Johanna-Maria Semik
Dr. med.

Diurnal cortisol patterns and its association with fatigue in breast cancer patients

Fach/Einrichtung: NCT (Nationales Centrum für Tumorerkrankungen)
Doktormutter: Prof. Dr. rer. nat. Karen Steindorf

Cancer-related fatigue is a subjective sensation of uncontrollable physical, emotional and/or cognitive exhaustion which emerges in the context of cancer or cancer treatment. Patients with cancer-related fatigue are profoundly affected in quality of life, psychic and physical well-being and in taking part in daily life routines. It is one of the most common and most distracting side effects of cancer therapy, independent of the type of tumor. Approximately 80% of the cancer patients report a permanent feeling of fatigue, about a third of them up to 6 months or more after finishing adjuvant therapy. It is generally assumed that CRF is a multi-factorial construct influenced by many biopsychosocial factors. However, the causal mechanisms and pathophysiology of cancer-related fatigue have not yet been determined.

The stress hormone cortisol is produced and secreted by the adrenal gland. Its circadian rhythm counts as an important indicator for an intact hypothalamus-pituitary-adrenal axis. Cortisol typically shows high morning levels and a peak approximately 30 minutes after awakening (cortisol awakening response) with a gradual decline afterwards reaching lowest levels around bedtime. In contrast to serum cortisol which includes the biologically inactive cortisol bound to carrier proteins, salivary cortisol is regarded as a good indicator for the amount of free or unbound cortisol in plasma and is easily assessable.

Prior studies hypothesized an association between cancer-related fatigue and dysregulations in the hypothalamus-pituitary-adrenal axis with its end product cortisol, but evidentiary data is rarely available. To my knowledge, only two other studies investigated potential associations between cancer-related fatigue and altered cortisol in breast cancer patients. Their findings suggested that fatigue is associated with a flatter diurnal cortisol slope. The pathomechanisms behind this correlation remains unclear. Elevated stress levels as well as an enhanced pro-inflammatory process might be possible trigger for increased cortisol secretion.

In the context of two prospective randomized controlled intervention trials (BEST and BEATE), enrolling breast cancer patients undergoing adjuvant radio- and/or chemotherapy, the participants (n=265) collected saliva samples at three time points (baseline, week 7, week

13), five times a day (awakening, +30 minutes, noon, 5pm, 10pm/bedtime). Fatigue was assessed using the multi-dimensional 20-item Fatigue Assessment Questionnaire. Cortisol in saliva was measured using a competitive enzyme-linked immunosorbent assay. The results of measurement were quality checked by evaluating the intra- and inter-assay variation coefficients: 7.7% and 9.3% respectively. For extreme cortisol values inclusion and exclusion criteria had to be defined. From the measured diurnal cortisol levels the following variables were derived: morning level, cortisol awakening response (CAR), bedtime level, diurnal slope and cortisol secretory activity. Subsequently multiple linear regressions were performed with the continuous fatigue scores (physical, affective, cognitive) as dependent variables. Potential confounding was investigated, considering several covariates, such as age, cancer treatment, depression, social support and sleep problems.

Cross- sectional and longitudinal analyses indicated consistently that physical fatigue in breast cancer patients undergoing adjuvant therapy is associated with higher cortisol bedtime levels and a higher overall cortisol secretory activity (AUC). At baseline only, physical fatigue was associated with a flatter slope and a higher CAR. The morning levels remained independent of fatigue. However, there were no associations seen between altered cortisol levels and the affective and cognitive dimensions of cancer-related fatigue.

One possible explanation of these associations is a dysregulated hypothalamus-pituitary-adrenal axis provoking an overactive pro-inflammatory response via altered cortisol levels with a reduced glucocorticoid receptor sensitivity which interrupt the feedback loop of NF-kB- and cytokine production (IL-2, IFN-α and TNF-α) by the suprachiasmatic nucleus. Chronically elevated pro-inflammatory cytokines are known to be capable of inducing behavioral changes, as the so-called ‘sickness behavior’ (such as symptoms of fatigue) via the central nervous system (basal ganglia, hippocampus), as well as triggering a physical feeling of exhaustion.

The association between cancer-related fatigue and cortisol dysregulations may also be explained by a higher cortisol secretion triggering a lower thyroid hormone production with a following reduction of energy supply and a sensation of physical fatigue. However there is no evidence about the direction of the association between CRF and altered cortisol yet. On the one hand, fatigue may induce higher stress levels which then lead to altered cortisol secretion. On the other hand altered cortisol and fatigue may be provoked by the same cause but are not underlain by the identical causal pathway. Next to the above named possible explanations, it is still essential to keep in mind that every patient undergoes a severe emotional strain when

diagnosed with cancer and that cancer therapy is capable of influencing HPA axis activity, as well.

Future research should be focused on potential causal pathways between cancer-related fatigue and altered cortisol, since a better understanding of the pathophysiology and pathomechanisms of cancer-related fatigue might provide opportunities to develop new treatment strategies for this troublesome side effect of cancer therapy.