term TPTD treatment.

Fourteen women with postmenopausal osteoporosis treated with 20 micrograms of TPTD daily, applied subcutaneously either in the morning or evening, were included in the first study. The concentration of serum C-terminal telopeptide of type I collagen ( $\beta$ CTX), N-terminal propeptide of type I procollagen (PINP), serum ionized calcium (iCa) and plasma intact PTH concentrations were evaluated within 24 hours. The results showed a significant dependence of all measured parameters on the time of day. Evening TPTD treatment significantly enhanced the amplitude of the circadian rhythm of bone resorption marker  $\beta$ CTX, while morning TPTD applications led to the flattening of  $\beta$ CTX rhythm. Circadian rhythm of bone formation marker PINP showed a significantly smaller amplitude than seen in  $\beta$ CTX. Changes in serum iCa were positively related to changes in serum  $\beta$ CTX ( $p < 0,001$ ) and negatively related to changes in PTH ( $p < 0,001$ ).

Fifty women with established postmenopausal osteoporosis were randomized to 12-month treatment with 20  $\mu$ g of TPTD, administered daily either in the morning (before breakfast, at 8.00 a.m.) or in the evening (after dinner, at 8.00 p.m.). After 6 months, the evening teriparatide treatment resulted in a more pronounced increase in bone formation marker - PINP (+358% vs. 215%) as well as bone resorption marker - tartrate-resistant acid phosphatase isoform 5b (+70% vs. +37%) when compared with the morning treatment arm ( $p < 0,05$ ). After 12 months of TPTD treatment, the lumbar spine BMD grew markedly in both treatment groups ( $p < 0,001$ ) with a significantly greater increase in the morning arm (+9,1%) compared to the evening arm (4,8%).

We have shown that timing of TPTD treatment significantly modulates the circadian rhythm of bone turnover markers as well as calcium-parathyroid axis in women with postmenopausal osteoporosis. 12-month morning administration of TPTD resulted in a larger increase in the lumbar spine BMD than the evening application. These results support the hypothesis that timing of TPTD administration significantly affects the skeletal response to TPTD treatment. Timing of TPTD treatment can be important for increasing its long-term efficacy.