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Deciphering Kidney Pathology in Type 1 Diabetes: Insights from Spatial Metabolomics and Oxidative Metabolism Analysis

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Objectives : Animal models show impaired TCA cycle turnover and oxidative phosphorylation, collectively termed oxidative metabolism, in diabetes but little is known about this relationship in humans with T1D.
Methods : Employing mass spectrometry imaging (MSI)-based spatial metabolomics, we analyzed kidney tissue from research biopsies obtained participants with and without T1D in the JDRF-funded CROCODILE study (n=16 T1D, n=7 healthy controls [HC]). Matrix-assisted laser desorption/ionization (MALDI)-MSI, using a Q Exactive HF-X hybrid quadrupole-Orbitrap mass spectrometer, was coupled with a novel MALDI/ESI interface. METASPACE facilitated metabolite annotation, while optical images (bright-field (BF) & autofluorescence (AF), and PAS) were overlaid with TCA cycle metabolites to assess their association with tubular cell features. Participants also underwent voxel-wise and region-of-interest (ROI) pharmacokinetic (PK) ^{11}C-acetate PET analyses (n=16 T1D; n=10 HC) to quantify kidney cortical oxidative metabolism (k_2).
Results : Young adults with T1D (age: 23±3 years, diabetes duration: 13±5 years, 53% female, HbA1c: 7.9±1.1%, BMI: 25±3 kg/m^2, UACR: 5[3,8] mg/g) and 20 HC (age: 25±3, 50% female, HbA1c: 5.2±0.3%, BMI: 23±2 kg/m^2, UACR: 5 [3,9] mg/g) were included in the analysis. Spatial metabolomics revealed that malic acid (p=0.0017), succinic acid (p=0.0084), fumaric acid (p=0.0004), α-ketoglutaric acid (p=0.0256) were lower in tubules of T1D vs. HC, and especially in regions of atrophic tubules (Figure). Cortical oxidative metabolism (k_2) was also lower in T1D vs. HC (0.16±0.02 vs. HC 0.18±0.02 min^{-1}, p=0.04). We found strong positive correlations between cortical k_2, aconitic acid (r: 0.636, p=0.048), fumaric acid (r:0.806, p=0.005), and malic acid (r:0.770, p=0.009). Fumarate (r:-0.558, p=0.048) and α-ketoglutaric acid (r:-0.579, p=0.038) correlated inversely with GBM thickness.
Conclusions : Our data integrating state-of-the-art spatial metabolomics and ^{11}C-acetate PET demonstrate diminished TCA cycle activity and a potential link between metabolic alterations and kidney injury in T1D, offering new insights into the pathophysiology of early diabetic kidney disease.

Picture1.png

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