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Opinion

Assessment of metabolic flexibility by measuring maximal fat oxidation during submaximal intensity exercise: Can we improve the analytical procedures?

Isaac A. Chávez-Guevara

Department of Chemical Sciences, Biomedical Sciences Institute, Autonomous University of Ciudad Juarez, Chihuahua, Mexico

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ABSTRACT

Assessment of maximal fat oxidation rate (MFO) during a submaximal exercise test has been employed by many studies to investigate the differences in metabolic flexibility (MetFlex) across several populations. Nevertheless, many incorrect assumptions and methodological limitations exist in the procedures employed by previous studies, which might lead to misinterpretation of the reported findings. Considering the data retrieved from 19 trained men (Age: [27 ± 4] years; %Body fat: [16.4 ± 4.5]%; maximal oxygen consumption: [55.8 ± 5.3] mL·kg^{-1}·min^{-1}) who performed a graded exercise test over a motor-driven treadmill, this opinion paper shows that MFO alone does not perfectly capture the MetFlex in response to submaximal intensity exercise and recommend a novel index that considers both fat oxidation and energy expenditure modifications for an accurate examination of MetFlex.

The ability of an organism to efficiently adapt nutrient oxidation in response to energy requirements and substrate availability fluctuations is termed metabolic flexibility (MetFlex).[1] Such ability for maintaining metabolic homeostasis is critical for disease prevention and survival. Indeed, an impaired MetFlex is a hallmark of several chronic diseases, including obesity and type 2 diabetes.[1–3]

In humans, several experimental protocols have been applied for the assessment of MetFlex (i.e., sleep-awake, postprandial-postabsortive, and rest-exercise transitions),[1–4] although many of these experimental protocols have not been properly validated. In this regard, measuring exercise-induced modifications in macronutrient oxidation for the assessment of MetFlex has gained particular interest in the past decade because both metabolic rate and substrate availability increase in several tissues, including skeletal muscle.[5,6] From all the physiological biomarkers proposed in the literature, the measurement of maximal fat oxidation rate (MFO) during a submaximal exercise intensity test has received particular attention (Fig. 1a), and several studies have used MFO to compare MetFlex across healthy individuals, patients with obesity and patients with type 2 diabetes.[7–10] The last, because of an impaired fat oxidation capacity, is often associated with diaclyglycerol and ceramides accumulation in skeletal muscle leading to insulin resistance.[11]

Despite a large body of literature that has employed MFO for the assessment of MetFlex, several weaknesses and incorrect assumptions exist in the current analytical procedures that might lead to interpretation bias regarding the association of fat oxidation capacity and metabolic health. In particular, researchers propose that a higher MFO indicates a greater MetFlex, assuming that 1) the higher the MFO, the greater the increment in fatty acid availability from rest to exercise; 2) the higher the MFO, the greater the fat oxidation increment from rest to exercise, 3) the higher the MFO, the greater the fat oxidation increment with respect to energy expenditure modifications. With regard to the first analytical assumption, Robinson et al.[12] reported that exercise-induced modifications on free fatty acids did not correlate to MFO in trained men, questioning the reliability of MFO for representing MetFlex. In addition, to argue the validity of the second and third assumptions, I will present data from 19 trained men (Age: [27 ± 4] years; %Body fat: [16.4 ± 4.5];% maximal oxygen consumption [$\dot{V}O_{2\ max}$]: [55.8 ± 5.3] mL·kg^{-1}·min^{-1}) collected through indirect calorimetry measurements at rest and during a graded exercise test (initial speed of 5 km·h^{-1} and subsequent gradual increments of +1 km·h^{-1} each 3 min) after overnight fasting (10–12 h). Moreover, through an analysis of exercise-induced modifications in metabolic rate and fat oxidation, I will provide further recommendations to improve MetFlex assessment, illustrating the relevance of establishing appropriate analytical procedures to avoid equivocal conclusions in clinical research.

In order to evaluate MetFlex, researchers would need to measure the metabolic transition from condition "A" (rest) to condition "B" (exercise). Nonetheless, previous studies evaluating MFO as a marker of metabolic flexibility rarely perform resting fat oxidation and metabolic rate

E-mail address: isaac.chavez@uacj.mx.

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Abbreviations

EE	Energy expenditure
EE/Fox	Index of fat oxidation increment with regard to energy expenditure
MetFlex	Metabolic flexibility
MFO	Maximal fat oxidation
$\dot{V}O_{2\ max}$	Maximal oxygen consumption

assessments. In this regard, a linear regression analysis of our collected data revealed that MFO is strongly associated with the fat oxidation increment induced by physical exercise (difference between MFO and fat oxidation at rest) (Fig. 1b). However, based on the concept of MetFlex, the exercise-induced modification of the fat oxidation rate need to be interpreted in the frame of energy expenditure or fatty acid availability modifications. Thus, we could perform a linear regression analysis by taking into account the fat oxidation rate and energy expenditure measured at rest and at MFO intensity (Fig. 1c), in order to obtain a new index of MetFlex (β coefficient or Slope) which represents the magnitude of the fat oxidation increment stimulated by an augment of 1 kJ·min^{-1} in energy expenditure. Interestingly, the MFO shows a modest association with the index of fat oxidation increment with regard to energy expenditure (Fig. 1d). Therefore, it seems that MFO alone does not perfectly capture the MetFlex in response to exercise and future studies must consider both fat oxidation and energy expenditure modifications for an accurate examination of MetFlex.

To illustrate the relevance of establishing reliable analytical procedures for the assessment of MetFlex, I would like to point out that several studies have proposed a link between obesity and impaired MetFlex, based on their observation that subjects with obesity exhibit a lower MFO in comparison to normal weight individuals.[8–10] Nevertheless, as discussed above, these studies equivocally assumed that a similar increment of energy expenditure and fatty acid availability occurs in response to exercise between lean individuals and subjects with obesity, overlooking the fact that both energy expenditure and fatty acid availability increases with obesity due to an elevation in free fat mass and fat mass respectively.[10,13] In a similar way, discrepancies in MetFlex between sexes have been proposed in the literature based on repeated observations that MFO is superior in women vs. men.[14] However, such studies did not consider that adipose tissue lipolysis during exercise is higher in women when compared to men.[15] Therefore, to avoid equivocal conclusions that may lead to incorrect theoretical models, future studies evaluating the MFO must take into account the modifications in energy expenditure and fatty acid availability for a reliable assessment of MetFlex.

Submission statement

This work is original and has not been published elsewhere, nor is currently under consideration for publication elsewhere.

Authors' contribution

IACG: Formal analysis, Writing – original draft conceived the study, performed the statistical analysis, elaborated the figures and drafted the manuscript.

Ethical approval statement

All the individuals who volunteered to participate in this study signed an informed consent prior to evaluations and the experimental procedures were approved by the Ethics committee of the Autonomous University of Ciudad Juarez (CEI-2020-2-60).

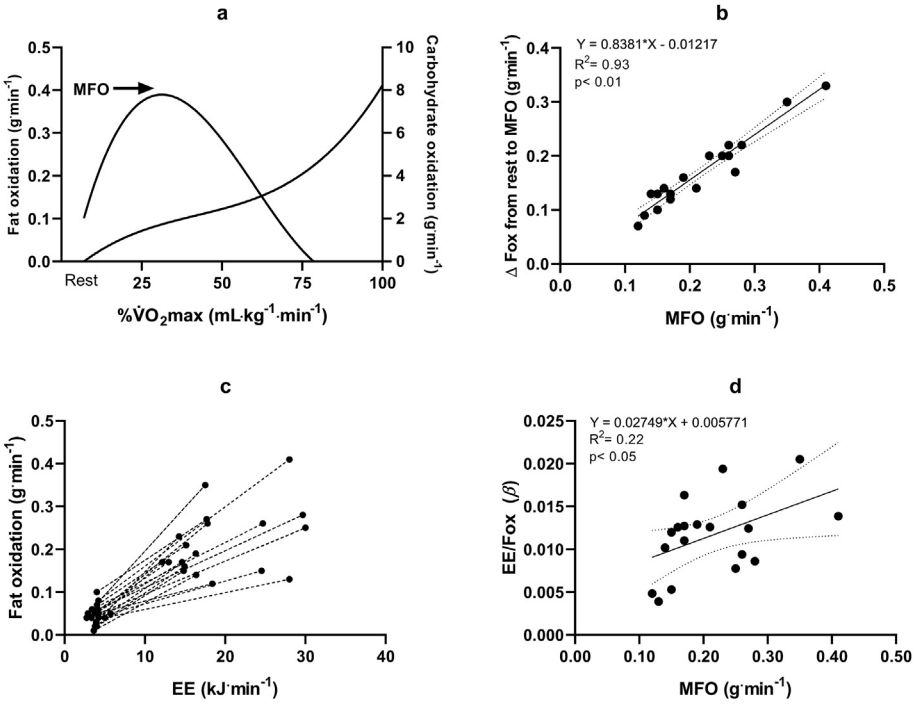

Fig. 1. a) Macronutrient oxidation kinetics with regard to exercise intensity modifications during an exercise test, expressed as percentage of $\dot{V}O_{2\ max}$. b) Association between maximal fat oxidation (MFO) and the increment in the fat oxidation rate from resting conditions to the exercise intensity eliciting MFO. c) Individual modifications in fat oxidation rate and energy expenditure (EE) from rest to exercise intensity eliciting MFO. d) Association between MFO and the index of fat oxidation increment with regard to energy expenditure (EE/Fox [β]) obtained through linear regression analysis.
*Macronutrient oxidation rates and metabolic rate at rest and during exercise were measured through indirect calorimetry after overnight fasting (10–12 h) and calculated with stoichiometric equations.[16,17] The exercise test was performed over a treadmill and the MFO was obtained by plotting the fat oxidation rates against exercise intensity. Body composition retrieved from bioelectrical bioimpedance, physical activity level, and medical history were screened prior to exercise testing and those participants who meet the following inclusion criteria were selected: i) age between 18 and 40 years; (ii) fat mass index < 6 kg·m^{-2}; (iii) high physical activity level according to the International Questionnaire of Physical Activity[18]; (iv) resting heart rate < 90 beats·min^{-1}; (v) blood pressure ≤ 120/80 mmHg; (vi) medical history free of cardiovascular, metabolic or respiratory diseases that impede physical exercise performance.

Conflict of interest

The author declares there is no conflict of interest for the conduction of this study.

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