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The effects of intermittent calorie restriction on metabolic health among overweight and obese individuals: a randomized controlled trial

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Intermittent calorie restriction (ICR) approaches, *i.e.*, dietary regimens based on alternating phases of very low and regular energy intake, have gained considerable interest among scientists for two main reasons: First, mechanistic research and preliminary human studies suggest that potentially beneficial metabolic effects of ICR, such as regulation of insulin sensitivity and insulin-like growth factor-1 signaling as well as control of leptin and adiponectin levels, exceed those of continuous calorie restriction (CCR), even at similar net-calorie restriction and weight loss. Second, it has been proposed that ICR may be more easily adhered to than CCR and be superior with regard to long-term weight control. However, the evidence base for these two claims from human studies is insufficient and there is a lack of large randomized controlled trials (RCT) over longer time periods. Thus, the HELENA Trial, a well-powered RCT to investigate the metabolic effects of ICR and CCR over one year was initiated at the German Cancer Research Center (DKFZ), Heidelberg.

Overall, 150 overweight and obese (50% women) non-smokers, free of diabetes and major chronic diseases, were recruited for the HELENA Trial. These individuals were randomly assigned to a ICR (five days without energy restriction and two days with 75% energy deficit, net weekly energy deficit ~ 20 %), a CCR (daily energy deficit ~ 20%) or a control group (no advise to restrict energy). The RCT included a 12-week intervention phase, a 12-week maintenance phase, and a 26-week follow-up phase.

The first aim of the study was to investigate if metabolic effects of ICR go beyond differences in net-energy intake (ICR vs. CCR), or are explained by these (ICR vs. control). Changes in subcutaneous adipose tissue (SAT) gene expression during the intervention phase were used to investigate metabolic effects of the calorie-restriction regimens and defined as the primary endpoint of the study. Mixed linear models showed no significant differences between the study groups for any of the 82 pre-defined genes. Neither did a transcriptome-wide analysis including all transcripts detected by the HT-12 Illumina microarray. However, *post hoc* analyses on the effects of overall weight loss, irrespective of the dietary intervention, showed that SAT gene expression profiles were differentially regulated with weight loss. Observed

decreases in expression of stearoyl-CoA desaturase-1 (*SCD*), secreted frizzled-related protein 2 (*SFRP2*), and hypoxia induced lipid droplet associated protein (*HILPDA*) with weight loss were validated by reverse transcription-quantitative polymerase chain reaction. These findings indicated that weight loss may induce a reversal of dysfunctional adipose tissue signaling, *e.g.* through down-regulation of *SCD*, *SFRP2*, and *HILPDA*, which are known to be possible metabolic check-points at the interface between obesity and major chronic diseases, even though further functional studies are needed.

The second aim of the present study was to evaluate the adherence to ICR under real-life conditions and to assess the sustainability of its metabolic effects over an extended follow-up phase. Thus, the effects of ICR vs. CCR and ICR vs. control on secondary trial endpoints, *e.g.* anthropometric parameters, body composition, circulating metabolic biomarkers, and health-related quality of life (HR-QoL), were analyzed across the 12-week intervention phase, 12-week maintenance phase, and 26-week follow-up phase. While the ICR group had shown the strongest weight change between baseline and post-intervention (-7.1 ± 0.7 %) compared to the CCR (-5.3 ± 0.6 %), and control group (-3.3 ± 0.6 %), the final study assessment indicated similar weight loss with ICR (-5.2 ± 1.2 %) and CCR (-4.9 ± 1.1 %), and slight weight loss in the control group (-1.7 ± 0.8 %). There were no significant differences in weight change between ICR and CCR at any time point. Changes in weight were paralleled by proportional changes in visceral and subcutaneous fat volumes and in hepatic fat content, again without significant differences between ICR and CCR. Similarly, the majority of blood-based biomarkers of glucose and insulin metabolism, lipid metabolism, liver function, inflammation, and adipokine signaling showed decreases in all groups across the 12-week intervention phase, but no significant between-group differences. With regard to decreases in fasting glucose levels and homeostatic model assessment of insulin resistance (HOMA-IR) index, there was an indication for superiority of CCR over ICR at week 12, while the significant differences were no longer observed after the maintenance and follow-up phase, and were neither detected at any time point when comparing ICR vs. control. HR-QoL, as assessed by the Short-Form Health Survey-12, did not change in any study group.

In summary, the HELENA Trial did not show differences in the effects of ICR and CCR on changes in anthropometric parameters, body composition, circulating metabolic biomarkers, and HR-QoL across the 12-week intervention phase, 12-week maintenance phase and 26-week follow-up phase. Overall, the present results suggest that ICR and CCR might be equivalent approaches to induce weight loss and to improve metabolic status. It is conceivable that the two calorie restriction regimens are suitable for different subgroups of overweight and obese individuals, while the long-term maintenance of weight loss and metabolic effects going beyond a one-year study phase remains to be investigated.