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Urinary metabotype of severe asthma evidences decreased carnitine metabolism independent of oral corticosteroid treatment in the U-BIOPRED study

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Metabolomics identified a urinary metabotype of asthma driven by lower carnitine levels in an oral corticosteroid-independent manner. The carnitine transporter SLC22A5 was also decreased, suggesting carnitine metabolism as a potential therapeutic target. https://bit.ly/3BJfvT0

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Abstract

Introduction Asthma is a heterogeneous disease with poorly defined phenotypes. Patients with severe asthma often receive multiple treatments including oral corticosteroids (OCS). Treatment may modify the

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observed metabotype, rendering it challenging to investigate underlying disease mechanisms. Here, we aimed to identify dysregulated metabolic processes in relation to asthma severity and medication.

Methods Baseline urine was collected prospectively from healthy participants (n=100), patients with mild-to-moderate asthma (n=87) and patients with severe asthma (n=418) in the cross-sectional U-BIOPRED cohort; 12–18-month longitudinal samples were collected from patients with severe asthma (n=305). Metabolomics data were acquired using high-resolution mass spectrometry and analysed using univariate and multivariate methods.

Results A total of 90 metabolites were identified, with 40 significantly altered ($p<0.05$, false discovery rate <0.05) in severe asthma and 23 by OCS use. Multivariate modelling showed that observed metabotypes in healthy participants and patients with mild-to-moderate asthma differed significantly from those in patients with severe asthma ($p=2.6\times10^{-20}$), OCS-treated asthmatic patients differed significantly from non-treated patients ($p=9.5\times10^{-4}$), and longitudinal metabotypes demonstrated temporal stability. Carnitine levels evidenced the strongest OCS-independent decrease in severe asthma. Reduced carnitine levels were associated with mitochondrial dysfunction *via* decreases in pathway enrichment scores of fatty acid metabolism and reduced expression of the carnitine transporter SLC22A5 in sputum and bronchial brushings.

Conclusions This is the first large-scale study to delineate disease- and OCS-associated metabolic differences in asthma. The widespread associations with different therapies upon the observed metabotypes demonstrate the need to evaluate potential modulating effects on a treatment- and metabolite-specific basis. Altered carnitine metabolism is a potentially actionable therapeutic target that is independent of OCS treatment, highlighting the role of mitochondrial dysfunction in severe asthma.