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Perspective

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Metabolic Health and Obesity: The Essential Role of Mitochondrial Function

Sandra Cutanda-Tesouro[1], Jorge Alvarez-Luis[1], Pau Gama-Perez[1], Pablo M. Garcia-Roves[1,2,3]

1 Department of Physiological Sciences, Universitat de Barcelona, 08907, Barcelona, Spain.
2 Metabolism and Gene Therapy Group; Diabetes and Metabolism Program; Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Barcelona, Spain.
3 Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, 28029, Madrid, Spain.

* Corresponding author: pgarciaroves@ub.edu

Summary

The management of obesity is critical and has traditionally included surgical interventions like bariatric surgery and pharmacological treatments. However, these methods have limitations when applied in isolation, which limits their effectiveness in completely reversing the condition. A comprehensive approach that considers the unique properties of adipose tissue and evaluates additional parameters can offer a more nuanced understanding of obesity. Moreover, lifestyle modifications have been shown to significantly influence the performance of cellular organelles responsible for maintaining bodily homeostasis, including mitochondria. This perspective delves into the impact of obesity on mitochondrial function and examines how lifestyle changes, in conjunction with current treatments, can influence this relationship.

Keywords – Obesity; Metabolic disease; White adipose tissue; Mitochondria; Metabolic plasticity

1. Introduction

Adipose tissue plays a vital role in the understanding of obesity. It consists of two main types, White adipose tissue (WAT) and brown adipose tissue (BAT). Histologically, WAT has elongated adipocytes with a large lipid droplet, occupying most of their

cytoplasm, together with a low number of mitochondria. This arrangement gives WAT an important role as an energy reserve and a control point for the organism's homeostasis (Reyes-Farias et al., 2021). Among other functions, it is necessary to highlight the secretion of signaling molecules called adipokines, such as leptin or adiponectin, with a range of action in the brain, pancreas, or immune system (Blüher & Mantzo, 2015). Similarly, WAT is involved to different extents in the metabolic functioning of the organism depending on its arrangement, with a distinction being made between vvisceral WAT (vWAT) and subcutaneous WAT (scWAT) (Kwok et al., 2016).

On the other hand, BAT is a highly thermogenic tissue, with high mitochondrial density and numerous small lipid droplets distributed within its cytoplasm. It is the main source of thermogenesis in infants and small mammals due to the high expression of mitochondrial uncoupling protein 1 (UCP1). In adults, particularly in women, BAT is distributed in the supraclavicular and paraspinal regions, activating its function of dissipating energy in the form of heat in response to exposure to low temperatures. BAT is currently under study as a potentially inducible tissue, which could become a great ally against numerous metabolic diseases, among them obesity (Singh et al., 2021).

In the case of patients with obesity, the WAT undergoes important changes in terms of distribution and morphology, unbalancing the scWAT/vWAT ratio in favor of vWAT, which correlates with the appearance of comorbidities associated with obesity itself, such as insulin resistance and poor glycemic control (Pinti et al., 2019, Reyes-Farias et al., 2021, Gonzalez-Franquesa et al., 2022). Along the same line, adipose tissue expansion tends to reduce cellular proliferation (hyperplasia), leading to an increase in cell size (hypertrophy), resulting in cell dysfunction characterized by decreased insulin sensitivity, hypoxia, increased intracellular stress parameters, increased autophagy and apoptosis, as well as tissue inflammation (Kusminski et al., 2016, Suárez-Carmona et al., 2017, Gonzalez-Franquesa et al., 2022).

1.1. Mitochondrial (dys)function in metabolic diseases

Metabolic plasticity, understood as the ability of any biological system to adapt its metabolic phenotype to different environmental stressors, is a primary concept to understand obesity-related pathophysiology, both in its prevention and treatment. In this regard, mitochondria have an indispensable role in orchestrating metabolic plasticity. Mitochondria accommodate core metabolic pathways and, by means of the oxidative phosphorylation (OXPHOS) system, play an essential role as cellular powerhouses. However, the relevance of mitochondria go beyond this elementary role. This organelle integrates the information about available resources, and through the constant flow of intermediary metabolites can orchestrate in accordance a plethora of physiological tasks and cellular decisions. Among others, mitochondria critically participate in the regulation of biosynthetic processes, control of redox states, the management of cellular waste and ROS formation, and communication with the nucleus and other cellular entities through stress responses and apoptotic signaling

(Monzel et al., 2023). Consequently, proper mitochondrial fitness and preserved metabolic plasticity are crucial elements in the management of obesity, and their potential involvement in concomitant metabolic diseases is still a hot topic of research.

Specifically, pronounced modulations of different mitochondrial parameters, such as reduced OXPHOS, decreased ATP synthesis or impaired fatty acid oxidation, have been observed in skeletal muscle (SkM) (Kelley et al., 2002, Rabol et al., 2010) and WAT (Schöttl et al., 2015) of patients with obesity and type 2 diabetes mellitus (T2DM) (Pinti et al. 2019). However, the role of mitochondrial respiratory capacity is more controversial in liver in the context of obesity (Guo et al., 2013, Lund et al., 2016, Formenty and Roden 2023). These alterations drive the accumulation of triglycerides and intermediary lipid species that ultimately promote the appearance of insulin resistance (Lowell and Shulman 2005, Koves et al., 2008). Yet, the position regarding mitochondrial dysfunction as the cause of T2DM is not entirely established, and controversial opinions need to be considered. In SkM, for instance, increased expression of factors such as peroxisome proliferator-activated receptor (PPAR), proliferator-activated receptor-γ coactivator-1α (PGC-1α), or subunits of the mitochondrial electron transfer system have been reported in animal models exposed to high-fat diets. An increase in mitochondrial biogenesis has even been replicated in genetic models of obesity, such as Zucker rats or db/db mice (Garcia-Roves et al., 2007, Turner et al., 2007). In addition, different response patterns are observed in mitochondrial functional readouts in obese conditions depending on the tissue under study, which highlights the tissue-specific heterogeneity in the mitochondrial adaptions to obesity and systemic insulin resistance (Holmström et al., 2012).

1.2. Obesity: Relevant interventions and treatments

Obesity is a disease primarily characterized by a significant increase in body weight due to excessive lipid accumulation. However, elevated weight is not the only concern associated with obesity; patients also experience metabolic deterioration across various tissues, primarily driven by mitochondrial dysfunction, with WAT being the most affected.

Thanks to the current understanding of the disease, weight-loss treatments are available and are expected to improve patients' quality of life. Nevertheless, bariatric surgery (BS) and pharmacological therapies, despite being effective in promoting weight reduction, may lead to additional complications.

1.2.1. Bariatric Surgery

There are six BS procedures; jejunoileal bypass (JIB), Roux-en-Y gastric bypass (RYGB), vertical banded gastroplasty (VBG), biliopancreatic diversion (BPD) with or without duodenal switch (DS), adjustable gastric banding (AGB), and sleeve gastrectomy (SG) (Lodhia & Morton 2012). The most common are AGB, SG, and RYGB resulting in body mass (BM) loss of 16 %, 30 % and 32 %, with post-operative BM retention for more than 10 years (Blüher et al., 2023). The beneficial effects of BS

are reflected at many levels, the most obvious being BM loss. This leads to improvements in various parameters affected by obesity, reducing markers associated with chronic low-grade inflammation, such as C-reactive protein (CRP). In the same way, treatment of pathologies concomitant to obesity also benefits from this surgical intervention. In the case of T2DM, 95 %-100 % of patients improve glucose control, which initiates remission of the disease, given the BM loss itself, together with the metabolic and hormonal processes involved (Ji et al., 2021). Similarly, BS reduces mortality and the incidence of cardiovascular disease compared to non-intervened obese patients (van Veldhuisen et al., 2022), positioning BS as the gold-standard intervention in the field of obesity.

However, beyond risks associated with a surgical intervention, such as bleeding, fistulas, or the appearance of hernias, other long-term outcomes must be considered. Gynecological, nutritional, hepato-biliary, neurological, and gastrointestinal complications occur, for instance, in patients with obesity (Kassir et al., 2016) , which should be taken into consideration before deciding to apply surgery. This, coupled with the sheer magnitude of medical needs in this field, has prompted the development of new pharmacological strategies to minimize risks and maximize benefits.

1.2.2. Pharmacotherapy

Historically, numerous compounds capable of succeeding in the BM loss process have been accepted, such as amphetamines, 2,4-dinitrophenol (2,4-DNP) or the combination of several drugs known that caused catastrophic side effects of their use, leading to their rapid cancellation (Müller et al., 2022).

Nowadays, there are several medications approved by the FDA for the treatment of obesity in adults (Yanovski and Yanovski, 2024): a) Orlistat, a gastrointestinal lipase inhibitor, which reduces the absorption of dietary fats (Braeckmans et al., 2022); b) Naltrexone-bupropione, a combination of an opioid receptor antagonist and a dopamine/norepinephrine reuptake inhibitor that results in a reduction of hunger sensation (Son & Kim, 2020); c) Phentermine-topiramate, which combines the activation of noradrenergic and GABAergic receptors with the inhibition of kainate/AMPA glutamate receptors, thereby increasing the feeling of satiety; d) Liraglutide and Semaglutide emerged as relevant options, with greater and more sustainable BM loss compared to other prescription drugs. Initially, these GLP-1 incretin receptors analogues were prescribed to treat T2DM as they stimulate insulin secretion, although their effects on appetite regulation and intake control led to their prescription in patients with obesity (Tamayo-Trujillo et al., 2024). In addition, studies with Semaglutide indicate improvements in markers of glucose homeostasis such as glycosylated hemoglobin (HbA1c) (Xie et al., 2022); e) Setmelanotide is a melanocortin-4 receptor (MC4R) agonist only used in specific types of genetic obesity, where there are specific mutations affecting the hunger/satiety hormones (Blüher et al., 2023); f) Tirzepatide is a dual agonist for GLP-1/GIP. This compound targets several organs in which it improves tissue functionality, such as β-pancreatic cell secretion and state, while at the same time reducing the BM of obese patients more

efficiently than their predecessors, achieving reductions of more than 20 % with respect to control groups (Sinha et al., 2023).

Although currently accepted as a pharmacological approach to obesity, they are not free of possible side effects, such as hypoglycemia or cholelithiasis, and are even contraindicated in specific population groups, e.g., patients affected by medullary thyroid cancer and pregnant or breastfeeding women (Komalski et al., 2023). For this reason, the search for new drugs continues, with the emergence of proposals with apparent preclinical projections such as the GLP-1 agonist receptor molecule known as Orforglipron. Unlike other molecules with a similar mechanism of action, this drug would be administered orally, rather than through the injectable route as is commonly the case. Orforglipron is also being evaluated as a T2DM treatment (Wharton et al. 2025). However, decreasing BM with BS or drugs is not equivalent to fat mass reduction as there is also a reduction in fat-free body mass (FFBM) implying some complications related to this loss.

2. Limitation of BMI and adipose tissue distribution in body mass loss interventions

A patient is considered to present obesity when the body mass is higher than 30 kg/m^2. In pronounced BM loss processes, it is essential to know which tissues have been most affected. After an appropriate intervention, the patient is expected to reduce its BMI range, trying not to compromise the patient's health. Even if this goal is achieved, the BMI lacks the ability to distinguish BM loss composition, which may not result in a fully regression to a healthy state (Rothman, 2008). Unfortunately, most clinical trials do not consider the composition of the BM that is lost, these only report total BM loss.

Some of the treatments target adipose tissue for mass reduction. WAT drastic reduction compromises its function as a fat reservoir, accompanied by a significant loss of FFBM, also relevant for skeletal muscle fueling, resulting in a skeletal muscle mass (SkMM) loss. This effect is also seen in patients that undergo BS, lasting up to two years after the intervention with subsequent impact on bone mass loss, malabsorption of nutrients, or the development of sarcopenia (Holanda et al., 2022).

The SkMM loss is also critical for patients with osteosarcopenic obesity, which is quite frequent among patients with obesity that are going through a BM loss, tissue-specific or not. In this type of obesity, fat mass contributes to bone and muscle loss (Hu et al., 2023), increasing the risk of metabolic disease associated with impaired crosstalk between these tissues. Significant reduction of FFBM impacts deleteriously on other health parameters such as insulin sensitivity or aerobic capacity (Ghachem et al., 2019). In adults over 65 years old, the risk of sarcopenia is increased particularly in hospitalized patients (Atmis et al. 2019), accompanied by a loss of strength (dynapenia) or limitations when performing various physical activities like walking or dressing up (Wadden et al., 2023).

In the context of pharmacotherapy, the potential side-effects are far from being fully elucidated due to a previous lack of attention and only recent implementation in several studies. Possible side effects reported in patients are alopecia, suicidal risks, or tumor development (Yang et al., 2022). However, the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) has been evaluating the report of suicidal attempts in patients who have been treated with GLP-1 Ras without finding a correlation between these events and the administration of this specific drug, accompanied by some other several contradictions within the scientific community (McIntyre et al., 2023).

2.1. Role of Exercise: Synergy with current treatments

To face some of the side effects mentioned before, the coadjutant intervention with the best reports is the inclusion of physical exercise. In the case of BS, it has been shown that the inclusion of postoperative physical exercise, strength, and aerobic exercise, mitigates the side effects derived from surgery, retaining a greater amount of bone mineral mass and muscle mass, together with an improvement in insulin sensitivity (Sayadi et al., 2020). Thus, a new randomized control trial, EXercise POst BARiatric (EXPOBAR), is being developed to verify in depth all potential benefits of physical exercise in the prevention of sarcopenia after BS (Amaro Santos et al., 2022). In addition to these postoperative results, some studies demonstrate its efficacy even weeks before surgery, reducing both anthropometric variables and parameters associated with cardiovascular health (Pouwels et al., 2020).

On the other hand, randomized control trials combining pharmacological treatment with physical exercise demonstrate a severe reduction in obesity-associated parameters, such as a decrease in abdominal fat, inflammation, and cardiovascular disease derivatives, while maintaining FFBM (Sandsdal et al., 2023). In addition, the effects of incretin-based drugs such as GLP-1 may be enhanced by the action of physical exercise due to the secretion of interleukins (IL) during muscle contraction, such as IL-6, IL-8 or IL-15, which are attributed to the ability to decrease ectopic fat (Hamasaki, 2018). This makes physical exercise a powerful ally in minimizing risks and maximizing benefits from current and, possibly, future treatments.

3. Lifestyle Matters Project: Obesity being decoded

As previously described, obesity is a complex disease that requires a thorough understanding of its systemic effects beyond the significant increase in BM. Nevertheless, the interventions and treatments commonly used in patients with obesity often fail to address the broader pathophysiological aspects.

Under these considerations materialized the Lifestyle Matters project (LiMa), a long-term undertaking focused on offering a comprehensive perspective of systemic and tissue-specific metabolic plasticity during the dietary-induced transitions towards an obese state and subsequent BM loss (Gonzalez-Franquesa et al., 2022). Inducing an

obese phenotype by high fat overfeeding, the LiMa project proved that, among the key metabolic organs under study, epididymal vWAT was the most vulnerable organ in terms of metabolic deterioration. This detrimental impact is primarily evidenced by the profound worsening of adipose tissue mitochondria, manifested at different levels; from alterations in mitochondrial-related transcripts, proteins and cardiolipin remodeling, to significant defects in the mitochondrial inner-membrane ultrastructure, their functionality as well as a profound reduction in mtDNA copy number. More evidences have mounted during recent years, provided by other authors who have delved into the molecular aspects of how mitochondrial derangements are intrinsically linked to WAT dysfunction in different experimental models of obesity and insulin resistance. In this sense, increased metabolic and oxidative stress, as well as defective recycling events are suggested as major drivers of alterations in several metabolic pathways, ultimately compromising the intracellular dynamics and stability of adipocytes, and its secretory activities (Kusminski & Scherer, 2012, de Mello et al., 2018, Paglialunga et al., 2015, Schöttl et al., 2020, Madsen et al., 2022). In addition, other studies indicate the obesity-related reduction in adipose mitochondrial respiratory capacities (Schöttle 2015, and 2015bis).

However, the most striking result of the first LiMa study, never noticed before, is the observation that all detrimental impacts on adipose mitochondria persist even after the successful implementation of a BM loss intervention. Obese animals were subjected to a combined nutritional and exercise intervention, which promoted the restoration of many obese-related phenotypical features. The intervention allowed a complete morphological remodeling of the adipose tissue but, this considerable normalization of metabolic status was not translated into a recovery of mitochondrial fitness. Taken together, these findings reveal an obesity-related mitochondrial fingerprint rooted in adipose tissue, which may ultimately compromise its metabolic plasticity. Convincing evidence for this phenomenon comes from BM cycling studies, where the visceral adipose tissue of lean but formerly obese mice fails to properly expand when facing new overfeeding conditions. The adipose phenotype of these animals is characterized by an exacerbation of adipocyte death and immune infiltration, along with an increase in hepatic mass, triglyceride content, and raised levels of circulating insulin and transaminases, pointing to an imprinted disability of WAT to functionally respond to repeated environmentally challenging conditions (Zamarron et al., 2020, Kyung DS et al., 2018).

The potential resonance of these discoveries coming from animal models opens new research horizons towards prevention and treatment of obesity. In the face of the current global obesity epidemic and the consequent explosion of innovative and successful treatment strategies to promote BM loss, it is critical to validate in humans the potential impact of BM fluctuations on adipose metabolic plasticity. Yet, the translational value of these findings remains to be addressed by properly focused studies. The major limitation for this undertaking is the restricted accessibility to human visceral fat for research purposes, due to ethic concerns. Visceral adipose biopsies, usually from omental fat pads, are always associated with surgical procedures and

side effects, such as cholecystectomy or abdominal hernias in the case of healthy lean subjects, or samples collected from obese patients undergoing BS.

Therefore, only few studies have moved forward towards exploration of human visceral adipose phenotype under obesity conditions. Nevertheless, there is growing evidence for strong similarities between transcriptional or proteome changes induced by obesity in human omental WAT and those reported in animal models (Pérez-Pérez et al., 2012; Gomez-Serrano et al., 2017; Zhou et al., 2020; Kolic et al., 2024) , highlighting the major vulnerability of visceral fat compared to other adipose depots (Pérez-Pérez et al., 2009). Along the same line, mitochondrial functional assessment of adipose tissue from obese patients reveals detrimental impacts on respiratory capacities compared to lean subjects, both in visceral and subcutaneous WAT (Pedersen et al., 2022). Interestingly, the decrease in respiratory capacities, particularly in the visceral depot, has been correlated with the appearance of tissue insulin resistance and inflammation, favoring the progression towards advanced stages in liver pathology (Pafili et al., 2022). Recent studies have confirmed the existence of an epigenetic and transcriptional memory of obesity in humans. Consequently, when patients undergo weight loss, as observed in mice, adipose tissue is more prone to deteriorate rapidly upon exposure to obesogenic stimuli (Hinte et al., 2024). These results are consistent with our murine model, in which mice that underwent weight loss after obesity, followed by interventions to maintain their reduced weight, still exhibited alterations in genes related to OXPHOS and metabolism, or developed such alterations during the interventions. This suggests that once obesity is established, an epigenetic imprint prevents the full reversion to a lean and metabolically healthy state. Moreover, transcriptional profiles were found to differ among adipocyte populations, with some subsets correlating with adverse metabolic conditions in patients with obesity (Reinisch et al, 2025)

4. Conclusions and future outcomes

In conclusion, evaluation of this plausible mitochondrial fingerprint caused by obesity after restoration of a healthier metabolic state becomes an urgent matter to be resolved, since it is potentially linked to the loss of tissue metabolic plasticity and the progression of associated comorbidities. Unfortunately, follow-up designs targeting visceral fat are very difficult to achieve and, accordingly, nearly all longitudinal studies conducted to address the adipose tissue response after BM-loss interventions have been limited to the subcutaneous depot. By overcoming such barriers, the formulation of new complex experimental designs may elucidate this critical question in the progression of obesity-related pathophysiology, offering novel knowledge for earlier diagnosis and tailored interventions, reducing costs, improving patient outcomes, and providing new biomarkers to assess treatment success. This could be a game-changer for obesity and associated diseases.

Future projections for obesity position it as a growing global challenge, with 51 % of the world's population expected to face preobesity by 2035, and 24 % facing obesity

(Hjorth et al., 2023). At present, interventions such as BS or the use of pharmacotherapy attempt to alleviate these poor prognoses, but fail to address the root of the problem, are not fully effective on their own, and lead to unwarranted side effects. In fact, both interventions ask patients to include physical exercise in their lives to prolong and amplify the potential benefits of both procedures (Lupianez-Merly et al., 2024; Kloock et al., 2021). Therefore, the inclusion of a sustainable model over time, modifying lifestyle towards a correct dietary pattern coupled with physical exercise, should be encouraged, both in the prevention and treatment of obesity. In addition, the incorporation of new, more robust parameters for determining the pathology, such as body mass excess (BME) (Gnaiger, 2019; Busetto et al., L. 2024) over the use of BMI, provides a less biased approach, not only to the "BM" variable, but also to the concept of metabolic plasticity by including both mitochondrial health and the population's own metabolism, thus achieving a more comprehensive perspective in the approach to this complex and multifactorial pathology.

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