Changes in DNA methylation of clock genes in obese adolescents after a short-term body weight reduction program: a possible metabolic and endocrine chrono-resynchronization.

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Circadian rhythms are generated by a series of genes, collectively named clock genes, which act as a self-sustained internal 24 h timing system in the body. Many physiological processes, including metabolism and the endocrine system, are regulated by clock genes in coordination with environmental cues. Loss of the circadian rhythms has been reported to contribute to widespread obesity, particularly in the pediatric population, which is increasingly exposed to chronodisruptors in industrialized society. The aim of the present study was to evaluate the DNA methylation status of seven clock genes, namely *clock, arntl, per1-3 and cry1-2*, in a cohort of chronobiologically characterized obese adolescents (n: 45: F/M: 28/17; age ± SD: 15.8 ± 1.4 yrs; BMI SDS: 2.94 [2.76; 3.12]) hospitalized for a 3-week multidisciplinary body weight reduction program (BWRP), as well as a series of cardiometabolic outcomes and markers of hypothalamo-pituitary-adrenal (HPA) function. At the end of the intervention, an improvement in body composition was observed (decreases in BMI SDS and fat mass), as well as glucometabolic homeostasis (decreases in glucose, insulin, HOMA-IR and Hb1Ac), lipid profiling (decreases in total cholesterol, LDL-C, triglycerides and NEFA) and cardiovascular function (decreases in systolic and diastolic blood pressures and heart rate). Moreover, the BWRP reduced systemic inflammatory status (i.e., decrease in C-reactive protein) and HPA activity (i.e., decreases in plasma ACTH/cortisol and 24 h urinary-free cortisol excretion). Post-BWRP changes in the methylation levels of *clock, cry2 and per2* genes occurred in the entire population, together with hypermethylation of clock and per3 genes in males and in subjects with metabolic syndrome. In contrast to the pre-BWRP data, at the end of the intervention, cardiometabolic parameters, such as fat mass, systolic and diastolic blood pressures, triglycerides and HDL-C, were associated with the methylation status of some clock genes. Finally, BWRP induced changes in clock genes that were associated with markers of HPA function. In conclusion, when administered to a chronodisrupted pediatric obese population, a short-term BWRP is capable of producing beneficial cardiometabolic effects, as well as an epigenetic remodeling of specific clock genes, suggesting the occurrence of a post-BWRP metabolic and endocrine chronoresynchronization, which might represent a “biomolecular” predictor of successful antiobesity intervention.