Physiologic Factors Related to the Onset and Persistence of Childhood and Adolescent Obesity

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Childhood obesity results from failure to modulate environmental pressures affecting the genetic substrate of the individual. The results of genetic and epidemiologic studies suggest that genetic factors are involved in determining susceptibility to fat gain in subjects exposed to a specific environment (1). The influential role played by the environment in the development of obesity in susceptible individuals is strongly supported by evidence that the prevalence of obesity is higher in industrialized countries, where lifestyles and nutritional habits have undergone greater changes over the past few decades (2).

In keeping with the first law of thermodynamics, the various factors involved in the complex genetic–environmental interactions that cause obesity will promote the prolonged positive energy balance that is responsible for fat gain. This process overcomes the efficient self-regulation of energy balance demonstrated in humans. Normally, a kind of homeostatic mechanism seems to promote the maintenance of appropriate body weight and body energy stores from birth to adulthood, and dynamically adjusts body mass and body composition to the varied needs of physical growth and sexual development in the two sexes (3,4). However, the clear evidence of progressively greater worldwide prevalence of childhood obesity suggests a failure of this system to adapt to rapid and profound environmental changes (5,6).

Our purpose in this chapter is to review the physiologic factors related to the development and maintenance of obesity in children, and to suggest future topics for research in this field.

In contrast to adults, children are physiologically in a minimal positive energy balance owing to the additional requirements for growth (energy content of new tissue and energy cost of tissue synthesis). In particular, about 2% of their total energy intake for 1- to 10-year-old children is devoted to growth. The energy cost of growth is about 20% of the total daily energy requirements in 3-month-old infants and about 3% in 6-month-olds (8). During puberty the energy cost of growth is about 5% to 7% of total daily energy requirements (9). This specificity of children does not modify the equation, as growth consists of a physiologic store of energy in new tissues (fat-free mass and fat mass).
ENERGY BALANCE

An average-sized woman may maintain her weight over 10 years by matching approximately 30 million kJ of food intake (intermittent and variable) with the same amount of energy expenditure (continuous and variable). Thus the regulation of this remarkable energy turnover must be very efficient, dynamic, and precise. In an attempt to introduce the concept of time-dependent variability of the components of energy balance, the following equation has been proposed (7):

Rate of energy intake − rate of energy expenditure = rate of change of energy stored

This allows the effect of changing energy stores on energy expenditure to enter into the calculation. In fact, in free-living conditions energy balance is spontaneously achieved by modifications in behavior (appetite and physical activity) over hours and days, and by changes in body weight and composition over weeks and months. Therefore variations in body weight and body composition as a result of a chronic positive (or negative) energy balance tend to promote a compensatory increase (or decrease) in energy expenditure, which opposes further weight gain (or loss) (Fig. 1) (10).

In spite of the self-regulating mechanism of energy balance, the progressively increasing number of obese individuals proves that a minimal mismatch between energy intake and energy expenditure—such that intake exceeds expenditure—may result in a net accumulation of energy stores in the body. A chronic imbalance of just 1% between energy intake and energy expenditure in a 10-year-old normal-weight girl may cause a difference of more than 25,000 kJ/year in her energy balance, which corresponds to around 0.7 kg of fat, or to an increase of approximately 15% of her total fat mass.

It is important to point out how extremely difficult it is, even with the techniques available today, to assess such a small imbalance between energy intake and energy expenditure in free-living conditions. The evidence that the prevalence of obesity is growing in spite of a progressively lower energy content of children’s diet (2,5,6) suggests that a reduction in total energy requirements may be occurring in these populations.

Each of the components of total daily energy expenditure may be responsible for these reduced requirements. Basal metabolic rate (BMR), thermogenesis (T), energy expenditure for growth (EEg) (negligible except in the first year of life and during puberty), and the energy expenditure for physical activity (EEAct) may all be reduced in preobese children, favoring weight gain and fat gain. Even though the hypothesis that preobese children may have a higher metabolic efficiency requires further investigation, it is not supported by available studies (11). In particular, BMR—which is quantitatively the main component of the total daily energy expenditure—is higher in obese than in nonobese children owing to their greater fat-free mass (i.e., their metabolically active tissue). However, when BMR is adjusted for fat-free mass, no difference is found between obese, postobese, and never obese children (12). Meal-induced thermogenesis, which is the main component of thermogenesis, appears to be slightly lower in obese than in nonobese children (13–15). However, weight loss can eliminate this modest difference, which suggests, by implication, that a reduction in meal-induced thermogenesis is unlikely to be a factor predisposing to obesity in preobese children (16). It follows that most of the relative reduction in energy requirement over energy intake in preobese children reflects a lower EEAct, which is the only discretionary component of total daily energy expenditure. This is not surprising, as sedentary behavior is common in today’s children and has been identified as a potential predictor of weight gain (17). Indeed, sedentary behavior may precede as well as accompany obesity.

What are the factors that evade the homeostatic control of energy balance and promote the development of obesity, and how do they work? One possible answer to these questions comes from the metabolic characteristics of the principal factors of the energy balance: the nutrients.

**NUTRIENT BALANCE**

Energy enters the body mainly in the form of three macronutrients: protein, carbohydrates, and fat. The contribution to total energy intake of the two other sources of energy, alcohol and fiber, is negligible, as alcohol is usually not consumed by children, and the energy intake from fiber is far less than 1% of the total energy intake in the typical Western diet (18).

Nutrients may be either oxidized or stored in the body. Thus the energy balance equation may be formulated as the sum of the three nutrient balances (19):

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\text{Energy balance} = \text{protein balance} + \text{carbohydrate balance} + \text{fat balance}
\]

where each nutrient balance is given by

\[
\text{Rate of nutrient intake} - \text{rate of nutrient oxidation} = \text{rate of change of nutrient stored}
\]
Theoretically, all three nutrient balances should, like energy balance, be efficiently self-regulated. However, there is convincing evidence that this is the case for protein and carbohydrate balance but not for fat balance. In fact, short-term measurement of the postprandial increase of thermogenesis following the ingestion of equienergetic meals consisting of pure macronutrients has shown that protein and carbohydrate intake stimulates protein and carbohydrate oxidation, whereas fat intake does not stimulate fat oxidation (20). This was clearly demonstrated by Schutz et al., who found only an imperceptible increase in fat oxidation (less than 1%) and total energy expenditure (less than 2%) following ingestion of a large fat supplement (approximately 106 g fat/24 h, or about 35% of total daily energy requirements) (21).

Furthermore, an oxidative “hierarchy” that prefers the oxidation of carbohydrates and protein to that of fat has been identified in the body (22). The efficiency of carbohydrate and protein oxidation reflects the relatively small storage capacity for these nutrients (confined to glycogen, the labile proteins, and the amino acid pool) and the absolute need to maintain circulating glucose levels within strict limits. In contrast, fat storage capacity is not limited. Thus ingested fat is preferentially stored unless it is oxidized, the latter process being independent of fat intake but dependent on the amount of carbohydrate and protein ingested and oxidized. In other words, fat may be considered as the “energetic buffer” of the organism.

Neosynthesis of fat by carbohydrate (de novo lipogenesis) has been demonstrated in adipose tissue (23). However, the situations in which de novo lipogenesis occurs are far from physiologic, and this process should be regarded as negligible under the dietary conditions prevailing in industrialized countries—in fact, the ingestion of an extremely large amount of simple sugar (500 g of dextrin-maltose, or about 8,500 kJ) resulted in only a few grams of lipid production (24). Moreover, massive carbohydrate overfeeding for several days (with an energy intake of around 21,000 kJ/day, 85% as carbohydrate) resulted in just 150 g/day of lipid synthesis after the saturation of glycogen stores (25). The fact that glucose conversion to fat occurs at negligible rates in adults on mixed diets suggests that, to achieve weight stability, the organism has to oxidize not only protein but also carbohydrate and fat in the same proportions as provided by the diet (19).

**FAT INTAKE AND FAT GAIN**

The accurate measurement of energy and fat intakes in free-living individuals is difficult and is an important drawback to defining the precise and independent role of food intake in the fat gain process. The validity of food intake reporting must be determined by simultaneous measurements of energy expenditure. This is impossible in epidemiologic studies, so one needs to be cautious about drawing conclusions from such studies (26–28). Energy-balance studies have shown that food intake underreporting is common in obese individuals, as well as in children and adolescents, and underreporting gets progressively more common as energy requirements increase (29–31). Furthermore, a selective underestimation of fat intake has been reported in obese adults (32). Despite these important methodological
PHYSIOLOGIC FACTORS RELATED TO OBESITY

issues, there is evidence to support the role of fat intake in the development and maintenance of obesity.

A physiologic example of fat gain is to be found in late intrauterine and early extrauterine life. During the first 4 months after birth, the infant's body weight doubles (from about 3,500 g to about 7,000 g) and the fat mass more than triples (from about 500 g to about 1,700 g) (9). During the first months of life, human milk or formula is the only food ingested by infants. The energy content of human milk is around 280 kJ/100 ml, and fat accounts for more than 50% of the total energy. Thus the ingestion of this "high-fat diet" physiologically promotes a positive energy balance as well as a significant fat gain.

Weaning causes a progressive change in diet composition, with an increase in the carbohydrate-to-fat ratio. Simultaneously, body composition changes, with slowing of fat mass growth in favor of the development of muscle and other tissues (9). The fact that a high-fat diet promotes fat gain in infants supports the hypothesis that a high fat intake may favor fat gain in older individuals as well. Studies on prepubertal children and adolescents have confirmed this hypothesis by showing a positive association between fat intake (expressed as energy intake percent) and adiposity (33,34). Moreover, a longitudinal study on a group of prepubertal children showed that fat intake was a risk factor for fat gain in these children (35).

Finally, the results of a long-term dietary manipulation study on adults showed that consuming diets ad libitum that looked identical but that had been covertly manipulated to contain 20%, 40%, or 60% fat, respectively, caused a slow fat loss for those on the low-fat diet, a slight fat accumulation for those on the 40% fat diet, and a rapid fat gain with the high-fat diet (36). These results strongly support the role of fat intake in promoting fat gain.

There are several mechanisms whereby fat intake favors fat gain: the higher energy density and palatability of fat-rich foods promote greater food consumption (37); satiation is lower with fat than with carbohydrates and proteins (38); self-compensation of energy intake is less likely after a high-fat meal (39); and meal-induced thermogenesis is lower after fat intake than after carbohydrate or protein intake (19). A recent study of a group of 10-year-old girls showed blunted thermogenesis after a mixed high-fat/low-carbohydrate meal, in comparison to the thermogenesis measured in the same girls after an isocaloric, isoproteic meal with a low-fat/high-carbohydrate content (40). The difference was around 30%. Although the impact on total daily energy turnover of the lower thermogenesis induced by a high-fat meal is fairly limited (about 2%), this slight energy saving could be relevant in the long run.

BODY COMPOSITION AND SKELETAL MUSCLE

A direct relation between fat mass and postabsorptive fat oxidation has been reported in both children and adolescents (41,42). An increase in fat stores will increase fatty acid turnover, which increases fasting free fatty acid concentrations and promotes substrate competition between free fatty acids and glucose in the muscles; this in turn enhances insulin resistance (43). Increased insulin levels tend to reduce lipolysis
(44). However, the sensitivity of lipolysis to insulin in the adipose tissue is higher than the sensitivity of fat oxidation to insulin in the muscle. Thus higher levels of circulating insulin are necessary to enhance glucose oxidation and, as a consequence, to reduce fat oxidation. This "mass effect" exerted by adiposity on fat oxidation may be interpreted as a limiting factor in the expansion of fat stores (45,46). Therefore, given a certain energy intake and diet composition, the progressive increase in fat stores promotes a simultaneous increase in fat oxidation, favoring a new fat balance obtained at a higher body weight and body fat content (Fig. 2).

A recent study on a group of 11-year-old children that used the stable isotope technique to differentiate between the postprandial oxidation of fat ingested with a mixed meal and fat of endogenous origin (adipose tissue) showed that around 11% of ingested fat was oxidized (during the nine hours of postprandial respiratory exchange recording), whereas the remaining fat that was oxidized came from the fat stores (47). Expressed as a proportion of the ingested fat, there was less oxidation of endogenous fat as the relative fat mass of the child increased. The relatively blunted oxidation of endogenous fat may be viewed as a protective mechanism to prevent a further increase in fat mass—and hence to maintain fat oxidation at a sufficient rate—when the body is exposed to exogenous fat in a meal.

Skeletal muscle plays an important role in fat balance regulation. The muscles oxidize a large proportion of the fatty acids in the body. Physical activity—especially if done on a regular basis—promotes fat oxidation in the muscles as well as postexercise oxygen consumption (48–50). The fat oxidation rate increased by 20% in a group

FIG. 2. Fat mass and fat balance. An increase of fat mass as a promoting factor of a new fat balance equation during fat overfeeding.
of adults who took part in a 12-week workout program (51). The kind of exercise (aerobic, anaerobic), its intensity and duration, the training level of the individual, and the environmental conditions (temperature, pressure, humidity) during workouts affect the fat oxidation rate both during and after exercise. Interestingly, the maximum percentage of fat is oxidized during moderate-intensity aerobic exercise (60% VO_{2max}) (52). Thus the fat oxidation caused by skeletal muscle activity may be enhanced by simply modifying one’s sedentary lifestyle, so common in the industrialized countries (53).

Finally, the level of physical activity seems to affect food intake. Strenuous exercise retards appetite in adults in the period immediately after an exercise session (54). In children, regular physical activity seems to be accompanied by a trend to self-select a diet with a higher carbohydrate-to-fat ratio (55).

**FACTORS AFFECTING FAT INTAKE AND FAT OXIDATION**

Several factors affect fat balance by influencing food intake or energy expenditure. One of these is early nutrition. Human milk and formulas have a similar energy content and composition, and the growth of formula-fed infants is little different from that of age-matched breast-fed infants. However, it has been suggested that breast-feeding protects against obesity in older children (56). One possible contributing factor may be the continuous changes in human milk composition and flavor during lactation. Human milk composition changes during feeding and from one feed to the next during the day (57). Moreover, food ingested by the mother affects the flavor of her milk, which thus changes between feeds. The flavor of breast milk may affect milk intake and later food acceptance and consumption (58). Formulas never change in composition or flavor. At present, the potential implications of these differences on later eating habits of the individual are largely unknown.

Finally, modes of feeding may contribute to a higher risk of obesity in later life in formula-fed infants. For instance, a vigorous feeding style—consisting of sucking more rapidly and at higher pressure, with longer suckling sessions and a shorter interval between feeds—has been associated with greater adiposity (59,60).

Early experiences with food, the association of food flavors with the context in which the food is taken, and the consequences of eating may theoretically affect children’s food acceptance and food habits. Although the precocious introduction of solid foods into the infant’s diet has not been proven to be associated with childhood obesity, further research is necessary to clarify this issue (61,62). Family eating habits, food availability, and access to food in the home affect a child’s food preferences (63). A clear association between parental adiposity and fat intake and children’s adiposity and fat intake exists (64). Moreover, the parents’ encouragement to eat promotes fat gain in their children (65). Another powerful contributor to the development of food preferences and food selection is advertisements for food products and the variety of models and messages about eating that children get through watching television (66,67).

Finally, partitioning of food intake, especially food intake at the time of the evening meal, has recently been associated with adiposity in 7- to 11-year-old
children (68). Although this relation requires further experimental investigation, a high food intake at supper—which is not usually followed by physical activity, as breakfast and lunch usually are—could promote efficient energy storage, mainly in the form of fat.

CONCLUSIONS

On the basis of the available studies, some general conclusions may be drawn:

- Net fat storage only occurs when fat intake exceeds fat requirement.
- In the short term, the source of the excess energy (carbohydrate versus fat versus protein) affects the kind and place of storage of the energy excess. A great excess of carbohydrates will be stored primarily as glycogen; in contrast, excess fat will be promptly stored in the adipose tissues, by an extremely efficient process.
- During phases of positive energy balance it is likely that most stored fat comes directly from dietary fat, whereas the suppression of fat oxidation following the ingestion of carbohydrates and protein favors the maintenance of fat that was previously stored.
- Fat intake favors fat gain by means of the high energy density typical of fatty foods and the high palatability of foods rich in fat—both factors promoting food ingestion.
- Meal-induced thermogenesis is lower after a high-fat meal, and this may be a further contributing factor to fat gain.
- Physical activity affects energy expenditure as well as nutrient oxidation; aerobic exercise may be helpful in increasing the overall fat oxidation rate of the organism.
- Other factors, such as early feeding experiences, family eating habits, food availability and accessibility, TV viewing, and food partitioning may contribute to promoting and maintaining obesity in children.

FUTURE CHALLENGES AND POLICY IMPLICATIONS

Although several factors affecting energy and fat balance have been identified, most of the mechanisms regulating fat deposition—especially during late intrauterine and early extrauterine life, but also during puberty and the other growth stages of the child—require further investigation. Moreover, we need more information on skeletal muscle metabolism and the metabolic consequences of physical activity in childhood. Finally, the discovery of more accurate techniques (or the improvement of those already in use) to assess nutrient storage and turnover in free-living conditions would be welcome.

On the basis of the available data, a reasonable approach to the prevention of childhood and adolescent obesity should include interventions at the level of the general population to reduce the energy density and the fat content of the diet. This might help to prevent passive overconsumption but cannot overcome active overconsumption, and it is just one part of a more structured intervention program. As is the case
for adults, appropriate lifestyle changes favoring more physical activity should be encouraged. Finally, all interventions designed for children should include the active and collaborative involvement of their parents.

REFERENCES


DISCUSSION

Dr. Zainudin: You showed data on the increase in fat oxidation rate among trained athletes and nontrained individuals. What duration of training program would be required to effectively increase the fat oxidation rate in children?

Dr. Maffeis: Muscle activity is associated with fat oxidation. If you chronically increase skeletal muscle activity, you have a contemporaneous increase in fat oxidation. But if you want this to be a persistent phenomenon, you need to prolong the exercise to the extent that muscle prefers to oxidize fat for energy. To stimulate fat oxidation in muscle in the long term, resistance training is best.

Dr. Dulloo: When you do experiments in the laboratory and compare high-fat versus high-carbohydrate intakes, it is an artificial situation. In real life, when we eat high-fat foods, we also drink coffee or Coca-Cola, which contain caffeine, and this increases fat oxidation, or we take polyphenols from vegetables or from green tea, which are also known to increase fat oxidation. In some countries they eat a diet high in coconut oil, which behaves like medium-chain triglycerides and increases fat oxidation. Thus in real life we take a lot of things that may balance our fat intake much better than laboratory experiments suggest.

Dr. Maffeis: I think that is a good point. However, in the Cambridge study (1), where they compared three different diets with a different fat content, they clearly showed that a high-fat diet is associated with a rapid increase in fatness and body weight, so there was definitely a positive energy balance. You are right, though, under real-life conditions we do indeed take in many different nutrients and combine them. However, on my knowledge, no data are available in children on the comparison between thermogenesis induced by mixed meals with different fat/carbohydrate ratios, supplemented or not with substances as caffeine, polyphenols, etc.

Dr. Uauy: Do you have any comments about the quality of carbohydrate or fat relative to storage versus oxidation? For example, the effect of a high glycemic or low glycemic index for
carbohydrates, and in the case of the fat the presence of omega-3 fatty acids, which may be preferentially oxidized or may even alter mitochondrial oxidation?

_Dr. Maffeis:_ The composition of the fat or carbohydrate does affect thermogenesis, but the effect is relatively small. Moreover, no studies in children, on my knowledge, explored the meal induced thermogenesis after mixed meals with different glycemic index or fatty acid composition.

_Dr. Uauy:_ You said the effect is not great, but 2% may make a significant contribution to body adiposity over time.

_Dr. Maffeis:_ Yes, I agree. However, with common mixed diets is difficult to obtain a difference of 2% or total daily energy expenditure.

_Dr. Buenaluz:_ Could you comment on the rationale of small frequent feeds? You said that this increases thermogenesis.

_Dr. Maffeis:_ We have no experience of measuring thermogenesis in children after small meals taken often compared with larger meals taken infrequently. But Dr. F. Bellisle from France has reviewed all the published reports in children on this specific topic, concluding that there is not a significant protective effect of frequent small meals. I think this topic needs to be studied further.

REFERENCES