Background: In a systemic lupus erythematosus (SLE) murine model, the translocation of a gut pathobiont induced an autoimmune response and death, which were prevented by antibiotics and a vaccine [1]. These findings suggest that the gut microbiota modulates SLE phenotype. Previously, we found increased circulating lipopolysaccharide (LPS) in SLE patients, which could be associated with decreased gut barrier integrity and translocation from the gut to the bloodstream [2]. We hypothesize that dysbiosis, impaired intestinal barrier integrity, and endotoxemia are crucial to the chronic activation of the immune system seen in SLE.

Objectives: To study diet, physical activity, body composition, gut microbiota, and gut permeability in SLE patients in comparison with healthy controls (HC).

Methods: Evaluation of HC and SLE patients (children and adults) who fulfill the 2019 EULAR/ACR SLE classification criteria. Individuals with inflammatory bowel disease, celiac disease, irritable bowel syndrome, diabetes, malignancy, or other immune-mediated diseases were excluded. The SLEDAI-2K score was used to evaluate disease activity. Diet and physical activity were assessed by three-day diet recall, PREDIMED, KIDMED, and the International Physical Activity questionnaires. Body composition was analysed by whole-body air-displacement plethysmography. Gut microbiota was studied by Next Generation Sequencing, with amplicon sequencing-based 16S rRNA analysis. The lactulose mannitol test, which directly assesses intestinal permeability, was quantified by mass spectrometry (LC-MS/MS). Serum markers of gut permeability and inflammation (zonulin, sCD14, IFABP) were measured by ELISA. The biological activity of LPS was assessed through serum-induced toll-like receptor 4 (TLR4) stimulation in a reporter cell line.

Results: We studied 16 HC (median age 35.5Y [14-50Y]; 88% females) and 45 SLE patients (11 children and 34 adults; median age 32Y [11-57Y]; 87% females; median age at diagnosis 19Y [8-43Y]; median disease duration 7Y [3M-29Y]; 64% had lupus nephritis; median SLEDAI-2K at sample collection 4).

SLE patients had lower physical activity and higher sitting time, lower adherence to the Mediterranean diet, and higher fat mass than HC (p<0.05). In addition, SLE patients had a lower intake of ω-3 polyunsaturated acid and manganese (p<0.05). A decreased ω-3 diversity of gut microbiota (p<0.05) was identified in SLE patients, reflecting dysbiosis. Lower adherence to the Mediterranean diet, higher zonulin levels, and longer SLE disease duration were significantly associated with decreased gut diversity in this cohort (p<0.05). The lactulose/mannoitol ratio was significantly higher in SLE patients compared to HC (p<0.05), reflecting greater gut permeability. Patients with lupus nephritis had a higher lactulose/mannoitol ratio than SLE patients without renal involvement (p=0.05). Interestingly, we found that zonulin was significantly increased in SLE patients (p<0.05). We also found significantly increased levels of sCD14 in SLE patients (p<0.05) and increased levels of IFABP, but only in adult patients (p<0.05). No significant correlation was observed between any evaluated biomarker and SLEDAI-2K.

The serum of SLE patients induced a significantly higher TLR4 response compared to HC (p<0.05), which may reflect endotoxemia.

Conclusion: Our data support the hypothesis that gut dysbiosis and higher intestinal permeability contribute to SLE pathogenesis, being two promising therapeutic targets in this disease.

REFERENCES:
[1] PMID: 29590047
[2] PMID: 24796678

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