Substrate Metabolism During Exercise in Children and the “Crossover Concept”

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This review addresses issues related to substrate metabolism in children and how this information compares and contrasts to that of adults. The relative percent of fat and carbohydrate (CHO) utilized by an individual can be estimated from respiratory exchange ratio (RER) values between 0.7 (100% fat, 0% CHO) and 1.0 (100% CHO, 0% fat). The rise in RER towards 1.0 in relation to increased exercise intensity demonstrates the augmented role of CHO as an energy source for muscle; however, fat oxidation also represents a major source of energy during exercise of moderate-to-heavy intensity. Preliminary reports suggest that children demonstrate patterns of fat and CHO use in response to exercise intensity similar to those of adults and also show a reduction in RER at submaximal exercise intensities after training. The use of the “crossover concept” may simplify the presentation of how metabolism is affected by exercise intensity and training.

Energy for muscular work is provided by the metabolism of substrates; consequently, issues related to substrate metabolism are fundamental to the study of exercise physiology. While substantial research has accumulated over the years related to substrate metabolism in adults under various experimental conditions, there is a paucity of data related to substrate metabolism in children. The purpose of this review is to summarize what we know about substrate metabolism during submaximal exercise in children and to compare and contrast this information with that obtained from adults. Finally, the application of the “crossover” concept consequent to cycle ergometer training in children will be discussed.

Substrate Metabolism During Exercise

Estimates of substrate metabolism during exercise come from indirect calorimetry and measurements of changes in blood gases, as well as more direct measurements of substrate concentrations in the muscle from biopsy samples and the more recent use of stable isotope tracer techniques. Among these various techniques, carefully measuring the exchange of metabolic gases is the most common approach and can

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give a good indication of the source of substrate being utilized (11). The relative contribution of fat and carbohydrate to metabolism can be estimated from non-protein respiratory quotient (NPRQ-ratio of carbon dioxide produced to oxygen consumed \(\frac{V_{CO,}}{V_{O,}}\)) values ranging between 0.70 (100% fat, 0% carbohydrate) and 1.00 (100% carbohydrate, 0% fat).

When the metabolic gases are measured at the mouth, the term respiratory exchange ratio (RER) is used. There are certain conditions in which the RER is affected by factors other than oxidative metabolism. For example, hyperventilation may increase the RER to values well over 1.00, and during hypoventilation the RER may fall below 0.70. An RER obtained under these circumstances reflects both the state of the respiration and oxidative metabolism, invalidating its use as an indicator of the latter (14). If this ratio is measured under well-controlled steady-state conditions, the RER compares quite well with the RQ (13) and can be used to evaluate oxidative processes (14). Furthermore, recent experiments using stable isotopes have shown that indirect calorimetry is a valid means of determining substrate oxidation even during high-intensity (80–85% \(VO_{max}\)) exercise in trained adults (21). Thus, the term RER will be used throughout this review as an estimate of the fuel mixture oxidized.

Although the basic principles of indirect calorimetry are well established, some methodological and interpretative problems may exist and deserve mention. From a methodological standpoint, subjects unaccustomed to breathing through a mouthpiece tend to involuntarily hyperventilate upon first exposure; this will yield inappropriately high rates of \(CO_2\) production (24). From an interpretative standpoint, measurement by indirect calorimetry provides the net disappearance rate of a substrate regardless of the metabolic inter-conversions that the substrate may undergo before its disappearance from its metabolic pool (24). Since direct oxidation represents the major route by which a substrate disappears from its metabolic pool, the terms oxidation and disappearance are often used interchangeably. However, under conditions when rates of gluconeogenesis, lipogenesis, or ketogenesis are elevated, the equivalence of these terms is questionable even though the actual measurements derived from indirect calorimetry remain valid (24). It is generally assumed that under most circumstances errors introduced into calculations of substrate oxidation from indirect calorimetry in healthy individuals, independent of measurements of gluconeogenesis, lipogenesis, and ketogenesis, are quantitatively small (23). Furthermore, neglecting protein metabolism may introduce certain errors into the estimation of fuel metabolism. Based on animal studies, the contribution of amino acids to the substrate supply during exercise is relatively small, representing approximately 5% but perhaps as high as 10% of the overall fuel mix (25). Whether this holds true in children is unknown.

The two main sources of energy used during exercise are fat (adipose and intramuscular triglycerides) and carbohydrate (blood glucose and muscle glycogen). The mixture of fuels oxidized by an exercising individual is dependent on factors such as the intensity and duration of exercise, the diet consumed on the days prior to exercise, and the state of physical training of the individual (11). The expected rise in RER towards 1.00 as the intensity of exercise increases demonstrates that carbohydrate plays an increasingly important role as an energy source for muscle, especially during severe exercise when it may be the exclusive fuel being used (11). Indeed, substantial evidence has accumulated demonstrating the importance of muscle and liver glycogen related to fatigue and athletic perfor-
The primary reason glycogen reserves are essential is that lipids cannot be mobilized and oxidized rapidly enough to meet the energy requirements of intense muscular exercise. However, lipid oxidation clearly represents the major source of energy during exercise of a low-intensity and long-duration (11), as well as making a substantial contribution during exercise of moderate-to-heavy intensity (7, 22), as will be discussed subsequently.

The rates of carbohydrate and fat metabolism in trained subjects performing cycle ergometer exercise of varying intensities and durations were recently reported by Romijn et al. (22). It can be seen in Figure 1 that although the percent contribution of plasma FFA to the fuel supply declined as exercise intensity was increased from 25% to 65% VO$_{2\text{max}}$, the rate of total fat oxidation (plasma FFA + muscle triglycerides) actually increased from 70 cal · kg$^{-1}$ · min$^{-1}$ to 110 cal · kg$^{-1}$ · min$^{-1}$ with increasing intensity. Thus, the contribution of intramuscular triglyceride stores to the rate of total fat oxidation increased along with exercise intensity. At 85% VO$_{2\text{max}}$, the rate of total fat oxidation decreased (from 65% VO$_{2\text{max}}$) but was still similar to that measured at 25% VO$_{2\text{max}}$. The similarity in the calculated rates of fat oxidation between 25 and 85% VO$_{2\text{max}}$ was due to a high percentage of fat metabolism coupled with a low metabolic rate on the one hand (25% VO$_{2\text{max}}$), and a low percentage of fat oxidation and a high metabolic rate on the other (85% VO$_{2\text{max}}$). These data demonstrate that the oxidation rate of a substrate is a func-

![Figure 1](image.png)

tion of the percentage of energy derived from that substrate and the overall rate of energy expenditure (i.e., level of VO\textsubscript{2}).

In addition to the effect of increasing fat oxidation as a function of exercise intensity, regular exercise training enhances the muscles’ ability to use fat as a fuel and increases the sensitivity of adipose cells to lipolytic stimuli. The demonstration of a downward shift in the whole-body RER represents some of the oldest, and arguably the strongest, data available supporting the conclusion of enhanced lipid oxidation after training (5, 11). For example, Bransford and Howley (1) found a lower RER at submaximal exercise intensities, in the presence of the same VO\textsubscript{2}, in subjects following a 4-week cycle ergometer training protocol. Indeed, it is well established that regularly performed endurance exercise induces adaptations in skeletal muscle, including increases in mitochondrial content and respiratory capacity of muscle fibers, that favor fat oxidation (12). The major metabolic consequences of the training-induced adaptations to endurance exercise are a slower metabolism of muscle glycogen and blood glucose, a greater reliance on fat as a fuel, and less lactate production during a given submaximal exercise intensity (12). Do these responses hold true for children?

While many studies have assessed substrate metabolism during exercise and how it is affected by training in adults, there is a paucity of data examining these issues in children. Recently, Duncan and Howley (9) examined this issue in children and reported results similar to those of Romijn et al. (22). The inverted U-shaped nature of the fat oxidation curve shown in Figure 2 demonstrates the increased use of fat as a fuel in relation to increasing exercise intensity, up to a level representing approximately 65% VO\textsubscript{2}max, and the augmented role of carbohydrate in response to the increased energy demands of moderate-to-heavy exercise intensities (i.e., above approximately 65% VO\textsubscript{2}max). Thus, it appears that children demonstrate patterns of fat and carbohydrate oxidation in response to increasing exercise intensity similar to those of adults. Furthermore, using the RER as a measure of substrate use, these authors found that the RER was decreased at several submaximal exercise intensities after a 4-week cycle ergometer training program as compared to a matched control group (9). This preliminary evidence suggests that children adapt to exercise training in a manner similar to adults. Specifically, the training-induced adaptations that result in increased fat oxidation and glycogen sparing in adults (12) appear to hold true for children (9). Future research could potentially examine this issue from a mechanistic standpoint in order to elucidate the factors responsible for the training-induced adaptations favoring fat oxidation in children.

Maffeis et al. (16) examined substrate metabolism in children at rest and determined that the rate of postabsorptive fat oxidation was significantly correlated ($r = 0.65$, $p < .001$) to fat mass in a group of obese prepubertal children as compared to nonobese age-matched controls. The slope of the relationship indicated that for each additional 10 kg of fat mass, resting fat oxidation increased by 18 g per day (16). An increased rate of fat oxidation (not absolute amount of fat oxidation) at rest in obese children is similar to findings in obese adults (20). It was concluded that a higher postabsorptive rate of fat oxidation in obese as compared to nonobese children may favor the achievement of a new equilibrium in fat balance, possibly opposing further adipose tissue gain (16).

Macek et al. (15) examined the cardiovascular and metabolic adjustments to prolonged exercise in prepubertal boys. Of particular note is the finding of an
increase in plasma glycerol (which reflects the rate of adipose tissue lipolysis) over time; this is consistent with previous reports (10). The pattern of rise in plasma glycerol with exercise in boys was similar to that described by Carlson et al. (3) in adults at similar relative exercise intensities, suggesting similar rates of adipose tissue lipolysis. Similarly, Martinez and Haymes (18) reported large increases in FFA and glycerol concentrations over time (30-min treadmill bout) in girls and women, but found no difference between groups with respect to these parameters at either the same relative or absolute exercise intensity.

Also of note from the study of Macek et al. are a nonsignificant decrease in RER and only minor changes in blood lactate over time (60-min treadmill bout), the lactate values being correspondingly higher in adults as compared with children at any time point during equivalent exercise (15). In line with this, Mahon et al. (17) reported that boys produce less lactate at levels of exercise representing 80, 100, and 120% of the individual VO\textsubscript{2} at ventilatory threshold as compared to adults (17). Martinez and Haymes (18) also found significantly lower lactate values in girls as compared to women after 30 min of exercise at the same relative intensity; however, they found significantly higher lactate values in the girls after exercise at the same absolute intensity. This is reasonable since at the same absolute intensity, the girls were working at a higher percentage of their VO\textsubscript{2}max as compared with the women.

It has been suggested that children may demonstrate a metabolic profile during exercise that is different from that of adults. Montoye (19) and Rowland et al. (23) found that the RER was significantly lower during submaximal steady-state exercise at equivalent absolute intensities in boys as compared to men, thus suggesting a greater reliance on fat as a substrate during exercise. Martinez and Haymes (18) reported that girls relied more on fat as a substrate as compared with women (as evidenced by significantly lower RER values) during treadmill exercise at the same relative intensity. However, when the exercise intensity was at the same absolute level, no significant differences (with the exception of values at the 5th minute) were observed for RER between girls and women (18). Finally, Delamarche et al. (8) demonstrated, in children, that exercise of moderate intensity (~60% VO\textsubscript{2}max) induced a small decrease in blood glucose which was combined with an abrupt increase of norepinephrine concentration during the first 15 min of a 60-min exercise bout. The FFA and glycerol concentrations increased throughout the exercise bout linearly with that of epinephrine. Compared to adults, the FFA uptake expressed per minute and per liter of VO\textsubscript{2} was greater in children (8). The authors suggested that it is difficult for children to maintain a constant blood glucose concentration and that prolonged exercise provides an impetus for hypoglycemia (8). In light of the previous data, it seems that an alternative explanation is that children do indeed rely more on fat as a fuel during exercise as compared to adults.

### The “Crossover” Concept

Recently, the crossover concept has been proposed as a means of understanding the effects of exercise intensity and endurance training on the balance of carbohydrate and fat metabolism during exercise (2). According to this concept, the pattern of substrate metabolism in an exercising individual is determined by the interaction between increased carbohydrate usage in response to exercise intensity and
increased fat usage in response to endurance training. Specifically, the crossover point is the power output at which energy from carbohydrate-derived fuels predominates over energy from lipids, with further increases in power eliciting a relative increment in carbohydrate metabolism and a decrement in lipid oxidation (2). Thus, the increase in RER witnessed by subjects during exercise of increasing intensity indicates a shift in relative substrate usage from fat to carbohydrate. However, this is not a new concept, and it is argued that the primary hypothesis of the crossover concept (as stated above) has been accepted since at least the 1930s (5). On the other hand, for the purposes of this review we are interested in describing how endurance training shifts fuel selection so that fat is indeed represented as a major fuel source at moderate-to-heavy levels of exercise. A slight modification of the original "crossover" figure from Brooks and Mercier's paper (2) may afford this opportunity. Thus, even if this concept does not add anything new to our understanding of substrate metabolism during exercise, it does simplify the presentation, particularly for new students in exercise physiology, of how metabolism changes during exercise.

Seen in the context of substrate use, the power output where the crossover between substrates occurs must represent the point at which the RER is increased above 0.85. Any RER above 0.85 indicates that more than 50% of the energy is derived from carbohydrate and any value below 0.85 indicates that more than 50% of the energy is derived from fat. Figure 3 depicts a theoretical representation of the crossover of substrates before (3a) and after (3b) training using the mean RER and relative power output values from the training group data presented by Duncan and Howley (9) in their short-term cycle ergometer training program in children. The crossover concept, as previously described, predicts that endurance training will shift the crossover point to the right, representing a "delay" in the dominance of carbohydrate to a greater relative power output. In line with this prediction, Figure 3b represents a rightward shift in the crossover point to a new relative power output equivalent to approximately 43% of VO_2_max after training. Thus, the crossover concept accurately predicts that endurance training will result in a shift in fuel selection resulting in increased fat and decreased metabolism of carbohydrate. The impact of this "shift" (i.e., 5% increase in the actual crossover point) on fuel selection is that the percent of energy derived from fat will predominate to at least a moderate level of exercise. Coupled with the increased metabolic rate witnessed as exercise intensity is increased, the overall rate of fat oxidation will increase so that fat can serve as an important fuel source even at moderate-to-heavy levels of exercise and at the same time serve to spare muscle glycogen reserves and allow for the maintenance of blood glucose homeostasis.

Conclusions and Directions for Future Research

The use of the RER remains a valid and noninvasive measure of the relative contribution of fat and carbohydrate utilized in a resting or exercising individual. The overall substrate oxidation rate can be quantified by measuring the percentage of energy derived from that substrate (RER) and the overall rate of energy expenditure (level of oxygen consumption). The demonstration of a downward shift in the RER supports the interpretation of enhanced fat use after endurance training. Limited research suggests that children do indeed demonstrate patterns of fat and CHO use in response to exercise intensity similar to that of adults, and that fat metabo-
Figure 3 — Examination of the crossover concept before (3a) and after (3b) short-term (4 weeks) cycle ergometer training in children.
lism is increased at submaximal exercise intensities in children after training as evidenced by a reduction in the RER from pre- to post-training. The use of the crossover concept may simplify the presentation of how metabolism is affected by exercise intensity and training. This concept accurately predicts that endurance training shifts the crossover of fuels (i.e., fat to carbohydrate) to the right on the independent axis (relative power output), representing a "delay" in the increase in carbohydrate metabolism as one exercises at higher power outputs. This shift results in increased fat and decreased carbohydrate metabolism at submaximal exercise intensities. This information aside, there appear to be several unanswered questions related to substrate metabolism in children. Some suggestions for future research include:

1. Determine whether children rely more on fat as an energy substrate as compared with adults, using more sophisticated tracer technologies (if ethically feasible) coupled with the measurement of metabolic gases.
2. Determine the influence of biological maturation on the pattern of substrate metabolism during exercise in the growing child, and describe the factors responsible for the apparent shift in fuel sources as the child ages.
3. Elucidate the factors responsible for the training-induced adaptations favoring fat oxidation in children.
4. Determine whether the contribution of protein as a fuel source during exercise in children is similar to that proposed for adults.

References


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