

PBMC mitochondrial bioenergetics as an integrative sensor of physiological and pathophysiological adaptations

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Introduction

Peripheral blood mononuclear cells (PBMC) provide a minimally invasive window into systemic mitochondrial function. From a metabolic perspective, these cells act as sentinel tissue capable of detecting multiple types of whole-body physiological perturbations, including changes in metabolic efficiency, inflammatory load, hormonal modulation and energetic stress. Their strong interaction with systemic physiology makes PBMC an attractive target for studying interventions such as physical exercise, obesity and the metabolic impact of bariatric surgery (BS) (Da Rosa et al., 2023). However, PBMC respiration becomes physiologically meaningful only when interpreted within the organism's metabolic context, such as, in our case, individuals living with obesity and to the other end of the spectra highly-trained individuals.

High-resolution respirometry (HRR) is considered the gold standard for assessing mitochondrial respiratory capacity, providing sensitive and direct measurements of oxygen consumption. The use of intact cells offers better insight into the real physiological state, enabling the assessment of mitochondrial bioenergetics under conditions that preserve endogenous metabolic, immune and hormonal signals.

In athletes, PBMC mitochondrial function mirrors training adaptation, hormonal balance and fatigue, providing insights into molecular responses related to athletic performance (Ramadoss et al., 2022). Although PBMC bioenergetics differ from skeletal muscle metabolism, their functional diversity and accessibility make them a valuable alternative for assessing metabolic adaptations induced by physical exercise (Da Rosa et al., 2023).

In patients with obesity, PBMC reflect chronic inflammation, altered substrate metabolism and mitochondrial functional alterations. After bariatric surgery, PBMC bioenergetics capture the abrupt metabolic transition induced by rapid weight loss,

caloric restriction and transient catabolism, which drives mitochondrial remodeling in skeletal muscle and alters respiration, dynamics and substrate oxidation. Weight-loss interventions also modify skeletal muscle mitochondrial efficiency and metabolic flexibility (Van der Kolk et al., 2026).

The aim of this study is to elucidate how intact-cell PBMC bioenergetics can be applied across different contexts—both in health and athletic performance—to identify physiological and metabolic changes. In individuals with obesity, we examine the adaptations induced by strength-training program (STP) used as prehabilitation and rehabilitation strategies, the bioenergetic impact of bariatric surgery, and how these responses differ from those observed in patients who do not perform the training program. In elite athletes, we investigate how PBMC bioenergetics reflect seasonal physiological and metabolic modulation in relation to training load across each phase of the competitive season.

Methods

Subjects with obesity, four adults (preliminary results), men and women aged 35–55 years awaiting bariatric surgery (BS) participated in a 12-week strength-training program (STP) with elastic bands in circuit training with a total of 8 exercises divide in 2 circuit of 4 set with 15 rep per exercise prior to surgery and will be compared with patients who do not perform the STP (control group) which received standard care. Functional capacity was assessed using cardiopulmonary exercise testing (CPET) and the 30-second Sit-to-Stand test (STS30). Muscle strength was measured through one-repetition maximum (1RM), body composition through bioelectrical impedance analysis (BIA), and muscle cross-sectional area through computed tomography (CT). Additional assessments included lipid profile, hematological parameters and PBMC bioenergetic capacity measured by high-resolution respirometry (HRR). Evaluations were and will be conducted at baseline (T1), after STP (12wks) as prehabilitation (T2), 3 months post-surgery (T3), and after STP (12wks) as rehabilitation (T4) at 6 months after surgery.

Top level elite athletes, nine sprint kayakers from the Spanish national team were monitored throughout an entire training season, from early pre-season phase to the pre-competition phase before the World Championships. Four training periods were analyzed using blood biomarkers and HRR in intact PBMC. These variables were examined through multivariate analysis in R, evaluating immunological and endocrine markers and their relationship with PBMC respiratory states and ratios within the framework of training-load-induced physiological stress across each period.

PBMC mitochondrial respiration was assessed in both cohorts using HRR with the Oxygraph-2k (O2k, Oroboros Instrument, Austria). Respiratory function was characterized using the substrate-uncoupler-inhibitor titration protocol SUI-003 (https://www.bioblast.at/index.php/SUI-003#SUI-003_O2_ce_D009), allowing sequential evaluation of LEAK respiration, electron transfer system (ETS) capacity and residual oxygen consumption.

Data were analyzed using R studio, DatLab and GraphPad Prism. Statistical comparisons were performed using parametric tests when appropriate, data are represented by means and standard deviation (Mean±SD)

Results

Patients living with obesity

Prehabilitation program

Subjects awaiting BS who completed the strength-training prehabilitation program (T1→T2) showed increases in functional capacity (power: 161.25 ± 14.36 vs 176.25 ± 14.36 W; $p = 0.045$), muscle strength (1RM: 50 ± 11.6 vs. 74 ± 10.8 kg; $p = 0.005$), and an improvement of immune function (lymphocytes: 2.69 ± 0.55 vs. $1.92 \pm 0.36 \times 10^9/L$; $p = 0.027$). PBMC bioenergetics indicate early improvement but without reaching significance, most probably due to small number of patients evaluated till date. Despite gains in strength and functional capacity, body composition measured by BIA did not change significantly.

After bariatric surgery

The post-surgery period (T2→T3) produced the most drastic physiological shift: rapid weight loss (25.67 ± 3.8 kg; $p = 0.0004$), caloric restriction, transient catabolism, reduced strength (1RM PRE-BS 74 ± 10.8 vs POST-BS 48.25 ± 6.55 kg; $p = 0.005$), functional capacity (VO₂max PRE-BS 2.31 ± 0.19 vs POST-BS 1.66 ± 0.11 L/min; $p = 0.005$, power 176.25 ± 14.36 vs 128.75 ± 7.50 W; $p = 0.002$) increased fat oxidation and altered ventilatory thresholds. PBMC respirometry showed decreased Routine (PRE-BS 3.78 ± 0.69 vs POST-BS 2.96 ± 0.51 pmol·s⁻¹·million cells⁻¹; $p = 0.07$) and ETS respiration (PRE-BS 11.32 ± 8.60 vs POST-BS 8.60 ± 1.26 pmol·s⁻¹·million cells⁻¹; $p = 0.01$), altered coupled/uncoupled balance and reduced Spare Capacity—consistent with acute energetic stress (preliminary results).

Top elite athletes

The integrated analysis revealed significant associations between PBMC mitochondrial bioenergetics and specific hormonal and hematological markers. Testosterone correlated positively with LEAK respiration ($r = 0.424$; $p = 0.0089$) and Uncoupled respiration ($r = 0.325$; $p = 0.0497$), and negatively with Routine respiration ($r = -0.325$; $p = 0.0497$) and Spare Capacity ($r = -0.424$; $p = 0.0089$). Hematocrit showed a positive association with Routine respiration ($r = 0.387$; $p = 0.0179$) and a negative association with Spare Capacity % ($r = -0.388$; $p = 0.0176$). HDL did not directly correlate with respirometry parameters, although it was positively associated with the testosterone-to-cortisol ratio ($r = 0.436$; $p = 0.0062$). In contrast, CK and cortisol showed no significant associations with PBMC respirometry.

Discussion and conclusion

PBMC mitochondrial bioenergetics emerge as a sensitive and integrative indicator of systemic physiological adaptation across contrasting metabolic conditions, from obesity to elite athletic performance. In individuals with obesity, PBMC reflected improvements in muscle strength and functional capacity following strength training, while changes in lymphocyte counts suggested immune modulation (Salimans et al., 2022). The elevated ETS capacity observed in this group, similar to values found in athletes, may represent a compensatory oxidative response driven by chronic systemic inflammation (Carvalho et al., 2025; Shirakawa et al., 2023). After bariatric surgery, PBMC respirometry captured the abrupt metabolic transition induced by

caloric restriction and rapid weight loss, showing reduced respiratory capacity and signs of acute energetic stress.

In elite athletes, PBMC bioenergetics dynamically tracked training-load fluctuations and mirrored improvements in mitochondrial efficiency consistent with reported skeletal muscle respiratory capacity in athletes (Garcia-Roves et al., 2025). Their association with hormonal and hematological markers enabled the identification of distinct bioenergetic phenotypes—anabolic-efficient, inflammatory-stressed and metabolically-compensated—highlighting their value for individualized monitoring throughout the season.

Together, these findings demonstrate that PBMC consistently reflect fluctuations of the metabolic, inflammatory and endocrine environment of the individual, in patients with obesity or in high-performance athletes.

KEYWORDS

PBMC; mitochondrial bioenergetics; bariatric surgery; obesity; exercise physiology

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