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PERSPECTIVE

The fat factor: rethinking adipose energetics with obesity, insulin resistance and surgeryJohn Noone^{1,2,3,4} ¹Department of Physical Education and Sport Sciences, Faculty of Education and Health Sciences, University of Limerick, Limerick, Ireland²Physical Activity for Health Research Cluster, Health Research Institute, University of Limerick, Limerick, Ireland³Sport and Human Performance Research Centre, University of Limerick, Limerick, Ireland⁴Health Research Institute, University of Limerick, Limerick, Ireland

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Adipose tissue is a complex, misunderstood and poorly studied metabolic organ. This is becoming more and more evident with the advent of single nuclei RNA sequencing, outlining clear discrepancy between subcutaneous and visceral adipocyte transcriptional profiles (Emont et al., 2023), implicated by a series of intrinsic (i.e. age, sex, hormonal status, race/ethnicity) and extrinsic (i.e. circadian rhythms, sleep, diet, medication) factors. Complementing these advances, the metabolic profile of adipose tissue, specifically relating to obesity, has been studied for some time now, with clear evidence outlining the disturbance that increased adiposity plays on disease susceptibility, particularly insulin resistance and type 2 diabetes. Nonetheless, comprehension of the bioenergetic demand posed by these distinct metabolic profiles relating to obesity within omental and subcutaneous adipose tissue is lacking and, given the intricate differences between these, from insulin sensitivity to type

2 diabetes, more appreciation of these bioenergetic processes is imperative.

The need for greater study here is further emphasized by the significant surge in the obesity epidemic worldwide, aligned with a complexity of approaches currently implemented in the treatment of this problem; be these gene and stem cell therapies, microbiome-based interventions, intermittent fasting, hormonal therapies or lifestyle modification, such as exercise. Yet, what impact these approaches have on adipose metabolic processes is limited. This is of particular importance given the advancement in pharmaceutical glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter 2 (SGLT-2) inhibitors, in accordance with surgical innovation in the management of obesity. Considering more than 30 years has now passed since the seminal work by Alan Wittgrove and colleagues conducting the first laparoscopic gastric bypass (Roux-en-Y) at the Alvarado Hospital Medical Centre in San Diego (Wittgrove et al., 1994), it is disconcerting that we are still unclear on the bioenergetic adaptation of adipose tissue in respect to these therapies – *we have put the metaphorical cart before the horse*.

In this issue of *The Journal of Physiology*, Pinho et al. (2025) interrogate the distinct mitochondrial bioenergetic profile within subcutaneous (SAT) and omental adipose tissue (OAT) of individuals with severe obesity at differing stages of metabolic dysregulation. The authors define these stages as insulin sensitive, insulin-resistant normoglycaemic (IR-NG), prediabetic and type 2 diabetic. Clarifying these stages is integral given the clear distinctions in their metabolic profiles – an approach which has not yet been considered with enough rigor. Cross-examination of mitochondrial bioenergetic flux throughout such stages was achieved through determination of adipose tissue (OAT, SAT) oxidative phosphorylation (OXPHOS) using sundry intuitive ratios and avenues in real-time through high-resolution respirometry (oxygraph-2k (Oroboros)) with substrate-uncoupler-inhibitor-titration (SUIT) protocols of biopsy-derived adipose specimens. This comprehensive work was successively complemented by the study of the mitochondrial respiratory capacity before and after bariatric surgery

in individuals suffering from severe obesity (>40 kg/m²).

Given the likely variability in mitochondrial number between samples, it was slightly surprising when Pinho and colleagues opted not to measure oxygraph-2k chamber content. However, by comprehending sample flux control ratios, such as LEAK to electron transport system (ETS) difference (L–E), direct measurement of mitochondrial coupling efficiency was achieved and at higher statistical resolution – an internal normalization, important, particularly when a sample is limited. Specifically in the context of this publication, the authors used the L–E ratio to uncover the balance between proton leak and maximal ETS capacity, offering an accurate assessment of OXPHOS control compared with other external mitochondrial control measures that may be influenced by substrate availability, membrane potential variations or sample quantity.

Perhaps unsurprisingly, the authors noted an increase in mitochondrial OXPHOS coupling efficiency within OAT compared with SAT and, furthermore, a dyscoupled state of mitochondrial respiration in the obese, insulin-resistant normoglycaemic and obese, insulin-resistant, type 2 diabetic groups. These findings support the higher mitochondrial content in OAT than in SAT. The authors propose that these outcomes could be explained by a potential internal mechanism within OAT to upregulate energy expenditure to counteract weight gain – that is, OAT mitochondria might act as internal regulators of adipose tissue weight, explained by an increased expression/activity of uncoupling protein-1 (UCP-1) or adipose browning (Bettini et al., 2019); a controversial hypothesis, needing further study within the human model.

Another complementary finding from this study was succinate's relative contribution to SAT and OAT mitochondrial respiration. Formed from succinyl-CoA and converted to fumarate by succinate dehydrogenase (Complex II) in the mitochondria, succinate is integral to the generation of NADH and FADH₂ to fuel ATP production via OXPHOS. Yet, unlike NADH-linked substrates (pyruvate, glucose etc.), succinate directly donates electrons to Complex II, bypassing Complex I. Given that Complex II does not pump protons, succinate

Linked articles: This Journal Club article highlights an article by Pinho et al. To read this article, visit <https://doi.org/10.1113/JP286103>.

contributes significantly fewer protons to the mitochondrial proton gradient than NADH-producing substrates. However, Pinho et al. (2025), found succinate to be the preferred mitochondrial substrate in those who have obesity and type 2 diabetes. Such an observation supports previous mechanistic indications of succinate's enhancement of ATP production when glucose metabolism is dysfunctional (Fernández-Veledo et al., 2024) – substrate for thought.

Building on these findings, Pinho et al. (2025) expanded our understanding of the adipose tissue bioenergetic response to bariatric metabolic surgery. Proven to be a highly effective, long-term solution for weight loss and improving metabolic health in individuals with severe obesity, the adipose tissue mitochondrial and metabolic response remains poorly understood. In this context, the authors highlight the role of bariatric metabolic surgery in increasing intrinsic uncoupled respiration in OAT and enhancing substrate oxidation in both OAT and SAT. Such findings provide strong, clinical implications, given the importance that mitochondrial energetics possess at promoting efficient nutrient utilization – impaired in those with obesity. Furthermore, these findings provide significant translational meaning, strengthening the importance of targeted mitochondrial interventions, in the context of traditional and emerging obesity treatments such as lifestyle modification or gene and stem cell therapies, possess in advancing the treatment of obesity.

This work is a visceral (and subcutaneous) reminder of adipose tissue's bioenergetic influence on metabolic disease status. In particular, these findings stress urgency for its interrogation as we navigate an increasingly obesogenic world, eager for impactful, lasting solutions.

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Additional information

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Sole author.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History