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RESEARCH LETTER

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Elevated liver enzymes and comorbidities in type 2 diabetes: A multicentre analysis of 51 645 patients from the Diabetes Prospective Follow-up (DPV) database

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Abstract

Aim: To assess the prevalence of elevated liver enzymes and associated diabetes-related comorbidities in type 2 diabetes (T2D).

Subjects and Methods: Between 2010 and 2019, 281 245 patients with T2D (aged 18-75 years) from 501 Diabetes Prospective Follow-up (DPV) centres were evaluated, resulting in analysis of 51 645 patients with complete data on demographics and liver enzymes.

Results: Elevated liver enzymes were found in 40.2% of all patients. However, only 8.6% of these patients had International Classification of Diseases-10 codes for non-alcoholic fatty liver disease and/or nonalcoholic steatohepatitis. Adjusted for age, sex, diabetes duration, body mass index and glycated haemoglobin, a higher prevalence of arterial hypertension ($P < 0.0001$), dyslipidaemia ($P < 0.0001$), peripheral artery disease ($P = 0.0029$), myocardial infarction ($P = 0.0003$), coronary artery disease ($P = 0.0001$), microalbuminuria ($P < 0.0001$) and chronic kidney disease ($P < 0.0001$) was seen in patients with elevated versus normal liver enzymes. The prevalence of elevated liver enzymes was lowest in patients receiving sodium-glucose cotransporter-2 (SGLT2) inhibitors or a combination of SGLT2 inhibitors and glucagon-like peptide-1 receptor agonists.

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Conclusion: Elevated liver enzymes are common in patients with T2D and clearly correlate with a higher prevalence of clinically relevant comorbidities. Assessing liver enzymes should be standard clinical routine in T2D due to a possible predictive role for comorbidities and complications.

KEYWORDS
GLP-1 receptor agonists, liver enzymes, metabolic syndrome, NAFLD, SGLT2 inhibitors, type 2 diabetes

1 | INTRODUCTION

The prevalence of fatty liver disease is rising continuously worldwide. Nonalcoholic fatty liver disease (NAFLD) is currently the most common form of fatty liver disease and is predicted to become the most frequent indication for liver transplantation by 2030.[1,2] In addition to type 2 diabetes (T2D), adiposity, especially in childhood, is one of the most important risk factors for NAFLD, further boosting its rising prevalence.[2] There is growing evidence for NAFLD representing a multisystem disorder associated with extra-hepatic disease such as cardiovascular disease (CVD) and chronic kidney disease (CKD).[1] Despite the increased extra-hepatic morbidity and mortality associated with NAFLD,[3] awareness regarding early detection of fatty liver disease in patients at risk is still low. The overall prevalence of NAFLD in Europe is estimated at approximately 24%.[2] However, clinical data on elevated liver enzymes in patients with T2D are scarce.

Insulin resistance per se is known to be involved in the pathogenesis of fatty liver as well as in disease progression from steatosis to nonalcoholic steatohepatitis (NASH).[4] T2D-associated insulin resistance and fatty liver disease constitute a vicious circle and further increase the risk of progression to NASH and fibrosis.[4,5] Current evidence demonstrates a strong association between liver fat content and elevated liver enzymes alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) as surrogate markers of liver injury.[6] In turn, elevated GGT and ALT have been demonstrated to represent relevant indicators for metabolic syndrome and independent predictors of T2D risk.[7] Furthermore, high GGT serum levels have been reported to be associated with risk of CVD.[8] Therefore, we hypothesize that elevated liver enzymes in patients with T2D can serve as markers of increased risk for diabetes-associated comorbidities.

The "Diabetes Prospective Follow-up" database (*Diabetes-Patienten-Verlaufsdokumentation* [DPV]) is a nationwide registry in Germany, Austria, Switzerland and Luxembourg, and has prospectively collected diabetes-related clinical data since 1995.[9] The registry holds datasets of 588 860 patients with diabetes mellitus as of March 2020.

The objective of the present analysis was to determine the prevalence of elevated liver enzymes in T2D and the potential association with extra-hepatic comorbidities and diabetes-related complications.

2 | METHODS

2.1 | Database

This analysis was based on data from the DPV registry which consists of 451 specialized diabetes care centres in Germany, 45 in Austria, four in Switzerland, and one in Luxembourg. Every 6 months, locally collected pseudonymized longitudinal data are transmitted to Ulm University, Germany, for central plausibility checks, quality assurance and analyses. Inconsistent data are reported back to participating centres for validation or correction. Afterwards, the data are anonymized for analysis. The DPV registry is a resource for clinical quality management and research. Analysis of anonymized routine data within the DPV initiative has been approved by the Ethics Committee of the Medical Faculty of the University of Ulm, Germany. This study is performed in accordance with the 1964 Helsinki declaration and its most recent amendments.

2.2 | Inclusion and exclusion criteria

In this analysis, people with T2D aged between 18 and 75 years with documented values of ALT, aspartate aminotransferase (AST) and/or GGT during the most recent documented treatment year within this 10-year period of January 2010 to December 2019 (Figure 1) were included. Patients with a history of coeliac disease, alpha-1 antitrypsin deficiency or a daily alcohol consumption of ≥24 g for men and ≥12 g for women were excluded from the analysis.

2.3 | Liver enzymes

Elevated liver enzymes were defined as one or more measurement of ALT or AST >50 U/L in men and > 35 U/L in women and/or GGT > 60 U/L in men and > 40 U/L in women, according to the definition of the German Liver Foundation (http://www.deutsche-leberstiftung.de), and the prevalence of elevated liver enzymes was calculated in this cohort.

2.4 | Demographic and disease-specific variables

The following demographic characteristics and disease-specific variables were assessed for each patient: age; gender; body mass index

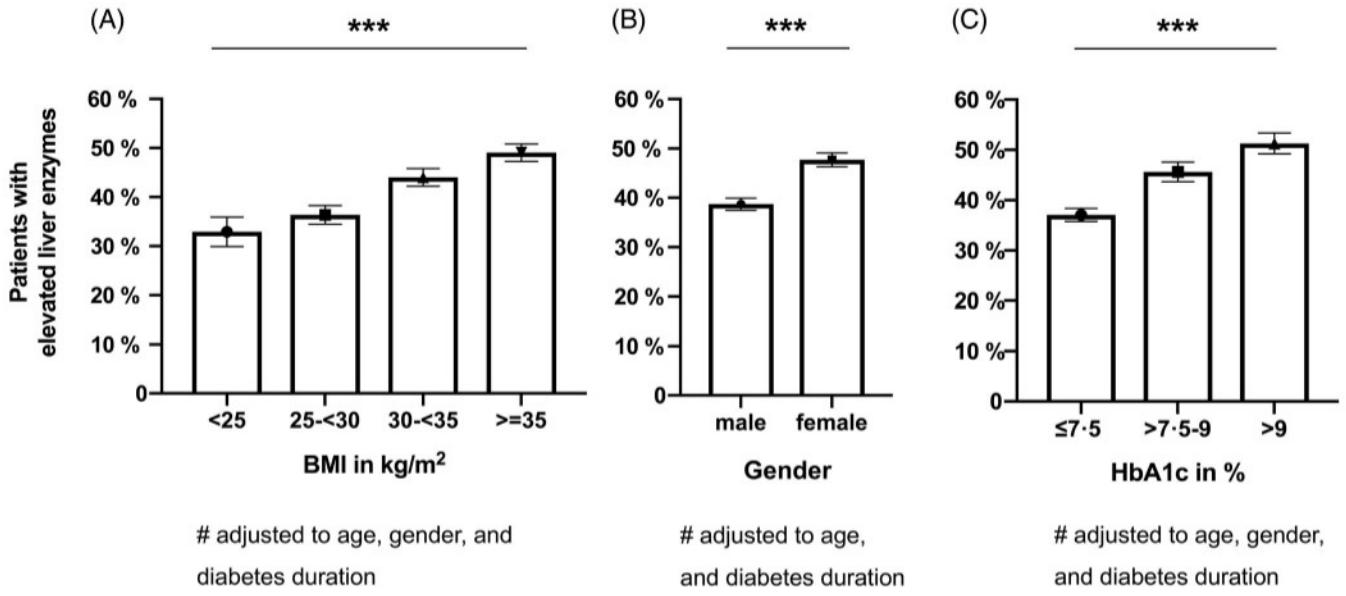

FIGURE 1 Proportion of patients with type 2 diabetes and elevated liver enzymes in %, comparing: A, body mass index (BMI): subclassified into <25, 25 to <30, 30 to <35, and ≥35 kg/m^2, adjusted for age, sex and diabetes duration; B, gender: male and female, adjusted for age and diabetes duration, and C, glycated haemoglobin (HbA1c; subclassified into ≤7.5% (59 mmol/mol), >7.5–9% (59-75 mmol/mol), >9% (75 mmol/mol), adjusted for age, gender, and diabetes duration. ***P < 0.0001

(BMI); waist circumference; glycated haemoglobin (HbA1c); blood pressure; estimated glomerular filtration rate (eGFR; according to the Modification of Diet in Renal Disease [MDRD] formula); lipid profiles, with total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol; triglycerides; diabetes duration; and antidiabetic therapy. Further, data on registry-documented and International Classification of Diseases (ICD)-coded NAFLD, NASH, autoimmune or viral hepatitis, liver cancer of any type as well as liver cirrhosis were assessed and analysed.

2.5 | Comorbidities and complications

The following concomitant diseases were assessed in people with T2D meeting the inclusion criteria: arterial hypertension (defined as use of antihypertensive drugs and/or a systolic and/or diastolic arterial blood pressure ≥140 mm Hg and/or ≥90 mm Hg) and dyslipidaemia (defined as use of lipid-lowering drugs and/or reduced HDL cholesterol levels [<0.9 mmol/L or <35 mg/dL] or elevated total cholesterol [>5.16 mmol/L or >200 mg/dL], LDL cholesterol [>3.35 mmol/L or >130 mg/dL] or triglyceride levels [fasting >1.69 mmol/L or >150 mg/dL], postprandial >4.0 mmol/L or >350 mg/dL]) (Table S1). Comorbidities were classified as extra-hepatic, macro- and microvascular diabetes complications. The following ICD-10-coded cardiovascular comorbidities were recorded: stroke (ischaemic and haemorrhagic); peripheral artery 30 to 300 mg/g) were documented. Patients with diagnosis of viral and autoimmune hepatitis, liver cirrhosis, and liver cancer were excluded from analyses.

2.6 | Antidiabetic therapy and liver enzymes

Six groups of antidiabetic therapy either as monotherapy or combination were defined: (a) lifestyle interventions; (b) oral antidiabetic therapy (OAD; metformin, dipeptidyl peptidase-4 inhibitors, acarbose, sulphonylureas); (c) insulin; (d) glucagon-like peptide-1 receptor agonists (GLP-1RAs); (e) sodium-glucose cotransporter-2 (SGLT2) inhibitors; and (f) SGLT2 inhibitors + GLP-1RAs. The proportions of patients with elevated liver enzymes were assessed for each group.

2.7 | Statistical analyses

Descriptive data are presented as median with quartiles (Q1 and Q3) for continuous variables using the Kruskal-Wallis test to compute unadjusted P values or as percentages for binary variables using the χ^2 test. Multivariable logistic regression models were applied to the following demographic characteristics: age groups (18-40, >40-65, >65-75 years), gender and diabetes duration groups (≤2, >2-10, >10 years). Regression models for comorbidities were adjusted for

(defined as use of lipid-lowering drugs and/or reduced HDL cholesterol levels [<0.9 mmol/L or <35 mg/dL] or elevated total cholesterol [>5.16 mmol/L or >200 mg/dL], LDL cholesterol [>3.35 mmol/L or >130 mg/dL] or triglyceride levels [fasting >1.69 mmol/L or >150 mg/dL], postprandial >4.0 mmol/L or >350 mg/dL]) (Table S1). Comorbidities were classified as extra-hepatic, macro- and microvascular diabetes complications. The following ICD-10-coded cardiovascular comorbidities were recorded: stroke (ischaemic and haemorrhagic); peripheral artery disease (PAD); myocardial infarction (non-ST-elevation myocardial infarction and ST-elevation myocardial infarction); and coronary artery disease (CAD). Furthermore, ICD-10-coded diagnoses of CKD (eGFR 20 to 60 mL/min/1.73 m^2 body surface area according to the MDRD formula), and microalbuminuria (defined as urinary albumin-to-creatinine ratio of

Descriptive data are presented as median with quartiles (Q1 and Q3) for continuous variables using the Kruskal-Wallis test to compute unadjusted *P* values or as percentages for binary variables using the χ^2 test. Multivariable logistic regression models were applied to the following demographic characteristics: age groups (18-40, >40-65, >65-75 years), gender and diabetes duration groups (≤2, >2-10, >10 years). Regression models for comorbidities were adjusted for age, gender, diabetes duration, HbA1c groups (≤7.5%, >7.5%-9%, >9%) and BMI groups (<25, 25 to <30, 30 to <35, ≥35 kg/m^2, according to the World Health Organisation). Regression models for antidiabetic therapy were adjusted for age, gender, diabetes duration and HbA1c group. The associations of comorbidities in patients with

elevated liver enzymes are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, North Carolina); the limit of significance of two-sided tests was set at $P < 0.05$.

3 | RESULTS

3.1 | Prevalence of liver disease and baseline characteristics

The study sample comprised 51 645 patients, aged 18 to 75 years, with T2D, and with available data on liver enzymes. Within the total population of 51 645 people with T2D, 20 748 patients (40.2%) had elevated liver enzymes. In contrast, only 1780 patients (8.6%) with elevated liver enzymes were identified to be ICD-10-coded with NAFLD and/or NASH, respectively. After adjusting for age, sex and diabetes duration, the proportion of patients with elevated liver enzymes rose with increasing BMI categories ($P < 0.0001$; Figure 1A). Female patients were more likely to have elevated liver enzymes than men ($P < 0.0001$; Figure 1B). Also, the proportions of patients with elevated liver enzymes were associated inversely with glycaemic control as assessed by HbA1c category ($P < 0.0001$; Figure 1C).

3.2 | Elevated liver enzymes and comorbidities

After excluding patients with ICD-10 diagnosis of viral and autoimmune hepatitis, liver cirrhosis, and liver cancer, this trial sample analysis comprises 48 840 patients with T2D. In this population, the proportion of patients with elevated liver enzymes was higher as compared to that with normal liver enzymes for each comorbidity: arterial hypertension ($P < 0.0001$), dyslipidaemia ($P < 0.0001$), PAD ($P = .0029$), myocardial infarction ($P = 0.0003$), CAD ($P = 0.0001$), microalbuminuria ($P < 0.0001$) and CKD ($P < 0.0001$). Accordingly, the ORs for macro- and microvascular diabetes complications (Figure 2A) were increased in patients with elevated liver enzymes: arterial hypertension (OR 1.20 [95% CI 1.14-1.26]), dyslipidaemia (OR 1.28 [95% CI 1.21-1.36]), myocardial infarction (OR 1.14 [95% CI 1.06-1.23]), CAD (OR 1.12 [95% CI 1.06-1.18]), PAD (OR 1.15 [95% CI 1.10-1.21]), microalbuminuria (OR 1.20 [95% CI 1.14-1.26]) and CKD (OR 1.31 [95% CI 1.24-1.37]). However, no significant difference in OR was found for stroke (OR 1.00 [95% CI 0.93-1.08]; Figure 2A).

3.3 | Liver enzymes and antidiabetic therapy

Elevated liver enzymes were documented in 9590 patients (39.7%) treated by lifestyle intervention only. Further, elevated liver enzymes were prevalent in 12 277 patients (41.1%) on OADs, in 18 403 patients (44.4%) on insulin, in 2755 patients (46.5%) on GLP-1RAs, in 2737 patients (37.0%) on SGLT2 inhibitors, and in 903 patients (36.5%) on combined SGLT2 inhibitor and GLP-1RA treatment (Figure 2B). Comparing the prevalence of elevated liver enzymes according to medication groups, the proportion of patients with elevated liver enzymes was significantly lower in those on SGLT2 inhibitors or on combined SGLT2 inhibitor and GLP-1RA treatment as compared to those on GLP-1RA ($P < .0001$) or insulin treatment ($P < 0.0001$). Moreover, significantly more patients on insulin therapy

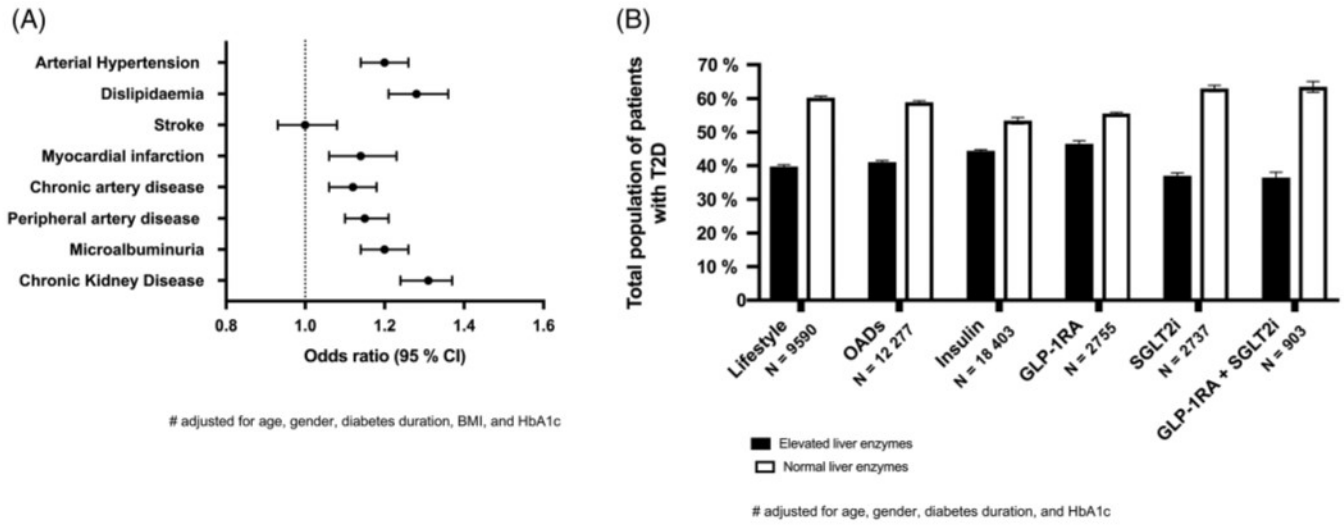

FIGURE 2 A, Adjusted odds ratios (95% confidence intervals [CIs]) for elevated liver enzymes, stratified by diabetes complications and comorbidities: arterial hypertension, dyslipidaemia, stroke, myocardial infarction, chronic artery disease, peripheral artery disease, microalbuminuria, and chronic kidney disease. All data adjusted for age, gender, diabetes duration and glycated haemoglobin (HbA1c). B, Proportion of type 2 diabetes (T2D) patients with elevated (black bars) and normal (white bars) liver enzymes stratified by antidiabetic therapies (lifestyle intervention, oral antidiabetic drugs (OADs), glucagon-like peptide-1 receptor agonists [GLP-1RAs], insulin, sodium-glucose cotransporter-2 inhibitors [SGLT2i], SGLT2i + GLP-1RA treatment). All data adjusted for age, gender, diabetes duration and HbA1c

had elevated liver enzymes as compared to those on OAD treatment ($P < 0.0001$) and lifestyle intervention only ($P < 0.0001$).

4 | DISCUSSION

In this large international population-based analysis, elevated liver enzymes in patients with T2D was common and significantly associated with extra-hepatic comorbidities and macro- as well as microvascular diabetes complications, such as arterial hypertension, dyslipidaemia, myocardial infarction, CAD, PAD, microalbuminuria and CKD.

A prevalence of 40.2% for elevated liver enzymes in this cohort of T2D patients suggests a strong association between T2D and liver injury. However, only 8.6% of all patients had a documented diagnosis of NAFLD within the registry. This discrepancy between frequency of measured elevation in liver surrogates and documented diagnosis of NAFLD indicates an alarmingly low awareness regarding liver disease in this T2D population in clinical practice.[10] Liver enzymes are usually not elevated in NAFLD, which impedes diagnosis of NAFLD at an early stage and requires further imaging or invasive, histological diagnostics.[6] This could be the reason for the low numbers of ICD-coded diagnoses of NAFLD in this large and accurately managed registry. However, measuring liver enzymes in combination with ultrasound diagnostics should be standard to further characterize CVD risk in patients with diabetes and might be feasible in clinical routine.

The relevance of insulin resistance for the development of NAFLD has also been shown in a recent analysis of the German Diabetes Study by clustering diabetes into subgroups[11,12] in patients with newly diagnosed diabetes. The cluster of patients with "severe insulin-resistant diabetes" displayed an excess risk of developing NAFLD as well as mild fibrosis at 5-year follow-up.[12,13]

Interestingly, a link between elevated liver enzymes and diabetes-associated complications within a large clinical cohort of patients with T2D has not yet been characterized. This analysis reveals a clear association between elevated liver enzymes and extra-hepatic comorbidities and macro- as well as microvascular diabetes complications such as arterial hypertension, dyslipidaemia, myocardial infarction, CAD, PAD, microalbuminuria and CKD. Elevated liver enzymes could represent an epiphenomenon in this context of high CVD risk patients who could benefit from multifactorial drug treatment.[14] Highlighting NAFLD as an integral part of the metabolic syndrome,[15] our data also show a significant association between elevated liver enzymes and dyslipidaemia.

In line with recent evidence,[16,17] we expected the lowest prevalence of elevated liver enzymes in patients on SGLT2 inhibitor and/or GLP-1RA treatment. As expected, the proportion of elevated liver enzymes was lowest in patients receiving SGLT2 inhibitors or a resolution have been reported recently.[18] However, it should be emphasized that this is a cross-sectional analysis that precludes conclusions on causality. Nevertheless, if the promising data[16,18] hold true, specific therapies may not only improve glucose control but also liver injury. In addition, these data underline the possible important role of lifestyle intervention as a treatment option for liver injury.

A major strength of this study is the large dataset obtained from the DPV registry and its potential to provide broad insight into routine clinical practice of diabetes care. The large dataset deriving from daily clinical practice further allows conclusions to be drawn on the general population of patients with T2D. To our knowledge, this is the largest analysis on elevated liver enzymes in T2D to date.

Nevertheless, the study has some major limitations that need to be addressed. Due to data structure and the observational nature of the DPV registry, this analysis was only able to find associations rather than causal effects. Longitudinal studies and more detailed assessment of insulin resistance and liver morphology are needed to further characterize the clinical relationship between elevated liver enzymes and comorbidities in T2D. Furthermore, as with all registry-based trials, certain systematic and nonsystematic reporting biases cannot be ruled out completely for the underlying database. Furthermore, we do not have histological evaluation for definitive diagnosis of NAFLD, Fibrosis-4 scoring and or other diagnostic informations.

In summary, this study demonstrates that, based on a surrogate variable, that is, elevated liver enzymes, NAFLD is widely underdiagnosed and the awareness of liver injury in patients with T2D is alarmingly low. Insulin resistance and other metabolic surrogates, for example, high BMI and HbA1c indicate an elevated risk of fatty liver disease. The strong association between liver enzymes and diabetes complications should raise awareness of the need to measure liver enzymes regularly and at an early stage of T2D.

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CONFLICT OF INTEREST

M.R. reports personal fees from Eli Lilly, Poxel S.A. Société, Boehringer-Ingelheim, Terra Firma, Sanofi, Servier Labatories, Novo Nordisk, Fishawack Group, Novartis, Target Pharmasolutions, Gilead Sciences, Kenes Group, Bristol-Myers Squibb, Intercept Pharma, Inventiva, AstraZeneca and Pfizer, all outside the submitted work.

who could benefit from multifactorial drug treatment.[14] Highlighting NAFLD as an integral part of the metabolic syndrome,[15] our data also show a significant association between elevated liver enzymes and dyslipidaemia.

In line with recent evidence,[16,17] we expected the lowest prevalence of elevated liver enzymes in patients on SGLT2 inhibitor and/or GLP-1RA treatment. As expected, the proportion of elevated liver enzymes was lowest in patients receiving SGLT2 inhibitors or a combination of SGLT2 inhibitors and GLP-1RAs. The proportion of patients with elevated liver enzymes in this analysis was highest in patients on GLP-1RAs. This unexpected finding could also be biased by recently initiated GLP-1RA treatment in patients with already elevated liver enzymes since promising effects of GLP-1 on NASH

analysis.

CONFLICT OF INTEREST

M.R. reports personal fees from Eli Lilly, Poxel S.A. Société, Boehringer-Ingelheim, Terra Firma, Sanofi, Servier Labatories, Novo Nordisk, Fishawack Group, Novartis, Target Pharmasolutions, Gilead Sciences, Kenes Group, Bristol-Myers Squibb, Intercept Pharma, Inventiva, AstraZeneca and Pfizer, all outside the submitted work. S.M.M. reports personal fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daichii-Sanyo, Gilead, Ipsen, Lilly, MSD, Novartis, Novo Nordisk, Pfizer, Sandoz and Sanofi, all outside the submitted work. S.M., A.J.E., M.H., M.L., S.K., J.S., M.R., S.M.M. and R.W.H. declare no competing interest.

AUTHOR CONTRIBUTIONS

Sebastian M. Meyhöfer, **Reinhard W. Holl**, **Alexander J. Eckert**, **Michael Roden** and **Svenja Meyhöfer**: designed the analysis. **Sebastian M. Meyhöfer**, **Reinhard W. Holl**, **Alexander J. Eckert**, **Michael Hummel**, **Markus Laimer**, **Michael Roden**, **Stephan Kress**, **Jochen Seufert**, and **Svenja Meyhöfer**: collected the data. **Sebastian M. Meyhöfer**, **Reinhard W. Holl**, **Alexander J. Eckert**, **Michael Roden** and **Svenja Meyhöfer**: interpreted data. **Svenja Meyhöfer**: researched the literature and wrote the manuscript. **Alexander J. Eckert**, **Michael Hummel**, **Markus Laimer**, **Stephan Kress**, **Jochen Seufert**, **Michael Roden**, **Sebastian M. Meyhöfer**, and **Reinhard W. Holl**: reviewed the manuscript. **Sebastian M. Meyhöfer** and **Reinhard W. Holl**: take responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14616.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol*. 2015;62(1):S47-S64.
2. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2018;15(1):11-20.
3. Lonardo A, Sookoian S, Pirola CJ, Targher G. Non-alcoholic fatty liver disease and risk of cardiovascular disease. *Metabolism*. 2016;65(8):1136-1150.
4. Roden M, Shulman GI. The integrative biology of type 2 diabetes. *Nature*. 2019;576(7785):51-60.
5. Masarone M, Rosato V, Aglitti A, et al. Liver biopsy in type 2 diabetes mellitus: steatohepatitis represents the sole feature of liver damage. Aspichueta P, editor. *PLoS ONE*. 2017;12(6):e0178473.
6. Ghouri N, Preiss D, Sattar N. Liver enzymes, nonalcoholic fatty liver disease, and incident cardiovascular disease: a narrative review and clinical perspective of prospective data. *Hepatology*. 2010;52(3):1156-1161.
7. Nannipieri M, Gonzales C, Baldi S, et al. Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City diabetes study. *Diabetes Care*. 2005;28(7):1757-1762.
8. Lee DY, Han K, Yu JH, et al. Prognostic value of long-term gamma-glutamyl transferase variability in individuals with diabetes: a nationwide population-based study. *Sci Rep*. 2020;10(1):15375.
9. Grabert M, Schweiggert F, Holl RW. A framework for diabetes documentation and quality management in Germany: 10 years of experience with DPV. *Comput Methods Programs Biomed*. 2002;69(2):115-121.
10. Ray K. NAFLD—the next global epidemic. *Nat Rev Gastroenterol Hepatol*. 2013;10(11):621-621.
11. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018;6(5):361-369.
12. Zaharia OP, Strassburger K, Strom A, et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol*. 2019;7(9):684-694.
13. Pafili K, Roden M. Non-alcoholic fatty liver disease (NAFLD) from pathogenesis to treatment concepts in humans. *Mol Metab*. 2020 Nov;50:101122.
14. Sasso FC, Pafundi PC, Simeon V, et al. Efficacy and durability of multifactorial intervention on mortality and MACEs: a randomized clinical trial in type-2 diabetic kidney disease. *Cardiovasc Diabetol*. 2021;20(1):145.
15. Galiero R, Caturano A, Vetrano E, et al. Pathophysiological mechanisms and clinical evidence of relationship between nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease. *Rev Cardiovasc Med*. 2021;22(3):755-768.
16. Kahl S, Gancheva S, Straßburger K, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: a randomized, double-blind, phase 4, placebo-controlled trial. *Diabetes Care*. 2020;43(2):298-305.
17. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387(10019):679-690.
18. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med*. 2020;384(12):1113-1124. NEJMoa2028395.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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