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Interplay between Mitochondrial Dysfunction, Lipid Dysregulation and Lipid Droplet dynamics in Parkinson's Disease

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Introduction

Parkinson's disease (PD) is a multifactorial neurodegenerative disease associated with dopaminergic neuronal loss and is characterized by both motor and non-motor symptoms. At the cellular level, these neurons are pushed to degeneration due to the accumulation of Lewy bodies (LBs) which are proteinaceous inclusions enriched in α-synuclein (α-syn). Over the past decade, region-specific lipidomic studies have uncovered a spectrum of lipid changes in post-mortem PD brains, suggesting a widespread disruption of cellular lipid homeostasis. The challenge of monitoring brain lipidomes in living patients at early disease stages has driven the search for identifying altered lipid signatures in peripheral blood for understanding the disease progression. Defects in mitochondrial respiration have been implicated in the etiology and pathogenesis of PD (Perier and Vila, 2012). Excess fatty acids get stored in lipid droplets and are detoxified by mitochondrial β-oxidation but dysfunctional mitochondria reduce FA metabolism, causing lipotoxicity and aggravating the PD process (Tong *et al.*, 2024). Several studies have reported altered lipidomic profiles in PD brain and peripheral samples, but studies correlating lipid dysregulation with mitochondrial respiration and lipid droplet dynamics are limited. In this work, we hypothesized that lipid dysregulation leads to lipid droplet accumulation and impaired mitochondrial respiration in peripheral blood samples of PD patients.

Methods

Ethics committee of SCTIMST, Thiruvananthapuram approved the study and participants provided informed consent according to the Declaration of Helsinki. Blood samples were collected from 60 sporadic PD patients, comprising 30 males and 30 females and 40 controls, comprising 20 males and 20 females. One male PD patient and one male control were excluded from the study as the samples failed QC. Plasma was isolated and total lipid extraction was performed as described

previously (Rajendran *et al.*, 2022). LC-MS runs were carried out using the Auto MS/MS acquisition method on an Agilent 6545 Q-TOF mass spectrometer fitted with an Agilent 1290 Infinity II UHPLC system (Chakraborty *et al.*, 2025). Library of different classes of lipids was curated as a Personal Compound Database Library (PCDL) using MassHunter PCDL manager B.08.00 (Agilent Technologies). This library was curated using the METLIN lipid library as a reference. The data files were processed in Agilent MassHunter Qualitative Analysis 10.0 using the PCDL library, and all the peaks were validated based on relative retention times and fragments obtained, if any. Data analysis was performed using Metaboanalyst 6.0 software. Missing value estimation was done using missForest multivariate statistical analysis. The data was log transformed (base 2) and autoscaled.

Blood samples were collected for High resolution respirometry experiments from 13 PD patients comprising 8 males and 5 females. Platelets were isolated as described in (Jayan *et al.*, 2026). High-resolution respirometry was performed using a modified SUIT-002 D007a (Substrate–Uncoupler–Inhibitor Titration) protocol (Jedlička, Kunc and Kuncová, 2021). The assay was performed at 37°C using a high-resolution respirometer (O_2k, Oroboros Instruments). Final platelet count was adjusted to 175×10^9cells/l per 0.5 ml volume chamber. DatLab software version 7.4.0.4 was used and O2 flux per cells (pmol/s/10^8cells) was measured.

Blood samples were collected from a different cohort of 28 sporadic PD patients, comprising 17 males and 11 females and 21 controls, comprising of 13 males and 8 females. Isolation of macrophages from peripheral blood mononuclear cells (PBMCs) was performed as described previously (Krishnan *et al.*, 2020). Cells were counted and seeded at a density of 1.0- 1.5×10^6 cells per coverslip, and differentiated for 9–12 days in RPMI medium supplemented with 5% FBS, with medium changes every 2 days. After that, cells were fixed with 4% paraformaldehyde (PFA). For immunostaining, cells were permeabilized with 0.05% saponin in PBS with 3% BSA. After blocking with PBS containing 3% BSA, the cells were incubated with CD68 antibody in PBS with 1% BSA at 4°C overnight. After washing, secondary antibody incubation was done for 1 hour at room temperature. LD were stained using BODIPY (Invitrogen, D3922) for 30 min. DAPI staining was done for 10 min, followed by washing using 1X PBS.

GraphPad Prism version 11.1.0 was used for statistical analysis. The normality of the distribution was checked using Shapiro-Wilk test. The distribution was non parametric and unpaired Mann-Whitney test was performed. The results were presented as Mean ± SEM. Values of $p<0.05$ were considered significant.

Results & Discussions

Lipidomics analysis of plasma samples revealed significant dysregulation of lipids. Principal component analysis (PCA) resulted in a good separation between control and PD groups. The data was able to explain approximately 64% of the variation between the groups. Gender was identified as a major confounding factor during the analysis. Hence, all further analysis was performed in a gender specific

manner. PLS-DA analysis resulted in good separation between the four groups (PD male, Control male, PD female, Control female) with a coefficient of determination of model fitting (R2) of 0.943 and a coefficient of prediction (Q2) of 0.902 by leave-one-out cross-validation. PD females depicted significantly increased concentrations of neutral lipids and fatty acids in comparison to control females. PD males when compared with control males, showed dysregulated neutral lipids along with alterations in sphingolipids. The differential expression of lipids and fatty acids may point to distinct gender specific pathogenic mechanisms. High resolution respirometry experiments in platelets isolated from PD patients and healthy volunteers revealed a trend of reduced mitochondrial respiration rates (Routine, Leak FAO, OXPHOS FAO, C4) in PD patients compared to controls. Leak and maximal respiration were elevated in disease conditions (Figure 1). The elevated uncoupled respiration might be a compensatory mechanism or because of an increased electron transfer system (ETS) capacity. We also compared the results based on gender. Interestingly, the analysis revealed a significant difference in fatty acid oxidation (Leak FAO, OXPHOS FAO and OXPHOS FAO+G) between PD males and females. Females depicted higher fatty acid oxidation compared to males. Immunofluorescence staining of lipid droplets of PBMC derived macrophages depicted a significant accumulation of lipid droplets in PD samples compared to controls. No gender-based difference in lipid droplet accumulation was observed.

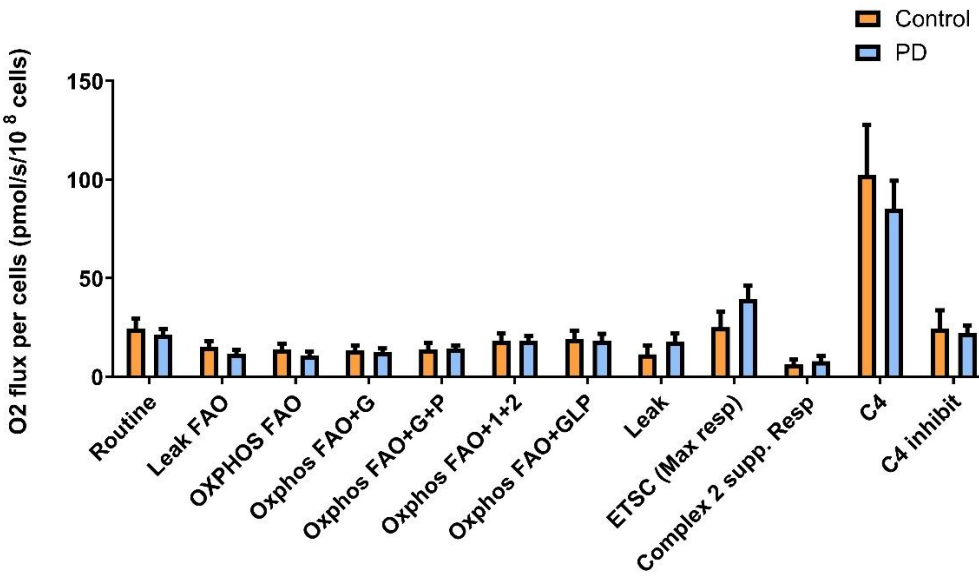

Figure 1: Platelet mitochondrial respiration of PD patients and healthy volunteers

Increased concentration of fatty acids in PD female plasma samples and significantly higher fatty acid oxidation in platelet samples point to functionally intact and active mitochondria in PD females compared to males. The abundant pool of substrates could have upregulated the enzymatic pathways involved in β-oxidation, thereby driving higher baseline LEAK-FAO and active OXPHOS-FAO rates. As there is no significant increase in lipid droplet accumulation in females compared to males, mitochondria in females might be efficiently oxidizing the fatty acids rather than

utilizing them for expanding the storage capacity. Also in males, the lower OXPHOS capacity pointing out to impaired mitochondria along with the lack of extra LD storage, implies that the excess fatty acids are not buffered effectively, leaving them vulnerable to cytosolic lipotoxicity. The results point to mitochondrial dysfunction as a central pathogenic mechanism differentiating males and females in vulnerability to PD. Lipid dysregulation interconnected with mitochondrial dysfunction, leads to lipid droplet accumulation in PD peripheral samples.

Limitations of the study involve the limited sample size in high resolution respirometry experiments. The patients recruited for the study are all under medications and hence the effect of medications in the experimental parameters are not addressed. Diet also plays a major role in the lipidomic profile. Authors acknowledge that influence of diet is also not addressed.

Keywords: Lipidomics, Lipid droplets, Neurodegeneration, Lewy bodies, BODIPY

Author contributions: MUK designed the study and obtained funding. PN performed data collection, evaluation and lipidomic analysis. SKS recruited patients and healthy volunteers for the study.

Conflicts of interest: All authors declare no conflicts of interest

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