Metabolic Flexibility, Energy Availability, and Substrate Utilisation: Extending the EPK Framework Beyond Static Calorie Models

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Status: conceptual/hypothesis-generating working paper. Not peer reviewed. This revision adds primary-study appraisal and prospective tests; it reports no new participant data.

Abstract

Human fat gain obeys energy balance, but carbohydrate and dietary fat are not metabolically identical. Under ordinary mixed-diet conditions, net de novo lipogenesis from carbohydrate is generally limited, whereas dietary fat can be stored efficiently during energy excess. Carbohydrate can still promote fat storage indirectly by suppressing fat oxidation. This paper asks whether chronic low-energy physiology, reduced metabolic throughput and a high dietary-fat proportion may combine to impair metabolic flexibility.1,2,3,4,5,6 This revision separates dietary intake from cellular utilisation and proposes prospective comparison of EPK with its component measurements; the added mechanistic evidence does not validate EPK.

De Novo Lipogenesis and Fat Storage

Classic overfeeding studies show that carbohydrate is preferentially oxidised and stored as glycogen before large-scale de novo lipogenesis becomes quantitatively important. Dietary fat can enter adipose storage with relatively little conversion. The implication is not that carbohydrate cannot contribute to fat gain; during energy surplus it can suppress fat oxidation and thereby spare dietary fat for storage.[1,2,3]

Low-Energy Physiology and Substrate Competition

Restriction can lower resting expenditure, spontaneous movement and thermogenesis. If a low-calorie diet remains high in fat percentage, carbohydrate availability may become low at the same time as total physiological output is falling. The Randle cycle provides a mechanism through which high fatty-acid availability can suppress glucose oxidation. This is normal physiology, but chronic inflexibility may become relevant when low movement, high fatty-acid exposure and poor glucose utilisation coexist.[7,8,4,5,6]

PUFA and Oxidative Stress

Highly unsaturated fatty acids are susceptible to lipid peroxidation, and oxidised lipid products can affect membranes, signalling and mitochondria. These mechanisms justify research into fatty-acid composition in aging and metabolic dysfunction. They do not justify the stronger claim that PUFA simply blocks cellular respiration or directly causes obesity.[9]

Fatty acid oxidation and the capacity to switch

In rodent and cultured-muscle experiments, Koves et al. connected incomplete fatty-acid oxidation with insulin resistance [R1]. The implication for EPK is a need to distinguish how much substrate enters oxidation from how effectively the system completes oxidation and switches fuels. A low fasting respiratory exchange ratio alone cannot identify healthy flexibility or pathological dependence on fat.

Kim et al. induced excessive cardiac fatty-acid oxidation by deleting both acetyl-CoA carboxylase isoforms in mouse cardiomyocytes; cardiolipin depletion and heart failure followed [R2]. This extreme genetic model challenges the assumption that greater fat oxidation is invariably beneficial. It does not make ordinary fat oxidation pathological or establish an EPK treatment.

Cluntun et al. provide complementary evidence that cardiac mitochondrial pyruvate handling matters [R3]. Taken together, these studies motivate a supply-and-utilisation hypothesis rather than a universal preference for one fuel. Dietary availability must not be equated with flux through a mitochondrial pathway.

Membrane context and senescence

Gupta et al. studied lipid–protein compatibility in respiratory complexes, with different effects of 18:3 and 18:2 fatty acids in engineered human cells [R4]. Kim et al. also identify an essential structural role for linoleate-containing cardiolipin [R2]. These results argue against treating all polyunsaturated fatty acids as equivalent respiratory inhibitors.

Yamauchi et al. identified a fatty-acid-oxidation-dependent pathway to senescence in experimental cells [R5]. Senescence in these models is not a demonstration of accelerated whole-person aging at a particular dietary fat intake or EPK. Any translational study must specify tissue, stimulus and outcome rather than treating senescence as a single universal process.

Human evidence from the PubMed search

A randomized crossover study of 12 endurance-trained women found poorer cycling performance after 14 days of low energy availability, with increased fat oxidation but unchanged measured muscle mitochondrial respiratory capacity. This supports a functional effect while challenging mitochondrial impairment as its necessary explanation. [H1]

In a six-month randomized study of 36 adults, calorie restriction increased muscle mitochondrial DNA content while key mitochondrial enzyme activities remained unchanged. The result separates mitochondrial quantity from measured functional capacity and challenges a universal decline-with-restriction model. [H2]

In a small 16-week comparison of weight loss (7 participants) and exercise (10), insulin sensitivity improved similarly while mitochondrial adaptations differed. This shows why insulin sensitivity and mitochondrial capacity should not be treated as equivalent outcomes. [H3]

These studies test energy restriction or sports energy availability, not EPK as an intake-to-total-mass ratio. Their populations and intervention durations bound interpretation; none validates an EPK threshold. The human literature requires the framework to allow beneficial, adverse and null responses in different contexts.

Testing the metabolic prediction

Does EPK predict functional outcomes beyond total energy intake, body composition, carbohydrate availability and activity, and could fuel switching or mitochondrial function explain any association?

For prospective testing, EPK is defined here as mean dietary energy intake in kcal per day divided by body mass in kg, expressed as kcal/kg/day. This intake ratio is not the sports energy-availability measure, which subtracts exercise energy expenditure from intake and divides by fat-free mass. Exercise expenditure, fat-free mass,

carbohydrate intake and weight trajectory must therefore be recorded separately. No diagnostic EPK threshold is established by this revision.

EPK is calculated from intake and mass and therefore contains no information absent from those inputs. Its value must be judged as a useful summary, not an independent biological variable. Compare a preregistered EPK model with a flexible model of energy intake and mass, including relevant nonlinear terms and interactions, under the same validation procedure. Adding the ratio to a simple linear baseline would not by itself establish unique physiological information. Report out-of-sample prediction error, calibration and uncertainty; favour the simpler model if performance is comparable.

Use a standardised fasting-to-fed challenge with indirect calorimetry to estimate substrate switching, controlling prior diet, exercise and energy balance. A clamp or tracer substudy could distinguish insulin responsiveness and substrate flux; muscle respiration would address a different level of mechanism. Circulating acylcarnitines may be informative but are not a stand-alone diagnosis of incomplete muscle oxidation. Prespecify whether improved switching, physical function or glycaemic control is the primary endpoint. A null EPK association or superior prediction from its separate inputs would count against the proposed practical advantage.

EPK Strategy and Conclusion

The EPK model seeks to restore sufficient energy relative to mass and demand while providing enough carbohydrate to support glucose oxidation, glycogen restoration, movement and recovery. Stored fat remains an important fuel during lower-demand and fasting periods, including overnight. The hypothesis is that a well-powered, metabolically flexible system can oxidise carbohydrate when appropriate and draw on stored fat when appropriate rather than continually supplying large amounts of dietary fat in a low-throughput state.[4,5,6]

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Primary studies added in version 1.1

[R1] Koves TR, et al. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. Cell Metab. 2008;7:45–56. https://doi.org/10.1016/j.cmet.2007.10.013

[R2] Kim CW, et al. Unrestrained fatty acid oxidation triggers heart failure in mice via cardiolipin loss and mitochondrial dysfunction. J Clin Invest. 2026;136:e202 528. https://doi.org/10.1172/JCI202 528

[R3] Cluntun AA, et al. The pyruvate-lactate axis modulates cardiac hypertrophy and heart failure. Cell Metab. 2021;33:629–648.e10. https://doi.org/10.1016/j.cmet.2020.12.003

[R4] Gupta P, et al. Kingdom-specific lipid unsaturation calibrates sequence evolution in membrane arm subunits of eukaryotic respiratory complexes. Nat Commun. 2025;16:2044. https://doi.org/10.1038/s41 467-025-57 295-7

[R5] Yamauchi S, et al. Mitochondrial fatty acid oxidation drives senescence. Sci Adv. 2024;10:eado5887. https://doi.org/10.1126/sciadv.ado5887

Human studies added in version 1.1

[H1] Caldwell HG, et al. The whole-body and skeletal muscle metabolic response to 14 days of highly controlled low energy availability in endurance-trained females. FASEB J. 2024;38:e70 157. doi:10.1096/fj.202401 780R. https://pubmed.ncbi.nlm.nih.gov/39 530 548/

[H2] Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. PLoS Med. 2007. PMID:17 341 128. https://pubmed.ncbi.nlm.nih.gov/17 341 128/

[H3] Calorie Restriction-induced Weight Loss and Exercise Have Differential Effects on Skeletal Muscle Mitochondria Despite Similar Effects on Insulin Sensitivity. 2017. PMID:28 158 621. https://pubmed.ncbi.nlm.nih.gov/28 158 621/

Publication Note

This manuscript is part of the EPK (Energy Per Kilogram) paper series developed by Billy Craig, MSc. The paper should be cited as a working/preprint paper until peer-reviewed publication. EPK-specific propositions are presented as hypotheses where they extend beyond the cited evidence.

Revision record

Version 1.1 adds the mechanistic discussion and prospective study design above. The original numbered bibliography remains distinct from the new R-prefixed mechanistic and H-prefixed human-study citations. Studies discovered through haidut.me are cited to their original research publications; the blog commentary is not treated as primary evidence.

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