

THE CIRCADIAN RHYTHM OF BIOCHEMICAL MARKERS OF BONE RESORPTION IS NORMALLY SYNCHRONIZED IN BREAST CANCER PATIENTS WITH BONE LYTIC METASTASES INDEPENDENTLY OF TUMOR LOAD

A. Dovio¹, D. Generali², A. Berruti¹, M. Tampellini¹, S. Tedoldi², S. Bonardi², M. Tucci¹, G. Allevi², S. Aguggini², M. Milani², A. Bottini², L. Dogliotti¹, A. Angeli¹

¹ Department of Clinical and Biological Sciences, Orbassano, University of Turin, Turin, Italy

² Azienda Ospedaliera Istituti Ospitalieri, Breast Cancer Unit, Cremona, Italy

Bone metastases are common devastating events in the natural history of malignant diseases. Their development results in a profound disruption of local bone remodelling processes. Physiological bone turnover has a circadian rhythm. No data are available on the circadian pattern of bone turnover markers in patients with bone metastases.

Twenty post-menopausal women with breast cancer (BC) at first relapse, at least one bone metastasis and no concomitant chemotherapy/endocrine therapy were consecutively recruited. Twenty healthy women served as controls. Throughout a 24-h period, urine and blood samples were collected at 2 to 4-h intervals. Serum osteocalcin (OC), total and bone-alkaline phosphatase (tALP and bALP, respectively) and C-terminal telopeptide of type I collagen (CTX), and urinary NTX and deoxypyridinoline (DPD) were measured together with serum PTH and serum and urinary calcium and phosphorus. Temporal variations of measured analytes were assessed by ANOVA and the COSINOR model. At 08:00, patients had higher levels of bone resorption indices (NTX, CTX and DPD) than controls ($p < 0.0001$). Total and bone-specific ALP, but not OC, was higher in patients than controls ($p < 0.001$). PTH, serum and urinary calcium and urinary phosphorus did not differ between groups, whereas serum phosphorus was higher in controls ($p < 0.0001$). In both patients and controls a circadian rhythm was evident for CTX and DPD values, with an acrophase respectively in the night (patients 02:40; controls 05:21) and in the morning (patients 09:30; controls 08:22). When considering absolute values, a circadian rhythm in NTX, osteocalcin and PTH was apparent only in controls; however, it was detected also in patients when considering percent changes from MESOR. Also serum phosphorus showed a circadian rhythm, while no rhythm was detected for tALP, bALP, serum and urinary calcium. In patients the rhythmicities were normally synchronized, and rhythmic parameters were independent of tumor load in the skeleton and age. To the best of our knowledge, this is the first study to yield information on the maintenance of the temporal program of bone turnover in bone-metastatic cancer patients. Research is needed to assess whether administration of bisphosphonates in the night time before the peak has a different outcome with respect to the current administration in the morning.