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GYNECOLOGY • HORMONE THERAPY
INTEGRATIVE MEDICINE

A Time to Eat ● A Time to Exercise

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Exercise Sport Sci Rev. 2020;48(1):4-10.

Optimal cardiometabolic health for individuals at risk of chronic lifestyle-related diseases results from interventions in which dietary intake is reduced and/or quality is improved, and exercise of sufficient mode, duration, and intensity is performed. However, adherence to changes in habitual dietary patterns is often considered more arduous than medical therapy, and most individuals report "a lack of time" as the major reason for not undertaking regular exercise. As such, the debate becomes "what priority should be given to modifying diet versus implementing exercise training for improving health outcomes?" As energy, via food, is required to sustain life, it is perhaps no surprise that dietary modifications are often the first in line of attack in the arsenal of lifestyle interventions to prevent/treat many metabolic diseases. Although there is an extensive menu of dietary options available to improve *metabolic health* outcomes, their success/failure, as with any exercise intervention, depends on long-term adherence.

Strategies to Improve Metabolic Health

The benefit of improving dietary quality combined with undertaking regular exercise is undoubtedly the best approach to prevent/treat noncommunicable diseases. However, adherence to lifestyle modifications is poor, and such behavioral changes have met with limited success at the population level. Consequently, diet and exercise strategies that focus on more socially acceptable and achievable interventions (*e.g.*, exercise "breaks" after meals, changing the timing of eating, high-intensity sprint interval training) may be more effective for improving metabolic health. The interactions between the timing of exercise and meals are complex: changes in energy and/or macronutrient intake *rapidly alter* the concentration of blood substrates and hormones causing marked changes in insulin-sensitive tissues, including skeletal muscle, liver, fat, and the brain. In turn, the energy status of muscle exerts marked effects on resting fuel metabolism and patterns of fuel use during exercise.

Diet Interventions

In the past decade, evidence has accumulated to suggest that *timing of meals* directly affects a wide variety of physiological functions, including the sleep/wake cycle, core body temperature, athletic performance, and mental alertness. Furthermore, the timing of meals has a profound effect on skeletal muscle insulin sensitivity, synchronization with the body's circadian rhythms. and whole-body metabolic health.

Numerous diet strategies have been proposed to curb the soaring prevalence of obesity and lifestyle-induced metabolic disorders (e.g., Type 2 Diabetes) A feature common to most of these diets is the manipulation of the feeding-fasting cycle**. Time-restricted eating (TRE),** in which eating is limited to a "window" of less than 10 hrs. per day, has emerged as a practical way of reducing the time over which energy is consumed (**Figure 1**). Gill and Panda were the first to show that 16 wks of **TRE** in overweight humans [body mass index >25] induced a modest weight loss (~3% body mass) after decreasing the eating window to <10 hrs. per day. This weight loss was maintained for 12 months, suggesting **TRE** may be a practical strategy for weight maintenance over the long term. Although the participants in that study[11] were not asked to change nutritional quality or quantity, reducing daily eating duration led to 20% reduction in energy intake!

Figure 1.

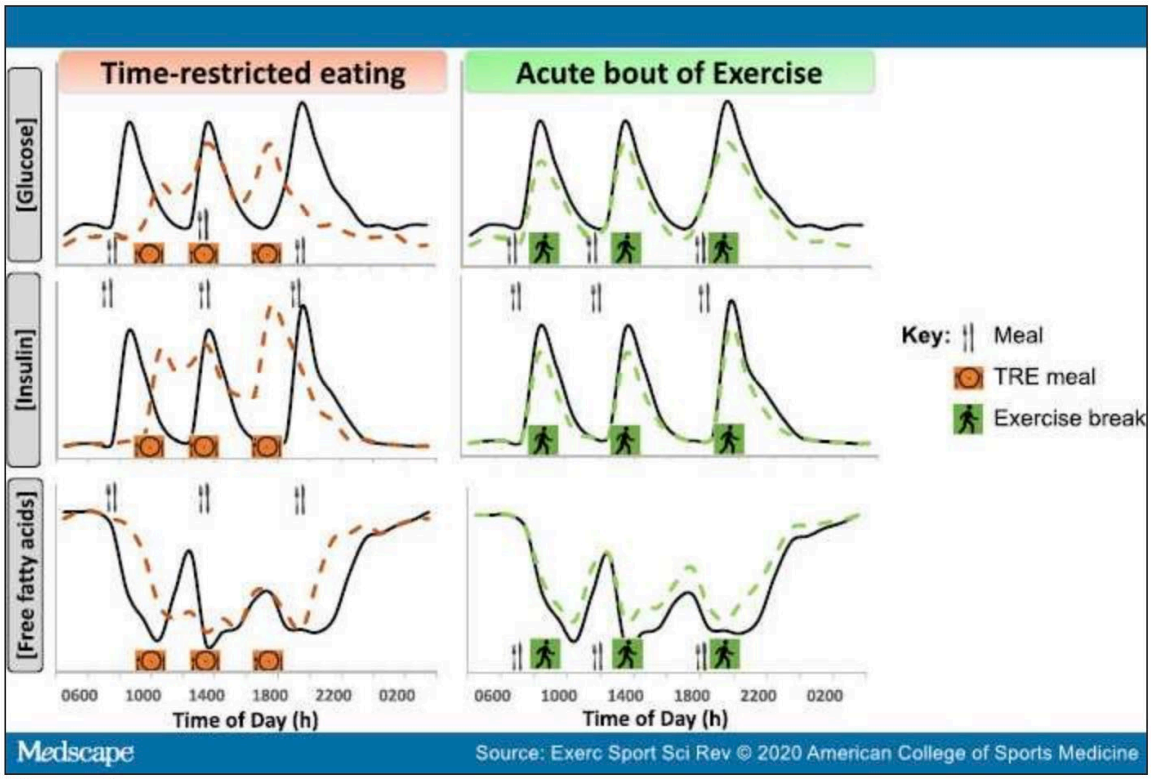

Figure 1.

Proposed marked changes to glucose, insulin, and free fatty acid (FFA) concentrations over a 24-hour period with *time-restricted eating* (**TRE**) (orange, dashed lines) or "exercise snacks" (~10 min walking; green, dashed lines) compared with typical circulating metabolite patterns in response to three meals consumed during waking hours.

The body's circadian clock affects hormonal metabolism, with the timing of meals fine-tuning endocrine biology regarding glycemic (glucose) control. An increase in blood glucose from cortisol-stimulated hepatic (liver) glucose production occurs around 10 am, when cortisol levels

typically peak after waking. Delaying (not skipping) breakfast to late morning (after 10 am) and missing the circadian-related release in hepatic glucose could improve postprandial glycemic control (Figure 1). Insulin secretion and sensitivity also are under circadian regulation: these parameters are increased early in the day and drop in the evening, even when there are equidistant 12-hour fasts between meals. **Thus**, the reduction in insulin sensitivity in the evening explains the impaired glucose tolerance measured in response to late-night dinner consumption.

An important question for both health outcomes and the practicality of implementing **TRE** interventions is whether the window of meal timing throughout the day (as well as the start/finish time of meals) is associated with the magnitude of improvement in health markers. The *early* time-restricted eating (**eTRE**) intervention by Sutton *et al.* revealed hyperinsulinemia was reduced when daily eating was completed by 3 pm, but such a strict eating protocol is not likely to be practical or socially acceptable at a population level. Studies of "late" **TRE**, when total energy intake was restricted to meals consumed after 4 pm, have resulted in impaired fasting glucose, lowered glucose tolerance, and increased ratings of hunger. Studies that have commenced **TRE** in the *middle of the day* have shown either no effect or tended to be beneficial regarding glycemic control.

In the only comparative time window **TRE** study to date, Hutchison *et al.* compared 1 wk. of ***early*** **eTRE** (8 am - 5 pm) with ***delayed*** **TRE** (12 pm – 9 pm) in men at risk of developing type 2 diabetes (T2D). Both protocols improved glycemic control in response to a test meal, but only **TRE** improved overnight fasting glucose levels. Clearly, there is a trade-off between the feasibility of undertaking **TRE** and adherence to an optimal **TRE** window that aligns with healthy circadian rhythms. Accordingly, future studies should determine whether it is the placement of the eating window, or the duration spent in the fasted state over each day that induces many of the improvements in metabolic health.

Physiologically, when food is ingested *neuroendocrine cells* in the intestine (ileum and colon) secret **satiety-inducing hormones** that create a sensation of fullness:

- ***Glucagon-like peptide-1*** **(GLP-1**), a family of hormones called the ***incretins***, so-called because they stimulate the secretion of insulin from the beta-cells of the pancreas.
- ***Glucose-inhibitory peptide*** **(GIP**), also known as *gastric inhibitory peptide*, is a gastric inhibiting hormone and stimulates insulin secretion.
- ***Peptide YY*** **(PYY)** has been shown to reduce appetite by slowing the gastric emptying; hence, it increases efficiency of digestion and nutrient absorption after a meal.
- ***Ghrelin*** is a **hunger-inducing hormone** which is suppressed in response to eating.

These intestinal hormones play a critical role in modulating appetite and the rate of gastric emptying (which slows in the evening), and, therefore, the glycemic (insulin) response to meals. Secretion of these hormones is also under circadian regulation. For example, ghrelin release peaks at mid evening (8 pm) and is lowest upon waking in the morning, explaining, in part, the strong biological drive to eat at night.

In terms of sustainability, **TRE** seems to offer a practical advantage over stricter energy-restricted diet interventions. However, the types of foods consumed often are aligned closely to distinct times of the day, e.g., alcohol typically is consumed at the end of the day, as are sweet (refined sugar) foods such as ice cream.

Exercise Interventions

TRE extends the length of time in the fasted state (Figure 1), inducing several responses that are like those observed after exercise training (Figure 2). However, when compared with dietary interventions, both the amplitude and extent of exercise training-induced responses/adaptations are likely to be greater in a head-to-head comparison (Figure 2). Evidence for such a premise comes from epidemiological data demonstrating that the association between low cardiometabolic fitness (*i.e.*, maximum oxygen uptake) and all-cause mortality is stronger than that of obesity. Exercise training delays the onset of multiple chronic metabolic conditions and diseases. However, getting people to comply with even the minimal recommended quantity and quality of exercise required to confer health benefits has proven difficult.

Figure 2.

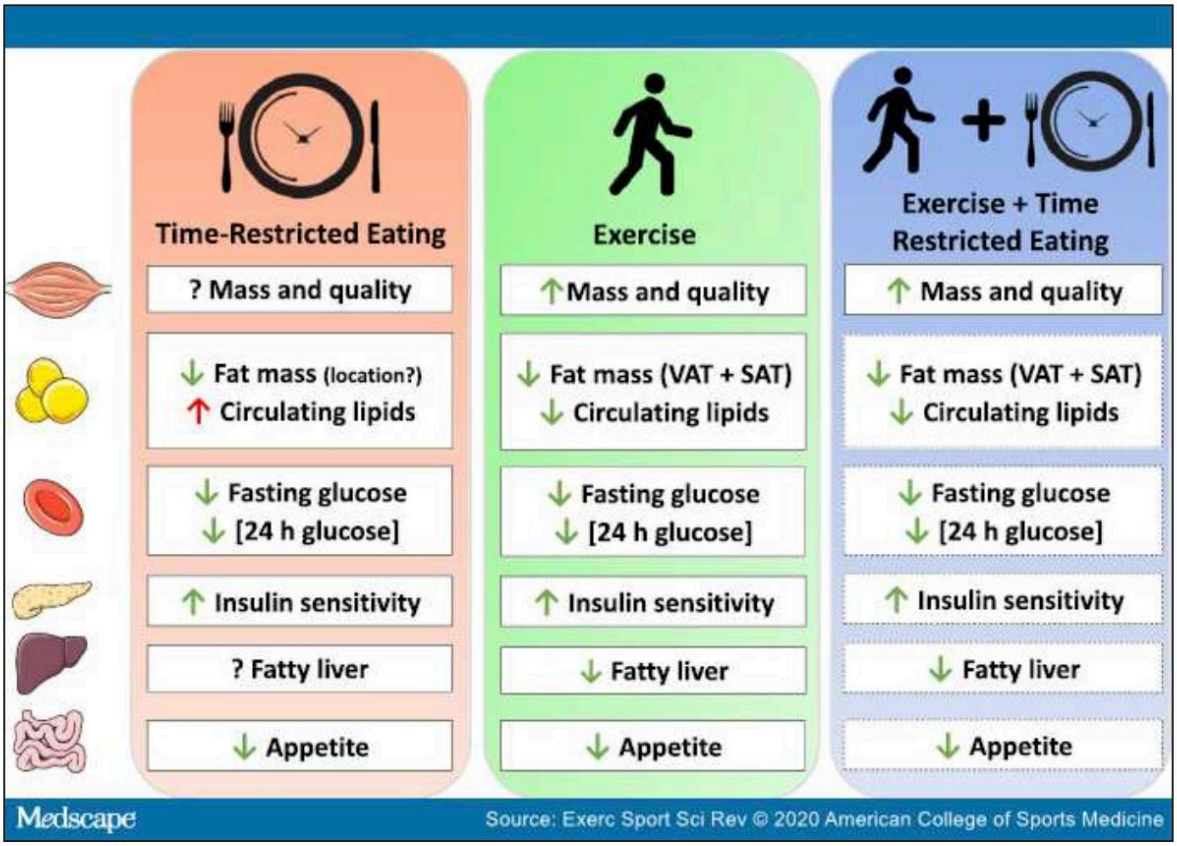

Figure 2.

Effects of time-restricted eating (TRE) and exercise training on metabolic health in humans (known, solid box; proposed, dashed box). Green arrows, positive change; red arrows, negative change; question mark, unknown effect. SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

A strong association exists between the increase in ***physical inactivity*** and the emergence of modern chronic diseases in 20th century industrialized societies. Approximately 250,000 deaths per year in the United States are premature due to physical inactivity. Epidemiological data have established that *physical inactivity* increases the incidence of at least 17 unhealthy conditions, almost all of which are chronic diseases or considered risk factors for chronic diseases. Consider the concept that the human genome evolved within an environment ***of high physical activity*,** until the 20th century. It has been proposed that exercise biologists study the effect of reintroducing exercise into an unhealthy sedentary population that is genetically programmed for significantly greater physical activity.

Exercise training has a significant impact on body composition, reducing both subcutaneous fat (SAT) and visceral fat (VAT), while preserving lean body mass (muscle). Aerobic-based exercise of sufficient duration/intensity promotes beneficial changes in whole-body metabolism and reduces fat mass; whereas resistance exercise preserves or increases lean (muscle) mass. Energy-restricted diets in isolation are effective short-term strategies for rapid weight loss but result in a reduction in both fat and muscle mass, predisposing one to an unfavorable body composition and poor health prognosis. Exercise typically results in only a modest increase in total daily energy expenditure but has minimal effects on long-term weight loss, depending on the volume/intensity of exercise performed. As such, the performance of regular and appropriate exercise is the only mechanism to improve body composition (*i.e.*, lose fat mass while maintaining lean mass).

Although **TRE** interventions have the potential to change habitual dietary practices, there may also be changes to physical activity patterns. The effect of increasing the amount of exercise on dietary intake, however, appears equivocal. In older adults with prediabetes, performing regular resistance-based exercise reduced self-reported intake of carbohydrate, sugar, sweets, and desserts, with little effect on protein intake. Such changes to total energy and macronutrient intake may be related to changes in the regulation of appetite with exercise. Acute physical activity transiently represses appetite in both lean and obese individuals via a ***suppression of ghrelin*** and ***increases in PYY and GLP-1*.** Exercise training may balance appetite responses by an increased satiety response to a meal despite an increased drive to eat. Exercise training also ***reduces circulating leptin*** concentrations, thereby reducing fat mass and positively affecting appetite and body composition. Therefore, exercise can reduce appetite and improve overall dietary intake.

A single bout of exercise increases skeletal muscle glucose uptake. However, this "insulin-sensitizing" effect is short-lived and dissipates after 48 hrs. In contrast, regular exercise training results in a persistent increase in insulin action in skeletal muscle in healthy individuals and in people with insulin resistance and obesity. Exercise training also improves glucose tolerance. The precise volume of exercise required to induce a clinically meaningful change in glycemia is a contentious issue. Dempsey *et al.* reported that less than 40 min of walking or body weight resistance exercises (12 × 3-min bouts) undertaken between 9 am and 3 pm improved both

waking and nocturnal glucose concentrations in individuals with T2D. Breaking up exercise bouts ("exercise snacking") into 3 × 10-min bouts after meals improved daily glycemic control in individuals with type 2 diabetes (T2D) to a greater magnitude than a continuous 30-min walk. In individuals with prediabetes, three "exercise snacks" (6 × 1 min of high-intensity activity before each meal) improved daily glycemia on both the day of exercise and over the subsequent 24 hrs. As such, adequate physical activity no matter how it is accumulated across a day is effective in attenuating postprandial glucose and insulin concentrations (Figure 1).

Regular exercise increases post exercise rates of whole-body fat oxidation and improves metabolic flexibility (the ability to respond to changes in hormonal milieu and switch between fuel sources in response to the prevailing metabolic demand). Exercise also has a positive effect on circulating lipid profiles, with decreased fasting and postprandial FFA (free fatty acids) concentrations, increased uptake of FFA by the muscle, and lower uptake of FFA to the liver contributing to improvement in nonalcoholic fatty liver disease (NAFLD).

A meta-analysis of aerobic-based exercise training programs performed for 12 wks or longer revealed reduced circulating TGs (triglycerides) and higher high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol. Reductions in cholesterol and circulating lipids have also been observed both in response to a single bout of resistance-based exercise and after resistance training, although the magnitude of reduction is typically less than that observed after aerobic exercise training. Even short bouts of physical activity accumulated for 40 min during a day improves the postprandial handling of lipids. Despite this evidence most individuals report "a lack of time" as the major reason for not undertaking regular exercise.

TRE and Exercise Training: Some Considerations

The discovery of muscle *"cross-talk"* with other organs, including adipose (fat) tissue, liver, pancreas, bone, and the brain, provides a framework for understanding how exercise mediates many of its beneficial whole-body effects. Although several acute responses to **TRE** are like those attained after exercise training (Figure 2), exercise evokes widespread and extensive remodeling of almost every organ/tissue in the body (*i.e.*, increased bone mineral density, improved cardiovascular dynamics and blood flow, increases in muscle oxidative capacity and capillarization, increases in muscle cross-sectional area, etc.). Indeed, it is the very complexity and multiplicity of networks involved in exercise responses that make it unlikely that such whole-body effects could be induced by **TRE** alone.

When individuals undertake regular exercise, complementing with **TRE** may help modify behavioral patterns of eating, (*i.e.*, reduced end-of-day snacking/alcohol consumption) and enhance overall health benefits. For individuals with medical conditions where physical activities cannot be performed, **TRE** offers a feasible strategy to improve or maintain metabolic health. Although there is an extensive menu of dietary options available to improve metabolic health outcomes, their success/failure, as with any exercise program, depends on long-term adherence.

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