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Abstract

Metabolic flexibility can be described as the sum of an organism's adaptive responses for the preferential oxidization of fuels relative to anatomical supply (intake and storage) and physiological demand (physical activity and inactivity). Metabolic flexibility has been observed using two methods during fasted and fed states: Indirect Calorimetry and a Euglycemic-Hyperinsulinemic clamp. Exploring additional methods that incorporate responses to physical activity may provide additional insight into metabolic flexibility. Mitochondria are intracellular organelles with a primary role in oxidative metabolism. Mitochondrial adaptability to substrate availability and physical activity/inactivity may be considered the primary functional components of metabolic flexibility. Blood lactate has been described as a proxy for mitochondrial function and as a surrogate of glycolytic and oxidative metabolism. Given the robust mitochondrial responses to increases or decreases in physical activity and exercise, metabolic flexibility may be observed through a blood lactate analysis. A method to describe performance within and between cyclists is the power to mass ratio (W/kg). We describe here a reconfiguring of this ratio in the MetFlex Index™: a method to describe the power produced at the first lactate threshold relative to an individual's Body Mass Index (BMI). The MetFlex Index™ may afford a useful framework for describing metabolic flexibility and fitness in individuals within the general population. The following perspective describes a novel scoring system, the MetFlex Index™, by way of a blood lactate biomarker to quantify metabolic flexibility.

1 Introduction

Metabolic Syndrome affects at least one-third of U.S. adults within the United States (1). Additional prevalence data demonstrates that 40% of adults are living with obesity and 10% of adults are living with diabetes (2-3). Recently, the severity of illness during a Covid-19 infection and higher mortality rates have been associated with adults living with metabolic syndrome (4) and additional chronic conditions, with accumulating risk relative to the increased number of positive risk factors for metabolic syndrome (5). Severity of illness was also higher in individuals with lower cardiorespiratory fitness (6). Physical inactivity and sedentary behavior contribute to increases in the severity of metabolic health risk factors (7-13). It is well established that physical activity and exercise can be effective attenuators of metabolic disease and contribute to improved tissue and organ function beyond skeletal muscle (14), independent of weight loss. Physical activity and exercise can directly affect metabolic health through changes to mitochondrial structure and function (15 -16). Increases in cardiorespiratory fitness, i.e. a higher VO2max, can reduce the risks associated with obesity and metabolic-related diseases by mitigating metabolic dysfunction and associated risk factors (17), also described as an "obesity paradox" in heart failure relative to cardiorespiratory fitness status (18). Given that movement is essential for metabolic health, the development of a process to quantify metabolic flexibility could prove useful in efforts for elevating physical fitness and bolstering metabolic-related disease prevention and mitigation efforts.

2 Metabolic Flexibility

Metabolic Flexibility is the ability to adapt fuel availability to energy demands. The terminology originally developed to describe energy use in skeletal muscle were 'plasticity' and 'adaptability' (19-20). Currently, descriptions are trending toward use of metabolic flexibility and inflexibility (21-22). Methodology and concepts related to metabolic flexibility are described in detail elsewhere (10,16, 23-32). The primary methodology for determining metabolic flexibility is indirect calorimetry during a euglycemic-hyperinsulinemic clamp. Recent research has demonstrated an impaired ability to switch from fat to glucose oxidation in the transition from fasting to fed states. Additionally, individuals with metabolic dysfunction including insulin resistance, obesity, and diabetes were found to have a higher preference for glucose relative to fat as an energy source when fasted, here described as metabolic inflexibility. Gaps persist in understanding the relationship between metabolic health and metabolic inflexibility, particularly with respect to metabolic inflexibility and ectopic lipid accumulation (32). It may be useful to develop less invasive methods and more scalable biomarkers for quantifying metabolic flexibility (10) in order to assess the efficacy of metabolic health-related interventions within clinical and nonclinical populations. One potential biomarker is blood lactate which serves as a metabolic bridge between glycolysis and oxidation.

3 Lactate

Historically, lactate was viewed as a waste product associated with hypoxia and fatigue (33). More recently, lactate has been reframed as the "fulcrum of metabolism" (34), demonstrating increased metabolic significance in health and disease (35-36), and harboring under-developed potential as a metabolic marker of health and disease (37). Lactate may be a useful metabolic biomarker (relative to other more vetted markers such as the waist/hip ratio, skeletal muscle fatty acid oxidation, HDL/LDL ratio, etc.), by measuring resting fasting plasma lactate (38-39) or by observing lactate clearance thru a graded exercise test (40). In one application, relationships between lactate and substrate oxidation were observed with indirect calorimetry during a graded exercise test comparing professional cyclists and less fit individuals, including very low fit individuals with metabolic syndrome (40). Exercise testing in this study was performed on a lower extremity ergometer with standardized stage durations and power increments. Blood lactate was sampled at the end of each stage duration with ventilatory data (VCO2/VO2) collected throughout. Strong relationships were observed between lactate clearance and substrate oxidation between the various groups. Endurance athletes prolonged fat oxidation (fat can only be oxidized within the mitochondria) and delayed substantial carbohydrate oxidation relative to the first lactate threshold (aka lactate clearance capacity). Less fit individuals, most pronounced in individuals with metabolic syndrome, demonstrated an impaired capacity for fat oxidation with reliance on carbohydrate oxidation and glycolysis at very low workloads including a very early onset of the first lactate threshold. Early lactate accumulation may have an impact on fat metabolism (lipolysis and oxidation)

(41) and the observation of an "early onset of lactate accumulation signifies poor capacity to mediate metabolic strain resulting in significant organismal stress" (37). Lactate clearance and associated lactate thresholds demonstrated strong relationships relative to substrate oxidation where lactate and fat oxidation were strongly negatively correlated, and lactate and carbohydrate oxidation were strongly positively correlated (40). Since lactate metabolism and fat oxidation occur at the level of the mitochondria, observing lactate clearance may offer a proxy into mitochondrial function. As such, lactate clearance may then demonstrate utility as a surrogate for measuring fat oxidation considering that fat oxidation begins decreasing at or near the first lactate threshold and is at near zero levels by the second lactate threshold. This relationship between lactate and fat oxidation contributes to our development of a novel method for quantifying metabolic flexibility.

Lactate metabolism relative to power output (Watts) is used to compare cyclists at different stages in training or across a career (42) and, in conjunction with additional metabolic data, may predict high performance and outcome prior to a competitive season (43). Power to mass ratios (W/kg) are traditionally derived from the sustained power maintained over a given duration, e.g. 30 or 60 minutes, and are typically observed at or near the second lactate threshold. At the second lactate threshold, fat oxidation is at or near lowest rates and carbohydrate oxidation rates continue to trend higher. Since fat oxidation begins to trend downward at or near the first lactate threshold, finding this first threshold, and the power (Watts) associated with it, may afford improved utility for describing metabolic flexibility in individuals.

4 Body Mass Index

Body Mass Index (BMI) was developed over 150 years ago but was not integrated with medical literature until the early 1970's (44). BMI persists as a statistical tool within the NIH and WHO for comparisons within and between populations (44), however not without limitations. Recently, integrating results from cardiopulmonary exercise testing to determine cardiorespiratory fitness (e.g.VO2peak) relative to body mass yielded a "fitness-to-mass ratio" (e.g. VO2peak/kg) which provided increased utility for establishing an obesity staging system, potentially identifying higher risk individuals for mortality (17). Here, accounting for physical capacity relative to BMI may prove useful for further identifying, treating, and monitoring metabolically at-risk individuals.

5 MetFlex Index™

The MetFlex Index™ is similar to the cycling-based W/kg metric with two primary differences: 1) the Index identifies the power attained at the first lactate threshold rather than at the second lactate threshold or other construct (i.e. functional threshold power) and 2) power is relative to an individual's BMI instead of their mass. Recall that the first lactate threshold indicates a point of transition in substrate utilization from peak or max fat oxidation toward predominantly carbohydrate oxidation by the second lactate threshold, partly explained by accumulating lactate may contribute to the inhibition of lipolysis and fat oxidation (41). Therefore, at the first lactate threshold, lactate clearance and fat metabolism may provide insight into metabolic flexibility including an indirect observation of mitochondria function given that fat can only be oxidized to ATP at the mitochondrial level. For instance, the lower the lactate threshold relative to power output, the lower the fat oxidization and the lower the metabolic flexibility. The higher the lactate threshold relative to power output, the higher the fat oxidization, and the higher the metabolic flexibility. Using BMI instead of kilograms affords use of the long-standing BMI biometric that has risk stratification incumbency in healthcare. Physical fitness relative to an individual's BMI provides increased utility for modulating BMI risk stratification, consistent with individualization or personalization trends in health and fitness. Examples of the variation between individual lactate curves (observed as lactate clearance capacities) and the calculated MetFlex Index™ at different BMIs are demonstrated below in Figure 1.

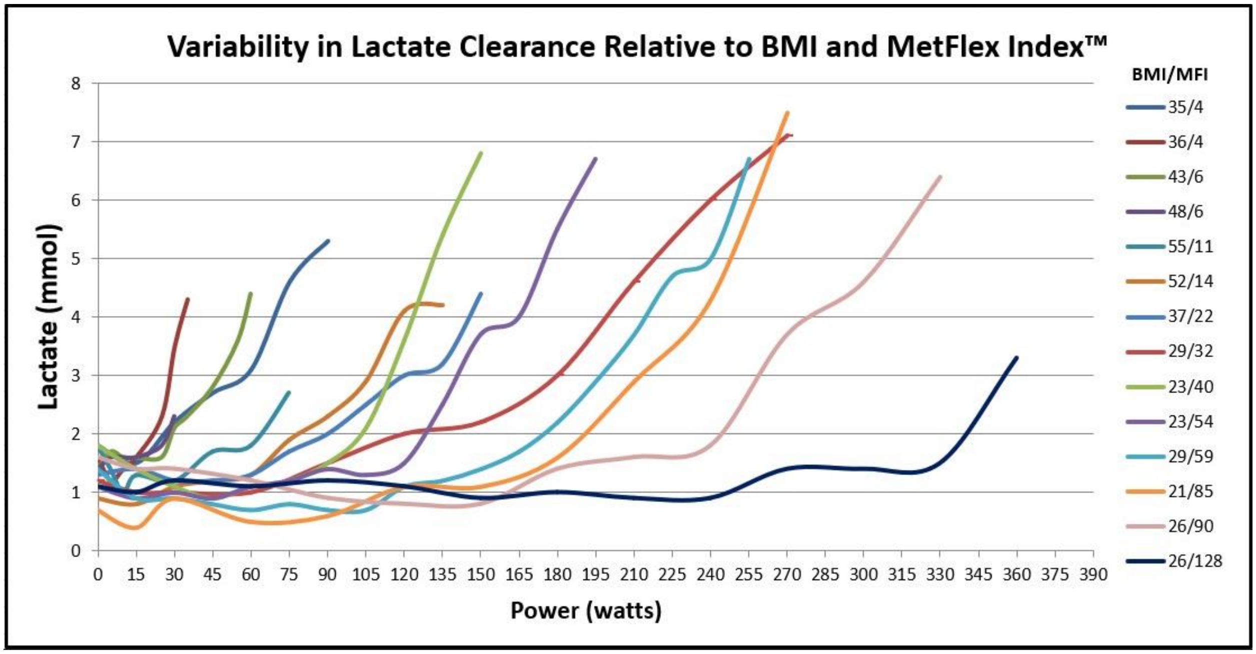

Figure 1. Fourteen individual lactate curves derived from graded exercise tests and performed on an upright cycle using capillary blood lactate sampled from an earlobe at three-minute stages. Notice the extent of variation in the curves from low power (left) to high power (right) between different individuals. Lower power indicates lower lactate clearance capacity as the first lactate threshold is reached very early in testing. The curves demonstrate, from left to right, a greater lactate clearance capacity indicating that the first lactate thresholds are reached at higher power outputs. Prolonged lactate clearance indirectly demonstrates a prolonged utilization of fat oxidation and delayed reliance on carbohydrate metabolism. The key on the right displays variation in lactate clearance capacity relative to different BMIs. This is described by a novel score for metabolic fitness: the MetFlex Index™. This relationship between BMI and MetFlex Index™ may be useful for comparing metabolic dysfunction within and between people of similar BMIs. For example, comparing two individuals above with BMIs of 29: one individual demonstrates a MetFlex Index™ of 32 (lower metabolic flexibility and fitness) and the other demonstrates an MetFlex Index™ of 59 (higher metabolic flexibility and fitness). The Index may be useful for monitoring and managing treatment responses in chronic condition management including the ability to stratify risk via metabolic fitness. Clinical trials will be required to further examine the relationship between the MetFlex Index™ and acute and chronic sequela of prolonged metabolic inflexibility (i.e. low lactate clearance capacity) such as in disease onset, progression, regression, and overall risk management and mitigation.

Considering one's current physical capacity defined as the Watts produced at the first lactate threshold, we can also compare efficacy and responsiveness to an exercise training program or any other intervention deemed to improve fitness or oxidative capacity. Here, the MetFlex Index™ could be used to determine a loss or gain in metabolic flexibility over time, regardless of the intervention (diet, medication, inactivity) or it could be used to monitor stability, progression, or regression of fitness in individuals living with chronic conditions. Figure 2, below, demonstrates the variability of the Index from low fitness (early onset of lactate accumulation at low power aka low lactate clearance capacity) to high fitness (late onset of lactate accumulation at high power aka high lactate clearance capacity) individuals independent of age, sex, race/ethnicity, and BMI. This ability to quantify the relationship of an external load or stress (e.g.Watts) to an internal load or stress (e.g. lactate) has potential value as a movement-based health metric (48).

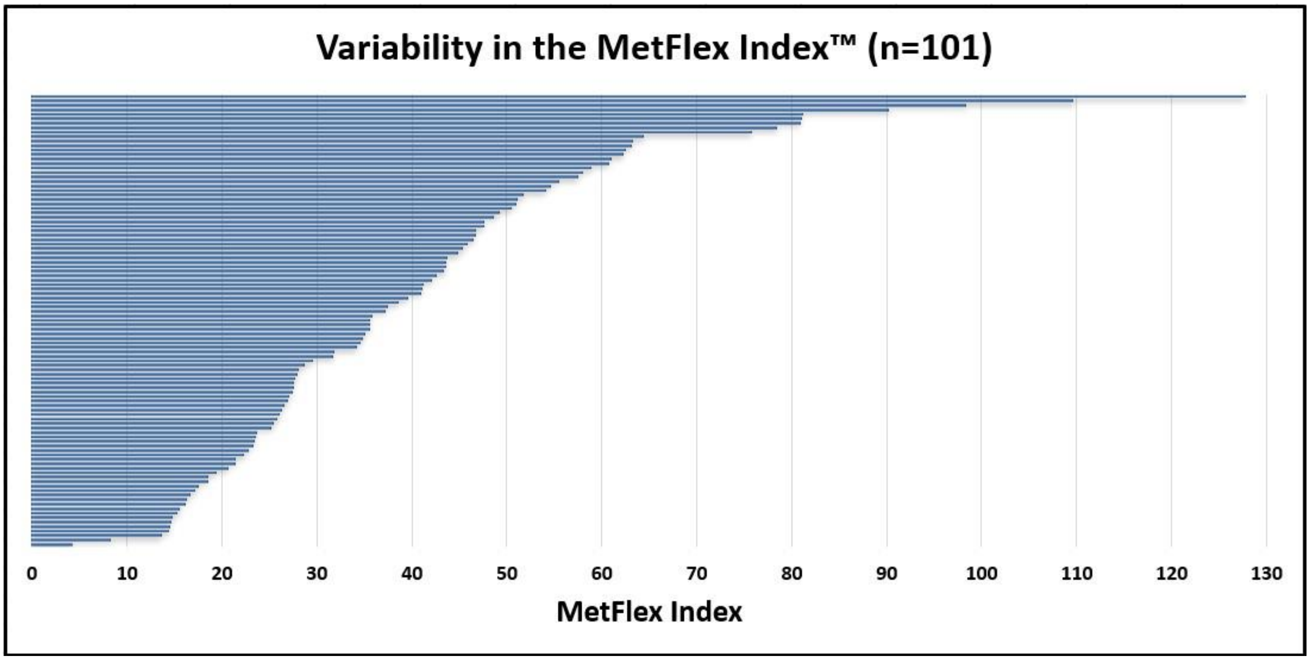

Figure 2. Demonstrates the variability in the MetFlex Index™ across 101 individuals (unpublished preliminary data). Recall that the MetFlex Index™ is the power generated (in Watts) at the first lactate threshold relative to an individual's BMI which corresponds to lactate clearance capacity, directly, and fat oxidation capacity, indirectly. The lower the MetFlex Index™ (bottom of the graph), the lower the lactate clearance capacity, the lower the capacity for fat oxidation, and the higher the reliance on glycolytic metabolism. The higher the MetFlex Index™ (top of the graph), the higher the capacity for lactate clearance, the higher the capacity for fat oxidation, and less reliance on glycolytic metabolism. Observing lactate during a graded exercise test affords direct observation of clearance capacity which, in this application, functions as a surrogate for fat oxidation. Both lactate clearance and fat oxidation are primary functions of skeletal muscle mitochondria which may be a useful surrogate for quantifying systemic mitochondrial function and capacity relative to metabolic health or dysfunction.

6 Conclusion

Using a lactate biomarker during a graded exercise test may be useful as a proxy for fat oxidation capacity indicating an individual's metabolic flexibility. Lactate may also provide for indirect insight into mitochondrial function and capacity as mitochondria are the foundation of metabolism and energy management. Mitochondria are reliant on physical activity and movement to stimulate biogenesis, reticulation, and beneficial fission/fusion behavior. Additional methods for quantifying metabolic flexibility in clinical and nonclinical settings are needed as current methods as euglycemic-hyperinsulinemic clamps are highly invasive and impractical at scale. Traditionally, cardiopulmonary exercise testing has been the gold standard for measuring fitness, yet it is typically not accessible to populations outside of major metro areas due to the need for skilled physiologists, expensive, high-tech equipment, and facility costs related to managing and maintaining an exercise lab. If an exercise lab were accessible, it appears at this time that an individual would require considerably poor health to participate in a cardiopulmonary exercise test as it is typically used for cardiopulmonary diagnostics during stress testing. Given the current state and trajectory of dysmetabolism in the U.S. and beyond and the importance of fitness for systemic health, fitness testing ought to be scaled for improved access. It may require a new standard of care, if not a new active vital sign, for measuring and managing physical capacity/fitness as it drives mitochondrial structure and function and, consequently, metabolic-related health. Accessibility, safety, ease of testing, and capacity to scale within urban and rural outpatient ambulatory facilities are some potential benefits to using a lactate-based biomarker for monitoring and managing metabolic flexibility and fitness in health and disease.

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