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Preoperative Metabolic Inflexibility Predicts Impaired Plasma Metabolite Clearance Following Radical Cystectomy

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Introduction:
Metabolic flexibility is a key determinant of physiological resilience and predictor of complications following radical cystectomy. We hypothesize that the change in the metabolomic profile of cystectomy patients throughout the perioperative period is associated with metabolic flexibility, as determined by preoperative carbohydrate oxidation (CHOox) (g/min).

Methods:
We retrospectively analysed changes in 538 plasma metabolites pre-to-post cystectomy (three-month interval) in N = 17 adult patients from an IRB-approved study (Duke IRB Pro00103570) who underwent preoperative CPET. Metabolites were measured using the MxP Quant 500 kit (Biocrates, Innsbruck, AUT). CHOox was derived from CPET measurements using standardised nonprotein respiratory exchange ratios, with AUC calculated to anaerobic threshold. Patients were stratified by median split into high and low CHOox AUC groups (n = 8, n = 9). Differential metabolite changes were assessed using Mann-Whitney U tests with exploratory FDR correction ($q < 0.2$).

Results:
For all ten significant metabolites ($q < 0.2$), low CHOox capacity was associated with longitudinal metabolite differences, and increases in concentrations. Median lactate (+0.63-fold vs -0.78-fold, q = 0.1402, low vs high CHOox) and glutamate (+0.25-fold vs -0.29-fold, q = 0.1992) reflect changes in carbohydrate oxidation. Long-chain acylcarnitines C16 (+0.23-fold vs -0.15-fold), C18:1 (+0.23-fold vs -0.13-fold), C18:2 (+0.17-fold vs -0.09-fold) (q = 0.1402) indicate changes in fatty acid oxidation and mitochondrial fat transport. Lysophosphatidylcholines C16:0 (+0.73-fold vs -0.71-fold, q = 0.1475), C17:0 (+0.38-fold vs -0.49-fold, q = 0.1475), C18:0 (+0.66-fold vs -0.78-fold, q = 0.1402) and glycosylceramides Hex2Cer d18:1/24:1 (+0.06-fold vs -0.09-fold, q = 0.1402), d18:1/24:0 (+0.02-fold vs -0.08-fold, q = 0.1475) reflect alterations in lipid processing and tissue uptake.

Conclusion:
Low preoperative CHOox predicts persistent metabolite accumulation across multiple pathways, indicating sustained and worsened substrate processing deficits following cystectomy. This identifies metabolic inflexibility as a mechanistic driver of perioperative dysfunction and a specific prehabilitation target.

Keywords

Metabolic Flexibility, Carbohydrate Oxidation, Plasma Metabolites, Prehabilitation

Conflict of Interest & Ethical Approval

yes

Abstract submitters declaration

yes

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