Metabolic flexibility and insulin resistance

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LIPID ACCUMULATION IN SKELETAL MUSCLE of sedentary people is associated with impaired insulin-stimulated glucose metabolism (31). A reduced capacity of oxidative tissues and organs to adjust lipid oxidation to lipid availability can lead to tissue accumulation of lipids as triglycerides. Excess lipid accretion and/or lower triglyceride turnover can induce lipotoxicity, as reflected by the cellular accumulation of ceramides and diglycerides (39). These lipid species ultimately impair insulin signaling through different mechanisms, either increased serine phosphorylation of the insulin receptor and insulin receptor substrate 1 and/or reduced serine phosphorylation of PKB/Akt (38, 60) (Fig. 1). Therefore, the ability to increase lipid oxidation as a function of their availability eventually reduces the formation of ceramides and diglycerides leading to improved insulin sensitivity.

In general, the ability of a system (i.e., whole organism, organ, tissue, or cell) to adjust fuel oxidation to fuel availability is known as metabolic flexibility. This term was coined by Kelley and Mandarino as “the capacity to switch from predominantly lipid oxidation and high rates of fatty acid uptake during fasting conditions to the suppression of lipid oxidation and increased glucose uptake, oxidation, and storage under insulin-stimulated conditions” (26). In line with the above definition, the switch from carbohydrate to lipid oxidation [drop in respiratory quotient (RQ)] during an overnight fast or in response to high-fat diets should also be part of the assessment of metabolic flexibility (Fig. 2).

There is now a growing interest to assess the influence of metabolic flexibility, particularly to dietary fat as a mechanism to explain how lipids can accumulate in skeletal muscle. The switch in fuel oxidation will depend on the type and amount of nutrient available for oxidation at the cellular level. In tissues and organs, fuel availability (glucose, fatty acids, and amino acids) is integrated at the cellular level by fuel sensors that activate or inhibit specific metabolic pathways (47, 50). In response to fuel oversupply, anabolic pathways are activated, whereas the activity of hydrolytic and lipolytic pathways is increased when fuel availability is restricted. In addition, the ability to change substrate oxidation in response to nutritional status will depend on the genetically determined balance between cellular oxidation and storage capacities.

For example, in skeletal muscle, white (glycolytic) or red (oxidative) muscle homogenates respond differently to a supply of fatty acids or glucose. Glycolytic fibers have low rates of
fat oxidation compared with oxidative fibers (30), which have high mitochondrial density and oxidative enzyme activities. As a consequence, the oxidative capacity of skeletal muscle may be of utmost importance to boost lipid oxidation to the level of lipid supply and therefore modulate insulin sensitivity. If skeletal muscle cannot match fat oxidation to lipid uptake, fat accumulation will ensue, which in turn will cause insulin resistance.

This review discusses the studies in which metabolic flexibility has been measured at the whole body level or specifically in skeletal muscle tissue or in muscle cells with particular emphasis on the comparison between insulin-resistant and insulin-sensitive individuals. In addition, we discuss the main determinants of metabolic flexibility, how metabolic flexibility should be measured, and which questions need to be answered to better understand the pathophysiology of insulin resistance.

Metabolic Flexibility and Macronutrient Oxidative Regulation

During long-term energy balance, macronutrient oxidation eventually has to match macronutrient intake such that no macronutrients are stored or lost (10). In other words, not only does 24-h energy expenditure have to be equal to 24-h energy intake, but 24-h RQ has to be equal to 24-h food quotient (FQ). The 24-h RQ corresponds to the mean proportion of macronutrient oxidized over a day, whereas 24-h FQ represents the proportion of daily dietary macronutrients available for oxidation (5). Many studies have shown that when people are in energy balance then 24-h RQ eventually matches 24-h FQ (6,
21, 44, 53, 56, 58). Increased availability of carbohydrate results in a rapid increase in carbohydrate oxidation associated with concomitant suppression of lipid oxidation. However, when dietary fat intake increases, one observes a much slower progressive increase in lipid oxidation paralleled by suppression of carbohydrate oxidation.

Both day-to-day variations in energy/macronutrient intake and day-to-day changes in energy expenditure lead to either slightly positive or negative energy balance. In response to these short-term variations in energy balance, carbohydrate and protein stores are closely regulated by an adjustment of oxidation to intake. Consequently, positive or negative energy balances are mostly buffered by changes in fat stores as evidenced by the tight correlation between fat storage and energy balance (1, 9). It is therefore only after short periods of time (one to a few days) that a difference in metabolic flexibility (switch from one type of fuel to another) can be observed. This situation can be particularly relevant in individuals exposed to an obesogenic environment (i.e., high-energy density diets and low physical activity). Whether the capacity to adapt fuel oxidation to fuel availability is preserved or impaired in states of insulin resistance is discussed below.

Metabolic Flexibility in Individuals with Insulin Resistance, Obesity or Family History of Type 2 Diabetes

Metabolic flexibility in response to fasting. Fatty acids are the main readily available energy sources during the transition from the fed to the overnight-fasted condition, as indicated by the progressive fall in RQ. An impaired drop in RQ during an overnight fast (high fasting RQ) may be defined as metabolic resistance is discussed below.

Metabolic flexibility in response to nutrients. Metabolic flexibility in response to high-carbohydrate meals has not been frequently compared in subjects with different insulin sensitivity. Recently, the change in whole body RQ in subjects with and without a family history of type 2 diabetes was assessed (20). Individuals with a family history of diabetes usually have a lower insulin-stimulated glucose disposal rate during a hyperinsulinemic clamp, although it was not the case in that study. However, in response to a high-carbohydrate meal (1,000 kcal, 76% energy from carbohydrate), individuals with a family history of diabetes had a higher plasma insulin concentration and a similar increase in RQ compared with control subjects.

Metabolic flexibility in response to high-fat meal. High-fat diets usually lead to positive energy balance, since fat-rich foods are more palatable and have higher energy density than other foods (49). Fat overload may represent a metabolic challenge for many individuals, even in energy balance conditions, who may indeed fail to appropriately upregulate skeletal muscle lipid oxidation, therefore causing intracellular lipid accumulation and insulin resistance. Although the rationale for metabolic flexibility in response to high-fat meals is less clear, the results from studies on insulin resistance highlight the importance of understanding the metabolic flexibility in response to high-carbohydrate meals.
inflexibility to lipid may appear obvious, few studies have so far investigated metabolic flexibility to lipid in individuals with contrasting degrees of insulin sensitivity.

Kelley and Simoneau (28) compared leg RQ in the postprandial state of nondiabetic vs. weight-matched diabetic subjects in response to a high-fat meal (737 kcal, 62% energy from fat). During postabsorptive conditions, diabetic individuals had higher RQ throughout the 6 h following the high-fat meal compared with nondiabetic subjects. Apparently, mitochondrial function was preserved, since key skeletal muscle mitochondrial markers such as citrate synthase (mitochondrial number), cytochrome c oxidase (electron transport chain activity), and 3-hydroxyacyl-CoA dehydrogenase activities were similar in both groups. On the other hand, the large difference in postprandial glycemia (~2-fold) and lower skeletal muscle FFA uptake observed in diabetic vs. nondiabetic subjects likely drove the difference in leg RQ.

At the whole body level, the drop in RQ after a high-fat meal (1,000 kcal, 76% energy from fat) was examined in individuals with similar insulin sensitivity but with positive or negative family history of type 2 diabetes (20). In both groups, the changes in plasma glucose, FFA, and insulin concentrations were similar; however, individuals without a history of diabetes had larger decrease in RQ compared with offspring from diabetic parents. The lower reliance on fat oxidation for energy supply in offspring from diabetic parents suggests that impaired fat oxidation might precede insulin resistance.

In contrast, a study in 113 lean and 701 obese subjects who ate ~50% of their daily energy requirement as fat, showed that insulin resistance measured by homeostasis model assessment of insulin resistance (HOMA-IR) was associated with increased postprandial fat oxidation (as percentage of energy expenditure) after controlling for confounding variables such as fat mass, fasting fat oxidation, sex, and physical activity (4).

**Prolonged metabolic flexibility in response to diets.** Metabolic flexibility in vitro. Prolonged metabolic flexibility in response to diets. A careful study of metabolic flexibility has been performed by Freymond et al. (12) compared children of obese and nonobese parents. Children of obese parents were heavier and tended to be fatter than children of nonobese parents. Both groups were evaluated under eucaloric conditions and after 3 days of progressive overfeeding with a mixed diet (2-fold energy excess on the 3rd day). There was no difference in the change in 24-h RQ between groups after the 3-day overfeeding period. Both studies suggest similar metabolic flexibility to carbohydrate-enriched diets in obese and lean individuals.

**Determinant Factors of Metabolic Flexibility**

Significant differences in mitochondrial number, structure and function have been described between insulin-resistant and insulin-sensitive subjects (3, 25, 36, 37, 40, 42, 43, 48, 59). The hypothesis that mitochondrial abnormalities may be a primary cause of metabolic inflexibility and insulin resistance has been
Baseline RQ. The difference between baseline and stimulated RQ (ΔRQ) is the usual way to estimate metabolic flexibility in response to meals, diets or euglycemic-hyperinsulinemic clamps. Depending on the testing paradigm, baseline RQ corresponds to the fasting RQ (hyperinsulinemic clamp or meal) or the initial 24-h RQ (diet). Accordingly, impaired metabolic flexibility may result from both a lower stimulated RQ and/or an elevated baseline RQ. In fact, fasting RQ is inversely related to metabolic flexibility to carbohydrate during a clamp (Fig. 3A). Fasting RQ is highly sensitive to differences in energy balance and diet composition within the few days preceding the measurement (22, 34, 54). Therefore, differences in metabolic flexibility may be explained by insufficient control of such variables. Subjects in negative energy balance or fed a high-fat diet have lower baseline RQ, increasing the potential to influence ΔRQ in response to energy macronutrients. The following example shows the influence of the baseline RQ on metabolic flexibility assessed by the ΔRQ (Table 1).

Two well-matched individuals (A and B) are maintained under energy balance conditions in a metabolic chamber. They are fed for 1 wk with diets having different FQs (subject A = 0.92 and subject B = 0.82). Then, for another week, both receive a diet with an FQ of 0.75. Since both subjects are in energy balance, 24-h RQ is expected to match FQ at the end of each week. Using the ΔRQ as an index of metabolic flexibility, subject A will be characterized as flexible (ΔRQ = −0.17) and subject B as inflexible (ΔRQ = −0.07). Since both subjects were able to match the 24-h RQ to FQ at the end of each week, both subjects should be considered similarly flexible.

This example clearly shows the relevance of having similar baseline RQ values when metabolic flexibility is assessed by the change in RQ. In addition, this example raises the concept of the time required to achieve a new equilibrium, since after 7–10 days it is generally expected that all individuals will be in equilibrium between 24-h RQ and FQ. However, subjects with higher metabolic flexibility will reach this equilibrium faster.

Consequently, the assessment of metabolic flexibility should take into account the differences in baseline RQ and the timing required to match 24-h RQ to FQ. One alternative to control for the baseline RQ is to include this factor as a covariate in a regression analysis model. Such an approach requires large sample sizes, something often difficult to afford in clinical studies. Undoubtedly, the best option to reduce the variability in baseline RQ is to maintain individuals for a period of time on a given diet under energy balance conditions to match 24-h RQ to FQ. The next step is to evaluate the differences in the timing required to reach the equilibrium between fuel oxidation and availability. To do that, one can measure the day-to-day change in RQ in a respiratory chamber and calculate the number of days necessary to reach 50% of the expected change in RQ (ΔRQ50%). Such a ΔRQ50% may be in the range of 1–2 days in response to high-carbohydrate diets and in the range of 3–5 days in response to high-fat diets.

Glucose disposal rate. Metabolic inflexibility to glucose and impaired glucose storage during a hyperinsulinemic clamp is consistently reported in insulin-resistant subjects. In fact, a direct relationship between metabolic flexibility to glucose and glucose disposal rate is described (14, 24, 61, 62) (Fig. 3B). We (14) recently described that insulin-stimulated glucose disposal rate is the main determinant of the change in RQ during a clamp, explaining ~50% of its variance. The commonly reported metabolic inflexibility and impaired glucose storage in insulin-resistant individuals is expected, since cellular glucose uptake is decreased and cellular glucose available for oxidation and storage is low (8). As a consequence, data corrected for glucose disposal rate, a mechanism proximal to glucose oxidation, indicates no difference in metabolic flexibility and nonoxidative glucose disposal rate between subjects with or without type 2 diabetes and matched for body mass index, sex, and race. Furthermore, after controlling for glucose disposal rate, no improvement in metabolic flexibility is observed after...
weight loss in type 2 diabetic individuals subjected to a 1-yr
intensive lifestyle intervention including energy restriction
and increased physical activity (14). When subjects were divided
into quartiles of insulin sensitivity, the insulin-sensitive group
(upper quartile; \( n = 25 \)) had about a fourfold higher glucose
disposal rate, nonoxidative glucose disposal rate, and increased
steady-state RQ compared with the insulin-resistant group
(lower quartile; \( n = 25 \)). However, after adjustment for differ-
ces in glucose disposal rates, there was no longer any differ-
ence in nonoxidative glucose disposal rate and steady-
state RQ between groups (Ref. 14; Table 2). Further support
for these findings comes from studies in which glucose dis-
posal rates were matched by increasing the glucose or insulin
infusion rates (27, 66). Together, the results indicate that the
impaired metabolic flexibility and glucose storage so often
observed during a clamp in insulin-resistant individuals are the
consequence of impaired glucose transport rather than a defec-
tive cellular glucose oxidative and nonoxidative metabolism.

Adipose tissue lipid storage capacity and plasma FFA con-
centration. Just as intracellular glucose availability influences
metabolic flexibility, higher plasma lipid concentration also
drives fuel oxidation by increasing fat oxidation (14, 33, 46,
52). Additionally, high plasma FFA concentration impairs
insulin-stimulated glucose disposal rate and decreases intracel-
lar glucose, which in turn reduces glucose oxidation and
consequently enhances lipid oxidation (2, 8).

Since adipose tissue is the main source of plasma FFA, the
capacity to store and release FFA from adipose tissue may
influence metabolic flexibility (11). For instance, patients with
lipodystrophy (partial or total absence of subcutaneous adipose
tissue) have similar fat oxidation than control individuals when
fed a eucaloric, mixed diet (51). However, in response to
excess energy as fat, lipodystrophic subjects have higher fat
oxidation compared with control individuals (51). Accord-
ingsly, a lesser decrease in RQ after a fat overload might be the
result of enhanced adipose tissue lipid storage capacity rather
than impaired lipid oxidative capacity.

Mitochondrial oxidative capacity. It is known that mito-
chondrial content and activity determine fatty acid oxidation
in response to lipid. This has been shown by comparing fatty acid
oxidation rates between homogenates of red (oxidative) and
white (glycolytic) skeletal muscles (30). These data and the
evidence indicating multiple mitochondrial abnormalities in
type 2 diabetic and insulin-resistant individuals (3, 25, 36, 37,
40, 42, 43, 48, 59) led to the hypothesis that lower mitochon-
drial capacity is associated with reduced resting lipid oxidation
and therefore increased muscle lipid accumulation. Such mus-
cle mitochondrial dysfunction was suggested to be an intrinsic
characteristic of muscle cells, since fat oxidation in response to
palmitate was lower in myotubes from insulin-resistant vs.
insulin-sensitive individuals (16, 61). However, comparisons
among obese, diabetic, and lean individuals have failed to
appropriately match the groups for physical fitness, opening up
the possibility that mitochondrial dysfunction may be related to
lower physical activity in metabolically inflexible subjects
(45).

Independently of the origin of these mitochondrial abnor-
malities, it is not clear whether the extent to which muscle
mitochondria are impaired is sufficient to influence metabolic
flexibility to lipid, especially in resting conditions. Some sug-
gestion comes from the comparison between subjects with and
without a history of type 2 diabetes (62). The former group had
on average a 22% less mitochondrial DNA copy number
(marker of mitochondrial number) than control subjects. In-
creased mitochondrial number was related to a higher decrease
in sleeping RQ in response to a 3-day isoenergetic high-fat
diet. However, when mitochondrial number was related to 24-h
RQ after the high-fat diet period, no association between mitochon-
drial number and the change in 24-h RQ was ob-
served. Sleeping RQ may be relevant, because under this
condition most of the energy comes from lipid. However, since
energy expenditure is minimal in resting conditions, the abso-
lute lipid oxidative demand is hardly a metabolic challenge for
muscle mitochondria. As indicated in the previous section, a
higher decrease in RQ after fat overload may well be a con-
sequence of reduced adipose tissue lipid storage capacity.

Another interesting experimental paradigm is to assess the
metabolic flexibility to lipids (e.g., meals or diets) between
athletes and sedentary individuals. Clearly, one knows that
athletes have better muscle oxidative capacity (i.e., mitochon-
drial number and activity); however, such a simple study has not
been performed yet. Alternatively, elderly individuals
matched for body mass and fat content to young volunteers
showed on average 26% lower maximal aerobic consumption
(\( \text{VO}_{2}\text{max} \)) vs. young individuals (6). Since \( \text{VO}_{2}\text{max} \) has been
shown to be directly related to muscle mitochondrial density
(62, 63), one could expect an improved metabolic flexibility in
young vs. elderly individuals. However, after 4 days of inter-
vention, both groups were similarly able to match whole body
fuel oxidation to fuel intake.

Table 1. Influence of baseline RQ on metabolic flexibility
assessed by the change in RQ (\( \Delta \text{RQ} \))

<table>
<thead>
<tr>
<th>Subject</th>
<th>First Week</th>
<th>Second Week</th>
<th>( \Delta \text{24-h RQ} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FQ 24-h RQ*</td>
<td>FQ 24-h RQ*</td>
<td>(2nd –1st week)</td>
</tr>
<tr>
<td>A</td>
<td>0.92</td>
<td>0.75</td>
<td>–0.17</td>
</tr>
<tr>
<td>B</td>
<td>0.82</td>
<td>0.75</td>
<td>–0.07</td>
</tr>
</tbody>
</table>

Subjects A and B are two well-matched individuals maintained under energy
balance conditions in a metabolic chamber. RQ, respiratory quotient. They
were fed for 1 wk with diets having different food quotients (FQ). Then, for
another week they received a diet with an FQ of 0.75. *Value at the end of the
respective week.

Table 2. Steady-state RQ between subjects with high
and low insulin-stimulated glucose disposal rate

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Female/male</th>
<th>19/6</th>
<th>12/13*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM/non-DM</td>
<td>4/21</td>
<td>23/2*</td>
<td></td>
</tr>
<tr>
<td>White/black/other</td>
<td>15/10/0</td>
<td>23/0/2*</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>54.3 ± 1.4</td>
<td>60.1 ± 1.6*</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.9 ± 0.5</td>
<td>33.0 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>Body fat, %</td>
<td>39.0 ± 1.5</td>
<td>35.3 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>GDR, mg·kg FFM⁻¹·min⁻¹</td>
<td>11.8 ± 0.4</td>
<td>4.0 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Nonoxidative GDR, mg·kg FFM⁻¹·min⁻¹</td>
<td>8.5 ± 0.5</td>
<td>2.3 ± 0.2†</td>
<td></td>
</tr>
<tr>
<td>Steady-state RQ</td>
<td>0.94 ± 0.01</td>
<td>0.87 ± 0.01†</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05, †P > 0.44 after controlling for sex,
race, presence of type 2 diabetes mellitus (DM), age, and insulin-stimulated
glucose disposal rate (GDR; \( P < 0.02 \) when values are not controlled for
GDR).
On the other hand, fuel oxidation may not necessarily be reduced in presence of mitochondrial dysfunction. For instance, frank mitochondrial dysfunction in humans (e.g., myopathies with impaired electron transport chain activity) is accompanied by increased fuel oxidation to compensate for the impaired mitochondrial ATP synthesis (13). Similarly, mice with muscle-specific PGC1α (PPARγ coactivator-1α) deletion have defective mitochondrial function (e.g., lower staining for cytochrome c oxidase and succinate dehydrogenase); however, they have increased metabolic rate, lower RQ, and improved insulin-stimulated glucose uptake in skeletal muscle compared with wild-type animals (19). Therefore, mitochondrial dysfunction may well be associated with high fuel oxidation and enhanced insulin sensitivity.

Another hypothesis has recently been proposed by Koves et al. (30), stating that lipid oversupply can promote excessive lipid oxidation, which will disconnect the coupling between β-oxidation and the TCA cycle, generating excessive amounts of incompletely oxidized acyl-carnitine intermediates. The latter lipid species may interfere with insulin signaling and glucose transport through currently unknown mechanisms. This is in line with the finding that high-fat diets increase mitochondrial biogenesis and fat oxidation in parallel with a decrease in insulin sensitivity (18), possibly as a consequence of increased partially oxidized lipid intermediates.

Taken together, the literature does not support the hypothesis that impaired mitochondrial function leads to lower metabolic flexibility to lipid. In fact, it remains largely unknown whether muscle mitochondrial abnormalities described in insulin-resistant individuals are sufficient to affect metabolic flexibility to lipid.

Other determinant factors of metabolic flexibility. In a recent study, we (14) identified other factors determining metabolic flexibility to glucose in humans. As expected, metabolic flexibility to glucose during a clamp was related to surrogate markers of insulin resistance such as fasting plasma glucose, FFA, and insulin concentrations. In addition, we observed that metabolic flexibility to glucose was directly related to plasma adiponectin concentration. Since most of these variables are interrelated, we performed a stepwise multiple regression analysis including these variables. Only glucose disposal rate and steady-state plasma FFA concentration (the latter explained 3% of the variance in metabolic flexibility) were independent determinants of the change in RQ (ΔRQ) during a euglycemic-hyperinsulinemic clamp accounting for half of its variance. It is now necessary to assess more deeply the cellular determinants of metabolic flexibility to lipid in order to improve our understanding of the underlying causes of impaired metabolic flexibility to lipid.

Conclusions

Most of the research on metabolic flexibility has focused on the capacity to metabolize glucose in response to an overload of carbohydrate during a euglycemic-hyperinsulinemic clamp. However, the difference in metabolic flexibility during the clamp in individuals with varying insulin sensitivity is mostly the consequence of variability in insulin-stimulated glucose disposal rate (14). Furthermore, the mitochondrial capacity to oxidize acetyl-CoA coming from glucose is conserved in insulin-resistant subjects even if mitochondrial defects have been reported in those individuals (3, 25, 36, 37, 40, 42, 43, 48, 59). These findings should not negate the potential role of mitochondrial defects in insulin resistance, since during a euglycemic-hyperinsulinemic clamp lipid demand as an energy source is mostly suppressed.

The assessment of metabolic flexibility to lipid will probably unravel defects in lipid oxidative capacity. Surprisingly, there are no studies evaluating metabolic flexibility to lipid in subjects with contrasting degree of insulin resistance. Furthermore, most studies have used fasting RQ as a marker of metabolic flexibility to lipid. However, fasting RQ is not a reliable indicator of lipid oxidation capacity, since RQ under fasting conditions is mostly influenced by energy balance and dietary macronutrient composition (22, 34, 54). In addition, under resting conditions, energy demand with concomitant fat oxidation requirement is hardly a metabolic challenge for muscle mitochondria. Consequently, an eventual defect in fat oxidation is unlikely to be evidenced in resting conditions.

The rate at which fat oxidation adjusts to high fat intake is variable among individuals (21, 53), but only scarce evidence exists about which factors determine this variability. However, this adaptation cannot take much more time than that required to deplete the glycogen stores, i.e., a few days to a week. The question then becomes: is there any importance in assessing the metabolic flexibility to lipid, since eventually fat oxidation will match fat intake in all individuals? The answer is yes, since the speed of the adaptation will probably impact the amount of lipid accumulation in the muscle and therefore impact insulin sensitivity. Individuals able to increase fat oxidation quickly in response to day-to-day changes in fat intake will eventually have lower muscle fat accumulation and be less prone to insulin resistance compared with slower adapters. On the basis of the RQ profile for metabolically flexible and inflexible subjects shown in Fig. 2D, and considering an energy intake of 2,500 kcal/day (protein intake 20% of total energy), the metabolically inflexible individuals would accumulate ~200 g more fat than flexible subjects after 1 wk of a high-fat diet (60% of total energy).

We propose that using the resting condition to test metabolic flexibility, particularly at the skeletal muscle level, is not appropriate, since the absolute lipid oxidation rate is minimal. Energy metabolism under exercise conditions provides a paradigm requiring highly coordinated regulation between fuel supply and the oxidative machinery. This approach in combination with muscle lipid and glycogen content determination may be useful to assess the role of mitochondrial density/function on metabolic flexibility to lipid.

In conclusion, evidence indicating mitochondrial defects as a driving factor of metabolic inflexibility and insulin resistance are far from conclusive or even unavailable. It will be important to test whether whole body or skeletal muscle metabolic flexibility to lipid is affected by muscle mitochondrial characteristics such as density, morphology, and activity. In addition, the role of metabolic flexibility in muscle lipid accumulation and the development of insulin resistance requires further studies. Only this kind of data will allow us to establish a causal link among impaired capacity to metabolize fat, muscle lipotoxicity, and insulin resistance.
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