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PATIENTS WITH SLE HAVE UNIQUE CHANGES IN SERUM METABOLOMIC PROFILES ACROSS AGE ASSOCIATED WITH CARDIOMETABOLIC RISK

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Introduction: Cardiovascular disease is a leading cause of mortality for patients with systemic lupus erythematosus (SLE) through accelerated atherosclerosis. This is likely due to chronic inflammation and cardiometabolic defects that exacerbate with age. Mechanisms of atherosclerosis begin from an early age, particularly in young patients with juvenile-onset SLE, highlighting the importance of studying cardiometabolic risk over age in SLE.
Objectives: This study investigated detailed age-associated changes in the circulating metabolomic profiles of SLE patients and healthy controls (HCs).
Methods: Serum NMR metabolomics (>250 metabolites) of female SLE patients (n=164, age=13-72, mean age=37) and matched HCs (n=123, age=15-76, mean age=37) was assessed by linear regression and Venn analysis. Multiple t-tests (FDR-corrected) and MetaboAnalyst assessed unique metabolic changes and pathways by age group between patients/HCs (≤25, n=62/46; 26-49, n=50/46; ≥50, n=52/31). The impact of inflammation, SLE disease activity, and treatments on metabolites were also investigated. Disease-wide association analysis of metabolites of interest was performed using the Nightingale Atlas web-tool (data from the UK Biobank cohort).
Results: Twenty-five metabolites were significantly altered in all SLE age groups vs HCs, dominated by decreased atheroprotective high-density lipoprotein (HDL) subsets and HDL-associated apolipoprotein(Apo)A1 ($p<0.0001$). Importantly, ApoA1 correlated negatively with disease activity measures (SLEDAI, p=0.005; BILAG, p=0.0009; dsDNA, p=0.003). Strikingly, the metabolite signature was significantly associated with both atherosclerosis incidence and myocardial infarction (MI) mortality through disease-wide association analysis. Altered metabolites unique to different age groups in SLE vs HCs included reduced amino acids (≤25), increased very-low-density lipoproteins (26-49), and increased low-density lipoproteins (≥50). Separately, metabolites in the glycolysis pathway (p=0.004), including acetone, citrate, creatinine, glycerol, lactate, and pyruvate, had positive correlations with age in SLE patients, but not in HCs. Pyruvate (p=0.01) and lactate (p=0.009) were upregulated in prednisolone-treated patients, whilst citrate (p=0.002) and creatinine (p= 0.005) were downregulated in hydroxychloroquine-treated patients. Importantly, all of these SLE age-associated glycolysis metabolites had a significant disease-wide association with both type 1 and type 2 diabetes.
Conclusion: Increasing HDL (ApoA1) levels through therapeutic/nutritional intervention, whilst maintaining low disease activity, in SLE patients from a young age could improve disease and cardiometabolic outcomes. Biomarkers from the glycolytic pathway could decrease the adverse metabolic effects of current therapies.
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