RESPONSE TO COMMENT ON JAKUBOWICZ ET AL.

Reduction in Glycated Hemoglobin and Daily Insulin Dose Alongside Circadian Clock Upregulation in Patients With Type 2 Diabetes Consuming a Three-Meal Diet: A Randomized Clinical Trial. Diabetes Care 2019;42:2171–2180

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The proposal that the protocol in our study (1) is not very different from implementing an intermittent fasting regimen with a feeding window of 5.5 h (0930–1500 h), corresponding to 18.5 h daily fasting (2), is correct. It has been shown that a feeding regimen with an inherent timing component provides a time cue for the circadian clock. For example, time-restricted feeding, which limits the time and duration of food availability without calorie reduction, affects circadian clocks in peripheral tissues causing uncoupling from the central pacemaker in the suprachiasmatic nuclei (3). As a result, many activities, such as body temperature, corticosterone secretion, gastrointestinal motility, and activity of digestive enzymes—all known output systems of the circadian clock—are altered. These timed regimens are accompanied by robust expression of the circadian clock and catabolic factors, improving metabolic output (3). Thus, the timing component of feeding is important to achieve robust rhythms and, as a result, more efficient metabolic regulation. The current study (1) is an example of timed feeding, as the meals were at designated hours and the majority of calories were consumed during the early hours of the day.

It is noteworthy that to achieve an optimal metabolic regulation, the timing of feeding needs to be aligned with the endogenous metabolic rhythmicity. Men with prediabetes assigned to early time-restricted feeding (a 6-h feeding period with dinner before 1500 h), which is aligned better with circadian rhythms in metabolism, or a control schedule (12-h feeding period) for 5 weeks had improved insulin sensitivity and β-cell responsiveness (4). In contrast, late eating has been shown to be predictive of weight-loss difficulties in obese and overweight individuals, and this effect was independent of the total 24-h caloric intake (3). Skipping breakfast has also been shown to be associated with weight gain and other adverse health outcomes, including insulin resistance and increased risk for developing type 2 diabetes (5). Thus, calorie consumption during the early hours of the days is beneficial, allowing hours of fasting each day. These benefits of fasting are implemented in various diet protocols, such as alternate-day fasting, 16:8 fasting, and others.

The notion of comparing high caloric intake at breakfast compared with dinner has been studied. A 12-week clinical study showed that those subjects assigned to a high caloric intake during dinner lost significantly less weight than those assigned to a high caloric intake during breakfast with no significant differences in the total amount of food or energy expenditure. Consumption of a high-energy breakfast and a low-energy dinner resulted in a significant reduction of all-day postprandial glycemia and body weight compared with patients who consumed large dinner and small breakfast (6). Indeed, breakfast has previously been demonstrated to be of major importance for the 24-h regulation of glucose. Thus, although there will always be an inherent long fasting component in these protocols, studies comparing high caloric intake during the early hours of the day versus the late hours of the day show better glucose homeostasis in the former.

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