Methods: 1) Cross-sectional study in 307 body mass index matched subjects: 55 healthy donors (HDs), 190 RA patients and 62 non-RA patients diagnosed with NAFLD through echography. Obese patients were excluded from the study. 2) Longitudinal study with 50 RA patients treated with MTX for 6 months. Clinical and laboratory parameters, subclinical liver disease biomarkers and 4 indexes to evaluate the presence of fibrosis and steatosis (APRI, \( \text{AST to platelet ratio index} \); FIB-4, \( \text{fibrosis 4 score} \); HSI, \( \text{hepatic steatosis index} \) and TyG, \( \text{triglycerides and glucose index} \)) were measured. Association studies of hepatic dysfunction with clinical parameters were performed; A panel of 15 proteins directly involved in hepatic disease was analyzed in serum (C1QTNF1, IL7R, TIE1, CCL5, REG3A, CAS3, LN2C, CCL14, NRPI, ICAM3, CD59, TIMP1, CNDP1, GNLY, IGFFB8). 3) In vitro experiments were carried out in hepatocyte cell line (HEPG2) treated with ACPAs.

Results: Using NAFLD patients as positive controls for the four liver disease indexes, RA patients showed significantly higher levels of HSI and TyG biomarkers. In fact, a high proportion of these patients (42.7%) were estimated to suffer NAFLD. The association studies in RA patients showed that liver disease biomarkers (HSI and TyG) were related to the insulin resistance state, inflammation, complement component C3, disease activity, and the levels of ACPAs. Serum levels of CNDP1, CCL5, GNLY, TIMP-1, CD59 and CCL14 were significantly increased in RA patients and correlated with hepatic damage indexes. Treatment with ACPAs on hepatocytes promoted the secretion of C3 in parallel with a significant alteration of genes related to glucose and lipid metabolisms, inflammation, fibrosis and apoptosis. MTX treatment, from the point of cross-sectional approach, was not associated with an increase of hepatic enzymes, serum proteins nor liver disease indexes. Treatment with MTX for 6 months did not affect those levels either.

Conclusion: 1) A high proportion of RA patients present an alteration in markers of NAFLD, associated with insulin resistance state, disease activity, inflammation, component C3 and ACPAs levels; 2) the autoantibodies could directly impact hepatocyte biology altering the expression of genes related to glucose and lipid metabolisms, inflammation, fibrosis and apoptosis. 3) Treatment with MTX did not promote any alteration in subclinical liver disease biomarkers after 6 months of treatment. Funded by Institute of Health Carlos III (PI20/0073).

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TIGLYLCARNITINE AS KEY FACTORS IN LIVER–JOINT AXIS

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Background: Gut microbiota could promote RA progression metabolites mediated gut–joint axis [1]. We previously reported that liver metabolism has a close linkage with Rheumatoid arthritis (RA) [2]. However, the inter-relational mechanisms between liver and joint are still unclear.

Objectives: This article aimed to explore the shared metabolites signatures of liver, plasma and joint in RA.

Methods: We integrated multomics datasets metabolites of liver and plasma from in the healthy group (n=10) and CIA group (n=10), and metabolites of knee-joint fluid (synovial fluid) from 40 participants in osteoarthritis (OA) group (n=20) and RA group (n=20). The Weighted Gene Co-Expression Network Analysis (WGCNA) was used to identify the co-expression modules related to liver, plasma and joint.

Results: The blue modules were negatively correlated with CIA \( (r = 0.74, \ p < 0.001) \), included 200 liver metabolites. The black modules were positively correlated with CIA \( (r = 0.63, \ p < 0.001) \), included 78 plasma metabolites. The yellow modules were positively correlated with RA \( (r = 0.53, \ p = 0.008) \), included 55 synovial fluid metabolites. There were only 1 metabolite (Tiglylcarnitine) overlapped in RA-related module of liver, plasma and joint.

Conclusion: Tiglylcarnitine may be the key factors to liver–joint axis.

REFERENCES: