Review
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Impact of Energy Turnover on the Regulation of Energy and Macronutrient Balance

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Energy turnover, defined as the average daily total metabolic rate, can be normalized for basal metabolic rate in order to compare physical activity level between individuals, whereas normalization of energy turnover for energy intake (energy flux) allows investigation of its impact on regulation of energy partitioning independent of energy balance. Appetite sensations better correspond to energy requirements at a high compared with a low energy turnover. Adaptation of energy intake to habitual energy turnover may, however, contribute to the risk of weight gain associated with accelerated growth, pregnancy, detraining in athletes, or after weight loss in people with obesity. The dose–response relationship between energy turnover and energy intake as well as the metabolic effects of energy turnover varies with the habitual level of physical activity and the etiology of energy turnover (e.g., cold-induced thermogenesis, growth, or lactation; aerobic vs. anaerobic exercise). Whether a high energy turnover due to physical activity or exercise may compensate for adverse effects of overfeeding or an unhealthy diet needs to be further investigated using the concept of energy flux. In summary, the beneficial effects of a high energy turnover on regulation of energy and macronutrient balance facilitate the prevention and treatment of obesity and associated metabolic risk.

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Study Importance

What is already known?

- When compared with low energy turnover, high energy turnover facilitates weight maintenance because of appetite sensations that better correspond to energy requirements.
- Normalization of energy turnover for energy intake allows for evaluation of the effects of energy flux on regulation of energy balance and metabolic risks.

What does this review add?

- During growth and development, a disproportionally higher increase in lean compared with fat mass may increase the risk of overweight and obesity in later life because of an increase in energy turnover.
- The dose–response relationship between energy turnover and energy intake may vary with the acute and habitual level of exercise.

How might these results change the direction of research or the focus of clinical practice?

- Different causes of energy turnover (due to different intensities of physical activity or a different contribution of organ and tissue masses during cold-induced thermogenesis, growth, or lactation) exert discrepant metabolic effects that need to be differentiated with respect to their impact on energy balance and metabolic risk.
- Appetite control adapts to the habitual energy turnover. The time to reach the adaptation remains to be investigated.

Introduction of the Concept of Energy Turnover Versus Energy Flux

Daily energy turnover is defined as the average diurnal total metabolic rate (which is the sum of basal metabolic rate [BMR], diet-induced thermogenesis, and physical activity level [PAL]) (1), which is higher in athletes compared with sedentary individuals. Turnover rates are measured as quotients of transfer rates divided by the energy content or energy pool of the body. In an attempt to normalize energy turnover in order to compare the metabolic rate of animals with different body size, Max Kleiber defined the energy turnover rate as metabolic rate divided by the chemical energy content of the body (2). Other authors have normalized energy turnover for BMR in order to compare the maximal sustainable metabolic rate between species (3). The importance of normalization for body size is evident when the metabolic effects of differences in energy turnover are compared between normal-weight people and people with obesity. The higher energy turnover in obesity is the effect of high body mass and therefore conveys no metabolic advantage when compared with a high energy turnover obtained by high physical activity. The concept of metabolic equivalent of task, which is commonly used in sports

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and exercise, defines the intensity of physical activity as multiples of resting metabolic rate (RMR). Normalizing energy turnover (i.e., total energy expenditure) for BMR thus allows comparison of PAL between individuals. In order to account for the higher energy requirement in people with obesity, energy turnover should be normalized for body composition or resting energy expenditure (4). Interestingly, in hunter–gatherer populations, Pontzer et al. found low resting energy expenditure that compensated for an increase in total energy expenditure at a higher PAL (5). Normalizing energy turnover for resting energy expenditure reveals that these hunter–gatherers indeed have a high energy turnover despite total energy expenditure that is comparable to industrialized populations.

Furthermore, normalization of energy turnover for energy intake is required to investigate whether energy turnover and the rate of change in energy turnover (timing, frequency, and intensity of energy turnover) can regulate energy and macronutrient balance and thus affect metabolic health (6-8). This is implemented in the concept of energy flux, which can be described as the level of energy balance, i.e., the rate of energy conversion from absorption to expenditure or storage (9). In physically active people, a high energy turnover coupled with high energy intake therefore corresponds to a high energy flux, whereas inactivity with a respective lower energy intake designates a low energy flux. A glossary of terms is given in Table 1.

Impact of Energy Turnover on Regulation of Energy Intake

From a teleological point of view, energy expenditure should directly impact the regulation of appetite and energy intake. There is evidence from a historic observational study that appetite is homeostatically controlled when the physical demand of work is high, but this control is lost at working activities with lower energy expenditure (10). In line with this hypothesis, 2 days' inactivity in normal-weight young men led to spontaneous overeating with a positive energy balance depending on the fat content of the diet (+2.6 MJ/d on a 35% fat diet and +5.1 MJ/d on a 60% fat diet) (11). This positive energy balance was prevented by increased energy expenditure of 2.8 MJ/d on a cycle ergometer (3 × 40 minutes at 75 W). Data from Stubbs et al. also showed that there was no compensatory decline in ad libitum food intake in response to large reductions in energy expenditure (12). In addition, a dramatic reduction in energy expenditure during 1 day of sitting was not accompanied by reduced appetite signals (13). Other authors have shown that acute physical activity transiently represses appetite in both lean individuals and individuals with obesity by suppression of ghrelin and increases in peptide YY and glucagon-like peptide-1 (GLP-1) (14). In a recent study, our group was able to verify that with increasing energy flux at equal energy balance (PAL of 1.3, 1.6, and 1.8 obtained by different durations of brisk walking on a treadmill), appetite control was improved in young men and women with normal weight and overweight (6). This was due to lower sensations of hunger and appetite as well as higher GLP-1 and lower ghrelin levels with a higher energy flux. The same results were obtained for controlled under- and overfeeding (−25% and +25% of energy balance). These findings confirm the hypothesis of an asymmetric regulation of appetite in which, in contrast to increased energy expenditure, reduced energy expenditure is not compensated by an appropriate adaptation in energy intake. In contrast to the prevailing concept of body weight control, the positive impact of physical activity is therefore not simply explained by burning up more calories but by improving appetite control.

Results from these short-term intervention studies are complemented by the effect of detraining due to injuries, vacation, overtraining, or seasonal sports on weight and fat gain in athletes. After 2 months of detraining, a 4.8-kg body weight gain was observed, including 4.3 kg of fat mass (15). The energy equivalent of these changes in body composition was about 179 MJ and corresponded to about the amount of energy that would have been normally expended during the detraining period.

The appetite-suppressant effect of exercise may not be linear over the full range of physical activity. In support of this hypothesis, a shorter running distance produced a fourfold-greater gain in BMI per kilometer per week between 0 and 8 km/wk than between 32 and 48 km/wk (16). In addition to different dynamics in the response of energy intake dependent on the level of energy expenditure, the impact of intensity of physical activity (e.g., brisk walking vs. running) on the energy balance-regulating effect of a high energy turnover needs to be investigated. In the study by Hägele et al., the appetite-suppressant effects

TABLE 1 Glossary of terminology

Term	Definition
Energy balance	Difference between energy intake and energy expenditure
Energy expenditure	Calories burned for the total daily energy requirement (sum of basal metabolic rate, diet-induced thermogenesis, physical activity energy expenditure, and energy expenditure for growth or lactation)
Energy flux	Level of energy balance, i.e., at a low energy flux, energy intake and energy expenditure are both low whereas at a high energy flux, energy intake and energy expenditure are high
Energy intake	Sum of consumed food calories
Energy partitioning	Deposition or mobilization of body fat-free mass and fat mass, more specifically, the allocation of nutrients between these compartments or between the various organs and tissues
Energy requirement	Amount of food energy needed to balance energy expenditure in order to maintain body composition and physical activity as well as energy for growth or deposition of tissues during pregnancy and lactation
Energy turnover	Total energy expenditure normalized for body composition
Metabolic equivalent of task	Total energy expenditure normalized for basal metabolic rate

of a higher energy turnover were obtained by low-intensity physical activity (brisk walking on a treadmill) (6). By contrast, other authors found that hunger and appetite regulatory hormones were insensitive to low-intensity bouts of physical activity (17). Likewise, with the same energy cost, high-intensity exercise exerted a greater reducing effect on energy intake relative to expenditure compared with low-intensity exercise (18). Increasing intensity of exercise also led to greater suppression of orexigenic signals and greater stimulation of anorexigenic signals in another study (19). So far, it remains unclear whether the intensity of exercise might alter appetite at the same amount of energy intake and energy expenditure (i.e., at the same energy flux). Exercise could also affect energy intake independently of energy turnover and thus act as a stimulus rather than by modulation of energy turnover. In line with this hypothesis, beta-adrenergic stimulation by vigorous exercise thus not only may increase energy expenditure (20) but also could lead to decreased energy intake.

The appetite-suppressant effect of physical activity or exercise likely also depends on the habitual level of physical activity. In sedentary individuals, an increase in PAL from 1.4 to 1.6 may therefore lead to weight loss, whereas the same PAL of 1.6 should lead to weight gain in an athlete who used to be more physically active (e.g., PAL 1.8). This idea suggests that appetite control adapts to the habitual amount of energy turnover. The necessary time to reach such an adaptation and the persistence of this phenomenon remain to be investigated. Interestingly, compensation of energy expenditure by energy intake appears to be greater for longer exercise interventions (21), suggesting progressive adaptation of appetite to a higher energy turnover.

In addition to weight gain after detraining, further evidence for a persistent adaptation of appetite to a high energy turnover comes from the increasing risk of weight gain after each pregnancy (22). Higher energy turnover during pregnancy with a sudden decrease in energy turnover after delivery (especially without breastfeeding) may therefore increase the risk of overweight or obesity.

Similarly to increased energy turnover during pregnancy, a high energy turnover with growth and development may change our perspective on the etiology of weight gain and obesity. Accelerated growth increases the energy requirement and may thus increase the risk for weight gain. High birth weight (23), high protein intake during the first 2 years of life (24), or early BMI rebound in young children (25,26), as well as precocious puberty (27) all have been shown to lead to a disproportional high increase in lean compared with fat mass and an increased later risk of obesity. Lean body mass and RMR (and other aspects of energy expenditure) were proposed to constitute a biological drive to eat, whereas fat mass was negatively associated with food intake, especially in leaner individuals (28). The energy requirement (i.e., due to accelerated growth or the increase in lean mass) may thus be the major determinant of appetite and energy intake rather than the adipocentric regulation of energy balance in which anabolic responses are triggered by adiposity-related signals that determine the drive for energy intake (29-31). Already in 1993 it was proposed that "the impetus for lean tissue growth, or protein accretion […] regulates nutrient supply" (32). The decrease in energy turnover with ageing is not only due to inactivity but also caused by the age-related loss in skeletal muscle mass that may contribute to a gain in fat mass with age (33). Because the RMR on fat-free mass association (and thus the specific metabolic rate) decreases with age, the decrease in high metabolically active organ masses per kilogram of lean mass (34) might also contribute to the age-related gain in fat mass.

A higher energy requirement in people with obesity due to high body mass may impede weight maintenance after successful weight loss because a loss in body mass is tantamount to a decrease in energy expenditure (35). The compensatory higher energy intake as a result of lower energy expenditure has been elegantly calculated from the difference between actual and predicted weight loss following therapy with sodium-glucose cotransporters, two inhibitors that lead to "energy loss" via glucosuria (36). The adaptive increase in energy intake above baseline was about 95 kcal/d for every kilogram of weight loss. This is a quantification of the appetite drive associated with energy flux. Such an increase in appetite contributes substantially to the apparent decrease in dietary adherence that limits weight-loss success (37). Attenuation of this biologic drive to regain weight can be achieved by filling the gap of energy flux by an increase in physical activity (38). The effect of additional energy expenditure by exercise on body weight regulation, however, shows a high interindividual variance (39). Further studies are necessary to systematically analyze the etiology of this variance that may depend on insulin sensitivity, aerobic fitness, differences in habitual PAL, or energy partitioning into fat and lean mass.

Weight loss also leads to a reduction in energy expenditure beyond what is expected from the decrease in fat-free mass and fat mass. This adaptive thermogenesis was explained by weight loss–induced changes in sympathetic nervous system activity, thyroid function, and leptinemia (40,41), it was found to be significantly correlated to the change in hunger in response to weight loss and may thus contribute to weight regain (42).

In contrast to exercise, small increases in energy turnover induced by a short sleep duration (43,44) or demanding mental work (45,46) resulted in overeating and thus a positive energy balance. The effect of energy turnover on energy intake therefore depends on the nature of the underlying stimulus that need not be energy expenditure per se but could also be other stimuli.

Impact of Energy Turnover on Energy Partitioning and Metabolic Health

The capacity to match metabolic fuel selection to changing rates of energy use and substrate availability ensures survival of all organisms. In humans, dysregulation of metabolic fuel selection between fat and glucose (metabolic inflexibility) is associated with disorders such as metabolic syndrome and type 2 diabetes, whereas caloric restriction and exercise improve energy partitioning and thus metabolic health (47). The interaction between fat and glucose use has therefore been intensely studied at the organ-tissue and whole-body level in the context of exercise, fed-fast transitions, caloric restriction, overfeeding, varying diet composition, and metabolic diseases (e.g., 48-50).

Energy turnover has the ability to appropriately regulate individual fluxes of fuels in response to changes in diet composition. Fuel selection at rest depends on individual preferences of organ and tissue masses (e.g., glucose oxidation in the brain and fat oxidation in muscle). At a low energy turnover, fuel selection is mainly determined by the metabolic requirement of organs (i.e., up to 70% of resting energy expenditure is due to high metabolically active organ mass) (51). Conversely, at a high energy turnover, physical activity is high, and substrate use increasingly relies on skeletal muscle and depends on the intensity of exercise as well as on aerobic fitness (52).

Different kinds of energy turnover (cold-induced thermogenesis, growth, pregnancy, and aerobic or anaerobic exercise) involve different metabolic pathways and tissues and may thus differently affect metabolic consequences or energy partitioning. The nature of energy turnover therefore needs to be considered in order to interpret health consequences. Exercise or cold exposure may have a positive effect on metabolic flexibility (i.e., the ability to switch between carbohydrate and fat oxidation with fasting and postprandial conditions) and appetite control, whereas hepatic insulin resistance with increased gluconeogenesis increases energy turnover without beneficial effects on health.

When intentionally overfed, participants failed to compensate by raising voluntary activity (11). This failure of a "push mechanism" by energy intake also applies to cellular bioenergetics, because energy expenditure in all cells is not directly coupled to energy supply but rather is determined by the rate of energy turnover (pull mechanism) (53). Hence, increased energy turnover was identified as a common underlying protective mechanism in various genetic models resistant to diet-induced metabolic disease (53-56).

It was recently proposed that an unhealthy Western diet may have less or even no adverse health consequences at a high energy turnover (57,58). At the extreme of energy turnover, endurance athletes consume high amounts of fructose during physical activity, and sports nutrition guidelines have consistently recommended high carbohydrate intake before, during, and after exercise to meet working muscle energy demands (59). For example, Tour de France cyclists reach a sugar intake of ∼460 g (∼1,720 kcal), at a total energy intake of ∼5,800 kcal/d (60) without developing metabolic impairment or hepatic steatosis. Likewise, some hunter–gatherer populations consume as much as 50% of energy intake from honey but also have a very low prevalence of metabolic disease (5). Even a hypercaloric diet may have no adverse consequences at a high energy flux. Sumo wrestlers consume 5,000 to 7,000 kcal/d, with ∼80% coming from carbohydrate. Although these athletes have obesity, most of them maintain normal glucose and triglyceride levels, presumably because of the ability to partition excess energy in expanding hyperplastic subcutaneous adipose tissue rather than in dysfunctional hypertrophic subcutaneous and visceral fat depots or ectopic liver fat (61,62). On the contrary, in physically inactive humans, overfeeding of a high-carbohydrate diet results in metabolic detriment and high rates of net de novo lipogenesis within days (63).

It remains unknown whether and how an unhealthy Western diet with a high glycemic load and a high intake of sugar and saturated fat can be less detrimental to health if people are involved in intense recreational physical activity (58). The impact of energy turnover on metabolic response to a diet remains remarkably understudied. This may be due to methodological challenges because the high standard of a metabolic chamber is required to carefully match energy intake to energy expenditure in order to avoid the confounding effect of a negative energy balance that is promoted by a high PAL (see concept of energy flux). Using the setting of a metabolic chamber, we investigated the impact of energy flux (different levels of energy turnover at the same energy balance) on the regulation of macronutrient balance and glucose metabolism. Relative fat balance (8), postprandial glycemia, and insulin secretion (7) were all improved with increasing levels of daylong energy turnover (PAL of 1.3, 1.6, and 1.8 achieved by different durations of brisk walking). These results were not only observed at equal energy balance but also when comparing a high versus low energy turnover during caloric restriction or overfeeding. The findings show that acute increases in energy turnover led to improved glucose metabolism despite an increased rate in fat oxidation. By contrast, increased fat oxidation by time-restricted feeding (breakfast skipping) contributed to higher insulin levels and metabolic inflexibility in another metabolic chamber study of our group (64).

The characteristics and underlying mechanisms for improved metabolism by increasing energy turnover involve improved mitochondrial function (47). Because different intensities of energy turnover modulate energy partitioning, the comparison of low- versus high-intensity exercise is proposed to reveal the causes of metabolic improvement. Interindividual differences in the phenotype characteristics of body composition, insulin sensitivity, and aerobic fitness are determinants of metabolic fuel selection that need to be measured as potential confounders and to be controlled by intraindividual comparison of different levels and intensity of energy turnover.

Impact of the Intensity of Energy Turnover on Energy Partitioning and Metabolic Health

During low- to moderate-intensity exercise (brisk walking) that was used in our previous study to induce different levels of energy turnover, glycogen breakdown and glycolysis should be barely stimulated, and fat oxidation rates were high (6,8). Despite higher fat oxidation, a higher energy turnover reduced overfeeding-induced postprandial glycemia and insulin secretion, presumably by increasing non-insulin-dependent glucose uptake (7).

Higher-intensity exercise increases hepatic and muscle glycogenolysis, especially in untrained individuals (65). Because high-intensity physical activity lowers glycogen stores, overfeeding and high glucose intake are proposed to stimulate glycogen synthesis and the flux through hepatic lipogenic pathways (increasing liver fat and very low-density lipoprotein export) should remain low (57). Because glycogen binds to the β-subunit of AMP-activated protein kinase (AMPK) and this inhibits AMPK activity in skeletal muscle (66), a low glycogen status may also exert favorable metabolic effects by increasing the activity of AMPK independent of the energy status of the cell (ATP:AMP ratio). In individuals with prediabetes, three "exercise snacks" (6 × 1 minute of high-intensity activity before each meal) improved daily glycemia on both the day of exercise and over the subsequent 24 hours (67). In patients with type 2 diabetes, high-intensity training confers superior glycemic improvement as compared with continuous moderate-intensity training, despite a lower time commitment of 1.5 versus 2.5 h/wk (for a review, see Savikj and Zierath (68)).

Substrate use (glucose vs. fat, endogenous vs. exogenous substrates) not only depends on exercise modality (low intensity vs. high intensity) but also on timing of training (fasting vs. postprandial). Interestingly, the effect of low-intensity exercise on glycemic control is further enhanced when work bouts are performed in the postprandial state (with high substrate availability), whereas the effect of high-intensity training on glycemic control is further enhanced when exercise is performed in the fasted state (68). The effects of timing and frequency of energy turnover on regulation of energy and macronutrient balance are beyond the scope of this review.

Post-exercise substrate partitioning is shifted toward higher fat oxidation in order to restore glycogen levels. Lipid oxidation rates can reach 25% of

that reported during exercise and contribute greater than 60% of oxidative metabolism during recovery (69). After heavy and prolonged exercise, the replenishment of muscle glycogen to pre-exercise levels may require 24 to 48 hours depending on the diet and glycogen synthase activity.

Improved appetite control with a higher energy turnover may not only depend on gut peptides, which are predominantly associated with signaling of postprandial satiety rather than the control of eating. From a teleological point of view, substrate metabolism may impact energy intake, satiety, and food preferences (70). Eating behavior is proposed to be regulated by the need to maintain limited glycogen stores of the body, according to the glycogenostatic theory by Flatt (71), which is based on the glucostatic theory by Mayer (72). This hypothesis is supported by the finding that carbohydrate balance on an isocaloric high-carbohydrate diet (55% carbohydrate) inversely correlated with the change in fat mass over the following 4 years (73). Likewise, 24-hour carbohydrate oxidation and 24-hour carbohydrate balance measured in a metabolic chamber in energy-stable adults predicted subsequent ad libitum energy intake over the next 3 days (74). Carbohydrate balance was also a predictor of ad libitum energy intake in men and women who switched from 1-day high-carbohydrate diet to an isoenergetic high-fat diet (75). In addition, a lower carbohydrate balance after a 6-hour high energy turnover condition (with immediate compensation of energy expenditure to maintain energy balance) was associated with higher ad libitum energy intake at a subsequent buffet (76).

A very high energy turnover may also bear risks and side effects because high fluctuations in energy turnover could lead to temporal imbalance between oxidative stress and anti-oxidant defense systems that may accelerate aging (77). Extremely high levels of energy turnover due to competitive exercise may therefore lead to compensatory reductions in resting energy expenditure (constrained energy expenditure model by Herman Pontzer) (1,78)).

Importance of Study Duration to Investigate the Impact of Energy Turnover on Body Weight Regulation and Metabolic Risk

Overweight and obesity are commonly explained as a consequence of a chronically positive energy balance (79). This interpretation is, however, an oversimplification that bears the risk of missing the underlying mechanisms contributing to long-term weight gain. In reality, energy intake and expenditure are highly variable from day to day and even within a day, e.g., the balance is negative overnight and positive at daytime, leading to a considerable fluctuation in energy balance. Brief periods in which energy intake far exceeds energy expenditure last from one meal to several days and regularly occur over the weekend, on holidays, at periods of celebration, or during vacations (80,81). Gradual weight gain, therefore, more likely results from repeated short periods of large positive energy balance that are inadequately compensated for. Although the regulation of energy balance is based on transient and short-lived fluctuations, the bulk of studies performed long-term overfeeding experiments that are difficult to interpret because accumulation in fat mass and ectopic fat lead to a decrease in insulin sensitivity. A few studies investigated the effect of only 1-day overfeeding on metabolic regulation (e.g., 6,7,64,82-85). These studies reveal a significant impairment in insulin sensitivity, an increase in 24-hour energy expenditure, and a decrease in fat oxidation with overfeeding. One-day 30% excess energy intake nearly doubled inactivity-induced decreases in peripheral insulin sensitivity in physically fit normal-weight men, whereas hepatic insulin sensitivity was maintained (82). Most importantly, metabolic changes in response to 1-day overfeeding (+100%) showed a good reproducibility (84) and were of prognostic relevance for body weight regulation: A smaller increase in energy expenditure response to low-protein overfeeding and a larger response to high-carbohydrate overfeeding both correlated with spontaneous 6-month weight change (85).

Conclusion

The beneficial effects of energy turnover on regulation of energy and macronutrient balance facilitate prevention and treatment of obesity and associated metabolic risk. A high energy turnover due to physical activity or exercise may even compensate for adverse effects of overfeeding or an unhealthy diet, but this hypothesis needs to be further investigated using the concept of energy flux. A high energy turnover cannot, however, be fully recommended because it also bears a risk for weight gain when it cannot be maintained in the long term.O

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