

**Background** Juvenile-onset systemic lupus erythematosus (JSLE) is an autoimmune disorder characterised by immune dysregulation, chronic inflammation and increased cardiovascular risk. Our findings in adult-onset SLE link immune cell dysregulation with defects in plasma membrane signalling platforms (lipid rafts). In JSLE little is known about the immune profile or whether abnormal lipid metabolism contributes to pathogenesis.

**Methods** Flow cytometry was used to measure metabolic marker expression on immune cell subsets from 39 healthy donors (HCs) and 35 JSLE patients. Metabolic biomarker analysis including lipoprotein composition was performed on matching serum.

**Results** JSLE patients had significantly elevated membrane lipid rafts in T-cells, B-cells and plasmacytoid dendritic cells compared to HCs suggesting deregulated membrane receptor signalling. Furthermore, lipid raft expression correlated positively with cell activation markers, disease activity, erythrocyte sedimentation rate and dsDNA titre and negatively with complement protein C3 supporting the hypothesis that altered metabolism is associated with JSLE pathogenesis. Importantly, ROC curve analysis showed that lipid raft expression on these cell types is an excellent diagnostic of high disease activity in JSLE. Metabolomic analysis of matching serum revealed that high disease activity patients had significantly decreased atherto-protective high density lipoproteins (HDL) and increased athero-protective low density lipoproteins (LDL) suggesting altered transport of lipids. In addition, lipids associated with membrane rafts such as sphingomyelin, phosphatidylcholine, phosphoglycerides and cholesterol correlated negatively with HDL in high disease activity patients but positively in low disease activity patients. Immune cell lipid rafts correlated positively with LDL and negatively with HDL together suggesting altered lipid uptake/efflux from these cells; this may alter immune cell signalling in JSLE patients. Stratification of patients based on their lipid profile by hierarchical clustering revealed 3 groups that were unique in both immunophenotype and clinical presentation.

**Conclusions** Differences in the metabolic profiles of immune cell subsets and lipoprotein lipid transport in JSLE contribute to disease pathogenesis and severity. Regulation of lipid metabolism may therefore have therapeutic benefit for JSLE patients providing a dual effect of reducing inflammation and atherosclerotic risk. These therapeutics may perform better in patients that present specific clinical and phenotypic features.