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BRIEF REPORT OPEN ACCESS

Systemic Inflammation and Peripheral T Cell Responses Associate With Hepatic Energy Metabolism in Recent-Onset Type 1 Diabetes

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ABSTRACT

People with type 1 diabetes feature lower concentrations of hepatic adenosine-triphosphate (ATP) and inorganic phosphate (Pi), which further decline during the early course of disease. However, it is unknown whether inflammatory pathways are involved in the diabetes-associated alterations of hepatic energy metabolism. Participants (median age 35 years, BMI 21.7 kg/m^2, HbA1c 6.0%) of the German Diabetes Study (GDS) with short type 1 diabetes duration (≤ 5 years) underwent ^{1}H/^{31}P magnetic resonance spectroscopy to quantify hepatic lipid content, γATP and Pi concentrations. Inflammatory proteins in serum and in supernatants of stimulated CD4$^+$ and CD8$^+$ T cells were measured by a multiplex assay (OLINK Target 96 Inflammation). Analyses were adjusted for multiple testing with false discovery rate (FDR)-correction. Hepatic γATP concentrations positively correlated with circulating TNFSF14 ($r = 0.98$, $p < 0.001$, $p_{FDR} = 0.009$) and MMP10 ($r = 0.71$, $p = 0.047$). Hepatic Pi was positively associated with circulating MMP10 ($r = 0.90$, $p = 0.002$), with CD4$^+$ T cell responses, particularly CCL3 ($r = 0.74$, $p = 0.010$) and CCL4 ($r = 0.75$, $p = 0.008$), and with CD8$^+$ T cell responses, particularly CCL3 ($r = 0.86$, $p = 0.014$), CCL4 ($r = 0.96$, $p < 0.001$) and TNFSF14 ($r = 0.89$, $p = 0.007$). Hepatic lipid content (median 0.4%) negatively correlated with IL-2, IL4, IL-13 and TNF release from CD8$^+$ T cells (all $p_{FDR} < 0.05$). Even in lean metabolically well-controlled persons with early type 1 diabetes, measures of hepatic energy metabolism strongly associate with a specific inflammatory profile and T cell responses, suggesting a role of pro-inflammatory mechanisms in the regulation of hepatic metabolism, even in the absence of steatotic liver disease.

Trial Registration: ClinicalTrial.gov identifier: NCT01055093

Abbreviations: BMI, body mass index; CCL, C-C motif chemokine ligand; CD, cluster of differentiation; FDR, false discovery rate; FGF21, fibroblast growth factor 21; HLC, hepatic lipid content; hsCRP, high sensitivity C-reactive protein; IFNγ, interferon gamma; IL, interleukin; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MMP10, matrix metalloproteinase 10; NEFA, non-esterified fatty acids; PBMCs, peripheral blood mononuclear cells; Pi, inorganic phosphate; TNF, tumour necrosis factor; TNFSF14, TNF superfamily member 14; TRAIL, TNF-related apoptosis-inducing ligand; γATP, gamma adenosine triphosphate.

Christian Herder and Michael Roden contributed equally to this work as last authors.

The GDS group consists of M. Roden (speaker), H. Al-Hasani, B. Belgardt, E. Lammert, G. Bönhof, G. Geerling, C. Herder, A. Icks, K. Jandeleit-Dahm, O. Kuß, S. Schlesinger, V. Schrauwen-Hinderling, J. Szendroedi, S. Trenkamp, R. Wagner, and their co-workers who are responsible for the design and conduct of the GDS.

Key Points

- In lean metabolically well-controlled persons with early type 1 diabetes, hepatic energy metabolism strongly associated with specific inflammatory proteins.
- Hepatic γATP concentrations positively correlated with circulating TNFSF14 and MMP10.
- Hepatic Pi was positively associated with CCL3 and CCL4 release from $CD4^+$ and $CD8^+$ T cells.
- Hepatic lipid content negatively correlated with IL-2, IL4, IL-13 and TNF release from $CD8^+$ T cells.

1 | Introduction

Hepatic oxidative capacity is increased in obesity without and with early metabolic dysfunction-associated steatotic liver disease (MASLD) [1]. In metabolic dysfunction-associated steatohepatitis (MASH) and particularly in type 2 diabetes, this mitochondrial adaptation progressively fails [2, 3], which may be due to insulin resistance, lipotoxicity and dysglycemia [4]. In line, lower hepatic adenosine triphosphate (ATP) and inorganic phosphate (Pi) concentrations have been reported both in people with type 2 diabetes and those with type 1 diabetes [5–7].

Interestingly, individuals with type 1 diabetes exhibit lower hepatic levels of phosphorus metabolites and ATP synthesis rates than glucose-tolerant humans, despite very low hepatic lipid contents and good metabolic control [6, 8]. Also, body mass index and age do not affect hepatic γATP and Pi levels in healthy individuals [9]. Thus, the factors determining hepatic energy metabolism in type 1 diabetes remain unclear. MASLD/MASH has been associated with increased levels of several circulating markers, including inflammatory proteins [2, 10, 11]. Alterations in multiple circulating inflammatory proteins also have been reported in people with type 1 diabetes compared with healthy humans [12]. Still, the relationship of systemic low-grade inflammation with hepatic energy metabolism in type 1 diabetes is unknown. In addition to innate immune cells, peripheral and hepatic T cells have been associated with alterations in hepatic energy metabolism, specifically in the context of MASLD progression to MASH [13–15]. In type 1 diabetes, peripheral T cell responses are altered and impaired responses to several pathogenic stimuli have been described [16]. It remains, however, unknown if or how alterations in T cells in type 1 diabetes may influence the crosstalk between immune cells and liver energy metabolism.

Here, we hypothesized that alterations of circulating inflammatory proteins and the function of peripheral T cells may explain liver energy metabolism in type 1 diabetes. In this exploratory study, we therefore measured hepatic γATP and Pi, circulating inflammatory proteins, and immune responses of peripheral $CD4^+$ and $CD8^+$ T cells in persons with type 1 diabetes, who featured younger age, normal body weight, near-normoglycemic control and short diabetes duration.

2 | Methods

2.1 | Study Participants

Study participants were recruited from the German Diabetes Study (GDS), an ongoing prospective observational cohort study. Key inclusion and exclusion criteria are described in the cohort profile [17]. For this exploratory analysis, we selected participants with type 1 diabetes at either their baseline (during the first year after diagnosis) or five-year follow-up visit with available data on liver magnetic resonance spectroscopy (MRS) and inflammatory proteins ($n = 14$). Furthermore, we excluded one participant taking non-steroidal anti-inflammatory drugs and two participants with hepatic lipid content (HLC) > 5.6% from our analysis to exclude steatosis, resulting in $n = 11$ participants. The GDS cohort was approved by the ethics committee of Heinrich Heine University, Düsseldorf, Germany (ref. 4508) and is performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2 | Measurement of Anthropometric and Clinical Variables

Measurements of anthropometric parameters and metabolic variables with routine laboratory procedures are described in the Methods S1 or were reported previously [17]. HLC and absolute concentrations of γATP and Pi were measured non-invasively by $^1H/^{31}P$ MRS as described previously [6].

2.3 | Measurement of Inflammatory Proteins

Proteins were measured by proximity extension assay technology in serum and in supernatants of cultured T cells (see Methods S1 for details) using the Target 96 Inflammation panel from Olink Proteomics (Uppsala, Sweden). Details on dilutions and normalization are reported in the Methods S1. Protein concentrations are given as normalized protein expression (NPX) values on a $\log_2$ scale. NPX values are calculated from cycle threshold values using normalization procedures to minimize intra- and inter-assay variations.

2.4 | Statistical Analysis

All statistical analysis was performed in RStudio (R version 4.4.0). Spearman correlation coefficients and corresponding p-values were calculated. False discovery rate (FDR)-correction was applied for multiple testing (per hepatic measurement (HLC, ATP, Pi) and sample type (serum, $CD4^+$ T cells, $CD8^+$ T cells)).

3 | Results

3.1 | Participants' Characteristics

Participants with type 1 diabetes were on average 35 years old, had normal body weight and showed excellent metabolic control with median HbA1c of 6.0% (see Table S1 for further clinical

characteristics). Median HLC (0.4%), γATP (2.55 mmol/L) and Pi (2.15 mmol/L) were comparable to those of previous studies in participants with type 1 diabetes [6].

3.2 | No Associations of Liver Energy Metabolism With Clinical Characteristics

HLC, γATP, Pi and the γATP/Pi ratio were not associated with clinical and metabolic parameters, such as age, BMI, fasting glucose, C-peptide, insulin sensitivity (*M*-value) and high sensitivity CRP (hsCRP) (all $p > 0.05$).

3.3 | Positive Associations of Hepatic γATP and Pi With Circulating Cytokines and Chemokines

We characterized serum samples, as well as 24-h supernatants from anti-CD3/anti-CD28-stimulated CD4$^+$ and CD8$^+$ T cells. HLC was negatively correlated with circulating tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/TNFSF10; $r = -0.81$, $p = 0.004$) and CCL25 (C-C motif chemokine ligand; $r = -0.77$, $p = 0.010$) levels, but positively correlated with circulating fibroblast growth factor 21 (FGF21; $r = 0.84$, $p = 0.002$) (Figure 1A,B). Hepatic Pi concentrations correlated positively with circulating matrix metalloproteinase 10 (MMP10; $r = 0.90$, $p = 0.002$; Figure 1A,C) and the chemokine CCL28 ($r = 0.79$, $p = 0.021$). Hepatic γATP also correlated positively with circulating MMP10 ($r = 0.71$, $p = 0.047$; Figure 1A) and CCL28 ($r = 0.74$, $p = 0.037$), as well as with circulating levels of TNF superfamily member 14 (TNFSF14/LIGHT; $r = 0.98$, $p < 0.001$; Figure 1A,D). This correlation remained after adjustment for multiple testing ($p_{FDR} = 0.009$). The γATP/Pi ratio was also positively correlated with circulating TNFSF14 ($r = 0.74$, $p = 0.037$) and interferon-γ (IFNγ; $r = 0.88$, $p = 0.004$) (Figure 1A,E).

3.4 | Associations of HLC and Pi With Release of Chemokines and Pro-Inflammatory Proteins From Stimulated CD4$^+$ and CD8$^+$ T Cells

CD4$^+$ T cell responses were positively correlated with hepatic Pi concentrations, specifically with levels of the chemokines CCL3 (MIP-1α; $r = 0.74$, $p = 0.010$) and CCL4 (MIP-1β; $r = 0.75$, $p = 0.008$) (Figure 2A–C). In contrast, there were no or only weak associations of inflammatory proteins released from stimulated CD4$^+$ T cells with HLC and γATP (Figure 2A).

HLC was negatively correlated with release of interleukin 2 (IL-2; $r = -0.95$, $p < 0.001$), IL4 ($r = -0.99$, $p < 0.001$), IL-13 ($r = -0.95$, $p < 0.001$) and TNF ($r = -0.95$, $p < 0.001$) from CD8$^+$ T cells, also after multiple testing correction (all $p_{FDR} < 0.05$; Figure 2D–G). Whereas no correlations with hepatic γATP were found, hepatic Pi was positively correlated with release of CCL3 ($r = 0.86$, $p = 0.014$), CCL4 ($r = 0.96$, $p < 0.001$) and TNFSF14 ($r = 0.89$, $p = 0.007$) from CD8$^+$ T cells (Figure 2D,H,I). The correlation with CCL4 remained significant after multiple testing correction ($p_{FDR} = 0.015$).

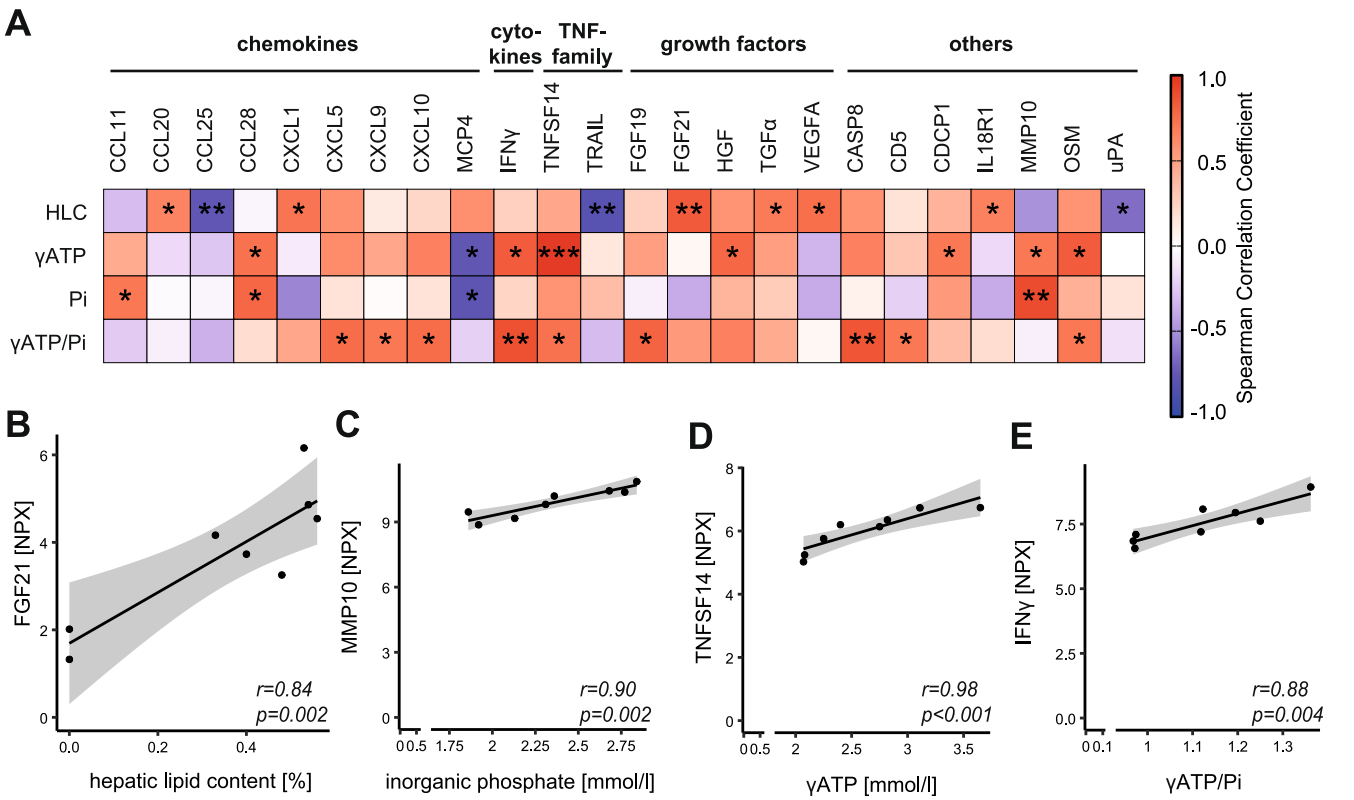

FIGURE 1 | Correlations between hepatic lipid content as well as phosphorus metabolites and inflammatory proteins in serum. (A) Heatmap showing correlations between measurements of hepatic energy metabolism and inflammatory proteins in serum. Only proteins with at least one significant correlation are shown. (B–E) Correlations of hepatic lipid content with FGF21 (B), of Pi with MMP10 (C), of γATP with TNFSF14 (D), and of γATP/Pi with IFNγ (E). (A–E) $n = 8$. Spearman correlation coefficients and corresponding *p*-values. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

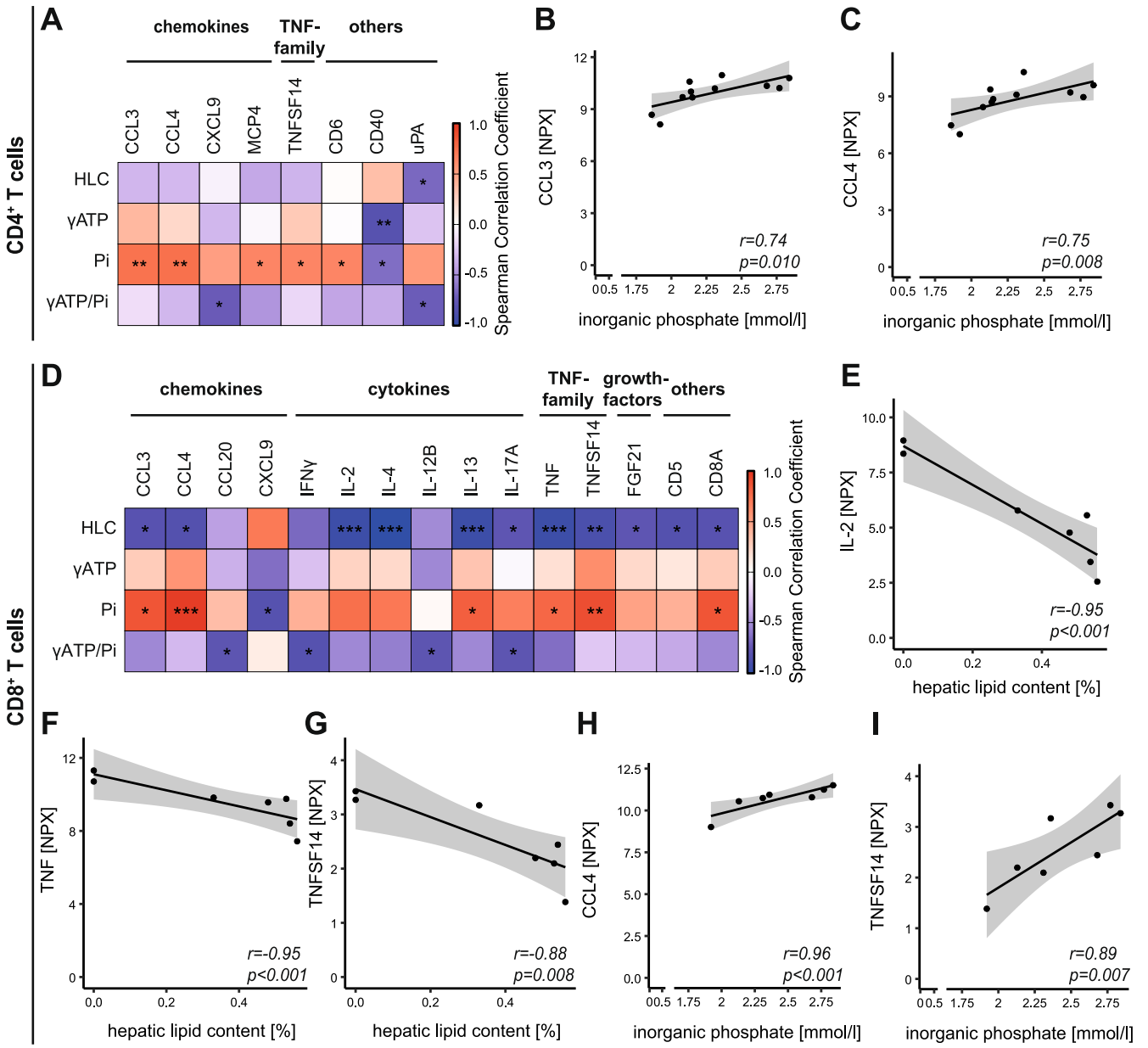

FIGURE 2 | Correlations between hepatic lipid content as well as absolute concentrations of phosphorus metabolites and inflammatory proteins in supernatants of stimulated CD4+ and CD8+ T cells. (A) Heatmap showing correlations between measurements of hepatic energy metabolism and inflammatory proteins in supernatants of stimulated CD4+ T cells. Only proteins with at least one significant correlation are shown. (B, C) Correlations of Pi with CCL3 (B) and CCL4 (C) in supernatants of stimulated CD4+ T cells. (D) Heatmap showing correlations between measurements of hepatic energy metabolism and inflammatory proteins in supernatants of stimulated CD8+ T cells. Only proteins with at least one significant correlation are shown. (E–I) Correlations of hepatic lipid content with IL-2 (E), TNF (F) as well as TNFSF14 (G), and of Pi with CCL4 (H) and TNFSF14 (I) in supernatants of stimulated CD8+ T cells. (A–C) $n = 11$, (D–I) $n = 7$. Spearman correlation coefficients and corresponding p-values. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

4 | Conclusions

This study shows strong correlations between hepatic energy metabolism and inflammatory proteins, but not other clinical variables, in type 1 diabetes. Specifically, we found negative correlations between hepatic lipid content and pro-inflammatory cytokine production (IL-2, IL-4, IL-13, TNF) by CD8+ T cells, and positive correlations between hepatic absolute concentrations of γATP and circulating TNFSF14, as well as between hepatic absolute Pi concentrations and release of CCL3, CCL4 and TNFSF14 from CD4+ and CD8+ T cells. Inflammatory mechanisms may therefore impact hepatic energy metabolism, even in the absence of overweight and MASLD.

Several inflammatory proteins correlated with hepatic energy metabolism in this study have previously been described to be associated with liver metabolism or function, mostly in the context of MASLD or MASH. MMP10, for instance, is induced during liver injury in mice and has an important function in liver tissue repair [18]. In a mouse model, MMP10 alleviated MASH by regulating macrophage M2 polarization [19]. Positive correlations of circulating MMP10 concentrations with hepatic γATP and Pi

concentrations indicate a regulatory role for MMP10, independent of fibrosis.

We found strong correlations between hepatic absolute γATP concentrations as well as the γATP/Pi ratio with circulating levels of TNFSF14, a protein of the TNF family. Genetic inactivation of TNFSF14 restores glucose homeostasis in mice and reduces hepatic steatosis [20]. Furthermore, hepatic TNFSF14 gene expression, probably originating from $CD8^+$ T cells and NK T cells, was found to be increased in people with MASH [21]. Mechanistically, TNFSF14 directly increased lipid uptake of hepatocytes, indicating a close interplay between lymphocyte function and liver metabolism [21]. Our results show that TNFSF14 may not only regulate hepatic metabolism in the context of steatosis but also in type 1 diabetes without steatosis. Interestingly, we also found positive correlations of TNFSF14 release from $CD4^+$ and $CD8^+$ T cells with hepatic γATP concentrations, supporting an important regulatory role of T cells.

We also found positive associations of hepatic Pi concentrations with CCL3- and CCL4-release from $CD4^+$ and in particular $CD8^+$ T cells. CCL3 and CCL4 are chemokines secreted both by conventional and regulatory T cells (T_{reg}) [22]. CCL3 has been shown to promote hepatitis by recruiting CCR1-expressing $CD4^+$ T cells to the liver [23]. Both CCL3 and CCL4 bind to the C-C chemokine receptor CCR5, which has been shown to promote hepatic fibrosis in mice [24] and has been targeted to treat liver fibrosis in MASH [25, 26]. Our results indicate that T cell-induced migration of immune cells may play a role in regulating hepatic energy metabolism in type 1 diabetes. Still, it is insufficiently understood how CCL3- and CCL4-secretion by T cells may modify hepatic metabolism.

This study benefits from gold-standard measurements of hepatic energy metabolism as well as the comprehensive assessment of inflammatory proteins in serum and supernatants of $CD4^+$ and $CD8^+$ T cells in individuals with short known type 1 diabetes duration. Still, some limitations of this study have to be considered. First, we only included participants with adult-onset diabetes and excellent glucometabolic control, which does not allow generalization of our findings to people with insufficiently controlled disease suffering from severe complications. Furthermore, we designed an exploratory, hypothesis-generating study. Consequently, results need to be validated in larger cohorts and supported by additional analyses to exclude false-positive risks due to multiple testing, and to investigate the causality of found associations, which is currently not supported by the cross-sectional study design.

In conclusion, this study indicates that pro-inflammatory mechanisms, in particular those involving TNFSF14 and T cell-induced chemotaxis, may regulate hepatic energy metabolism in type 1 diabetes, even in the absence of MASLD/MASH.

Author Contributions

J.M.R.-R. designed the study, performed experiments, analysed, interpreted and visualized data, and wrote the original manuscript draft. A.Z. performed experiments and assisted in data curation. M.H. collected blood samples and clinical data from study participants. Y.K. and V.S.-H. performed and analysed the metabolic imaging data. A.P. was responsible for Olink measurements. S.T. was responsible for clinical laboratory measurements. R.W. supervised the clinical study. M.R. is the primary investigator of the German Diabetes Study. C.H. and M.R. supervised the study, and reviewed and edited the manuscript. All authors were involved in critically revising the article and approved the final version. J.M.R.-R. and M.R. are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of Interest

M.R. received fees for consulting or lecturing from Astra Zeneca, Boehringer-Ingelheim, Echosens, Eli Lilly, Madrigal, MSD, Novo Nordisk, Pfizer, Synlab and TARGET_RWE and has performed investigator-initiated research with support from Boehringer Ingelheim, Novo Nordisk and Sanofi. The other authors declare no conflicts of interest.

Data Availability Statement

The datasets generated or analysed during the current study are not available publicly because they are subject to national data protection laws and restrictions imposed by the ethics committee to ensure privacy of study participants. However, they can be applied for through an individual project agreement with the principal investigator of the German Diabetes Study (GDS). The study protocol and the individual methods have been published in the cohort profile [17] and are unrestrictedly available.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Methods. **Table S1:** Participants' characteristics.