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Prevalence of elevated liver enzymes in adults with type 1 diabetes mellitus in routine clinical care

A multicenter analysis in 9226 adults with type 1 diabetes mellitus from the Austrian/German Diabetes prospective documentation system

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Abstract

Aims. To assess the prevalence of elevated liver enzymes in adults with type 1 diabetes mellitus (T1DM) in routine clinical care and the association with cardiovascular risk profile in the Diabetes-Prospective-Documentation (DPV) network in Germany and Austria.

Methods. This cross sectional observational study from the DPV registry includes data from 45519 adults with T1DM at 478 centers up to 9/2016. Liver enzyme measurements were available in 9226 (29%) patients at 270 centers and were analyzed for increased alanine aminotransferase (ALT; men>50 U/l, women: >35U/l) and/or aspartate aminotransferase (AST; men >50 U/l, women >35U/l) and/or gamma-glutamyltransferase (GGT; men >60U/l, women>40 U/l). A subgroup analysis in patients in whom two or more ALT measurements were available (n=2335, 25%) and whose ALT was increased at least twice (men:>30 U/l, women >19U/) was performed. Associations with glycemic control, cardiovascular risk factors and late complications were investigated with multiple regression analyses.

Results. Twenty percent (19.8%, n=1824) had increased liver enzyme(s) on one or more occasions. Increased liver enzymes were associated with worse glycemic control and higher BMI (both p<0.0001), dyslipidemia (OR:1.75, 95%CI: 1.54-2.0), hypertension (OR:1.48, 95%CI:1.31-1.68), myocardial infarction (OR:1.49; 95%CI:1.17-1.91) and end stage renal disease (OR:1.59; 95%CI:1.17-2.17). ALT was increased twice in 29% and was associated with worse glycemic control (p<0.0001), higher BMI (p<0.0001), hypertension (OR:1.58, 95%CI:1.26-1.97) and dyslipidemia (OR:1.89, 95%CI:1.51-2.37).

Conclusions. In this clinical audit in adults with T1DM, elevated liver enzymes on routine assessment were associated with a less favorable cardiovascular risk profile and with poorer glycemic control.

Abbreviations:
T1DM- type 1 diabetes mellitus
DPV- Diabetes-Prospective-Documentation network in Germany and Austria
ALT- alanine aminotransferase
AST- aspartate aminotransferase
GGT- gamma-glutamyl transferase

Introduction

The clinical management of Type 1 diabetes mellitus (T1DM) focuses on preventing and treating acute as well as chronic complications by optimizing glycemic control and tackling additional risk factors. This includes routine screening for nephropathy, retinopathy and neuropathy to allow early secondary prevention [1]. Annual assessment of liver function is recommended in diabetes clinical practice guidelines [1] because diabetes mellitus doubles the risk for chronic non alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma [2, 3]. Type 2 diabetes and NAFLD share insulin resistance/hyperinsulinemia as underlying pathophysiology, therefore NAFLD is a well documented comorbidity of type 2 diabetes [4-6].

In contrast, the clinical significance of measuring liver enzymes in T1DM as part of the annual screening for complications is unclear: T1DM is an autoimmune condition with absolute insulin deficiency and is not per se usually accompanied by features of metabolic syndrome. However, the prevalence of the metabolic syndrome is increasing in both the general population, and in people with T1DM [7]. The cardiovascular risk profile in people with T1DM demands prescription of drugs that can have hepatotoxic side effects.

The real-life clinical practice of routinely measuring liver enzymes as well as the prevalence of increased liver enzymes in people with T1DM in routine clinical care, have not as yet been documented in larger surveys. Therefore it seemed timely to assess the prevalence of elevated liver enzymes in adults with T1DM in a cross sectional multicenter and multinational clinical audit database. Further we wanted to investigate associations between increased liver enzymes, glycemic control, cardiovascular risk profile and diabetes late complications in people with T1DM.

Subjects and Methods

Data collection.

The German/Austrian Diabetes Patienten Verlaufsdokumentation (DPV) prospective documentation system is a nationwide multicentre survey [8] founded in 1990, comprising up until September 2016 data from 452508 patients.

The individual centers enter their patient data into a standardized electronic patient record. The anonymized data sets are exported biannually to the central database in Ulm, Germany, where the data and diagnoses undergo a plausibility check and queries are returned to participating centers. Once the queries have been resolved the data are aggregated into a cumulative database for clinical research and quality assurance. The DPV database is a resource for clinical quality management and benchmarking as well as for research .

All people with T1DM over the age of 20 years, in whom insulin therapy was clearly documented, were considered for this analysis. People with type 2 diabetes, people with other forms of diabetes (secondary to e.g. cystic fibrosis or hemochromatosis, gestational diabetes) were excluded. Of the 111498 people with T1DM in the DPV registry, there were 45519 adults with T1DM over the age of 20 years. Liver enzymes had to be measured at least once in the previous 12 months (from the date of data extraction). Patients with a history of hepatitis, celiac disease, alpha-1-antitrypsin deficiency, alcoholism and persons consuming >=24g (males) or >=12g (females) alcohol per day were excluded from the analysis as per national recommendations for maximum alcohol consumption (http://www.drinkingandyou.com/site/pdf/Sensibledrinking.pdf).

History of celiac disease was an exclusion criterion, because celiac disease per se can be associated with increased liver transaminases [9]. A detailed flow-chart is provided in figure 1.

The analyses of the anonymized routine clinical data within the German/Austrian Diabetes Prospective Documentation Initiative (DPV) have been approved by the Ethics Committee of the Medical Faculty of the University of Ulm and the local institutional review boards.

The data forming the basis of this report are anthropometry (age, sex, body mass index, waist circumference, diabetes duration), diabetes therapy modality (conventional insulin therapy- i.e. twice daily mix-insulin, intensified insulin therapy according to basis-bolus-principle, continuous subcutaneous insulin infusion with insulin pumps), general data on medication and self reported alcohol intake. Migration background was defined as having either a mother and/or a father who was not born in Austria or Germany. Laboratory data were derived from each center's local routine laboratory measurements and included HbA1c, lipid profile and liver enzymes [including Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT)]. Local HbA1c values were mathematically standardized to the Diabetes Control and Complications Trial (DCCT) reference range (20-42mmol/l; 4.05-6.05%) using the multiple-of-the-mean transformation method [10, 11].

Data analyses.

Increased liver enzymes

Increased liver enzymes were defined as one or more measurement of:

Alanine aminotransferase (ALT) >50 U/l in men/ >35 U/l in women, aspartate aminotransferase (AST) >50 U/l in men/ >35 U/l in women and/or γ -glutamyl transferase (GGT) >60 U/l in men/>40 U/l, according to the definition of the German Liver Foundation (http://www.deutsche-leberstiftung.de/check-up/GPT-Faltblatt-0109-NETZ.pdf).

An additional analysis was performed with lower cut-off values for ALT (males >=30 U/L and females (>=19 U/L) [12], categorizing those patients into the group of T1DM with increased ALT, whose ALT was above this threshold in at least two measurements.

Comorbidities and complications.

Hypertension was defined by the use of antihypertensive medication or by increased systolic (>=140mmHg) and/or diastolic (>=90mmHg) arterial blood pressure according to current guidelines [13]. Dyslipidemia was defined as either taking lipid modifying drugs or having decreased high-density lipoprotein (HDL) cholesterol values (<35mg/dl), or by at least one increased value of total cholesterol (>200mg/dl), low density lipoprotein (LDL) cholesterol (>130mg/dl), or triglycerides (>150mg/dl) values.

Data on prevalence of late complications including end stage renal disease, myocardial infarction, stroke, or major lower limb amputation were available from the DPV database. End stage renal disease was defined as either having received a renal transplantation, being on hemo- or peritoneal dialysis treatment, or a calculated eGFR below 15ml/min/1.73 [14].

In order to address the issue of potential heterogeneity between centers as to the frequency with which they are measuring liver enzymes, we conducted two additional

analyses to better understand the data set available: We compared data from centers in which liver enzymes were measured in more than 50% of their patients with data from centers that conduct less frequent measurements.

A comparison was made between patients in whom liver enzymes were available and those patients whose liver enzymes were not measured/ reported. The results are provided as supplemental material.

Statistical analyses were performed using the software package SAS version 9.4 (Statistical Anlaysis Software, SAS Institute; Cary, NC). Sociodemographic and clinical characteristics are presented as median and interquartile range (Q1,Q3) or as percentage, unless stated otherwise. Two-sided *p* value of <0.05 was considered to be significant. For group comparison, Wilcoxon testing for continuous and X^2 tests for categorical data were used. The Holm method was applied to adjust p-values for multiple comparisons. Multiple logistic regression models for dichotomous variables (prevalence of hypertension, dyslipidemia, macrovascular complications and end stage renal disease) and multiple linear regression analyses for continuous variables (age, BMI, HbA1c, insulin doses) were applied for adjustment.

Results

Data on liver enzymes from the previous 12 months were available from 270 centres. A total of 9226 patients (29%) of the 32075 patients fulfilling the inclusion criteria had their liver transaminases measured and reported at least once in the 12 months observation period (Figure 1). Of the 270 centers that were reporting liver enzyme measurements in their patients, 83 centres measured liver enzymes in at least 50% of their patients (Table 4, supplemental material).

Total cohort.

More than half (56%) of the patients were using intensified basis bolus insulin therapy using insulin pens, an additional 29% were using insulin pumps and 15% were on conventional insulin therapy. In this cohort there is a high proportion of well-controlled patients (40% with an HbA1c below or equaling 7.5%), but 33% have an HbA1c above 9% (Table 1, third column).

Of the 9226 patients, 1824 (19.8%) had increased liver enzymes in one or more measurement(s), of which 1254 (69%) had increased GGT, 870 (48%) had increased ALT and 566 (31%) increased AST. In 243 (13%) patients all three liver enzymes were increased.

Hypertension was present in 47% (38% on antihypertensive drugs) and dyslipidemia in 63% (21% on lipid lowering drugs). A history of myocardial infarction was present in 3.9%, 2.8% had suffered a stroke, 0.7% had a major limb amputation and 2.7% had end stage renal disease (Table 1, third column).

Subgroup comparison between patients with increased and normal liver enzymes.

Characteristics of both groups are shown in the fourth and fifth columns of Table 1. Patients with increased liver enzymes were older, had a higher BMI (both p values <0.0001) and larger waist circumference ($p<0.0005$) than the patients with normal liver enzymes, while duration of diabetes, sex distribution and proportion of people with background of migration did not differ (Table 1). The group with increased liver enzymes had worse glycemic control ($p<0.00001$), a higher proportion of patients using conventional insulin therapy and a lower proportion of patients using intensified or insulin pump therapy than in those with normal liver enzyme levels (all $p<0.01$)

(Table 1). Lipid modifying drugs were taken by 19% in the group with normal liver enzymes and 29% in the group with increased liver enzymes (both p<0.00001).

After adjustment for age, sex, HbA1c, diabetes duration, migration background and treatment center in linear regression models, age, BMI, HbA1c and the daily insulin per body weight doses were significantly higher in the group with increased liver enzymes than in the group with normal liver enzyme measurements (all adjusted values are presented in Table 2; corresponding p-values <0.0001, Table 2). In logistic regression models adjusting for age, sex, HbA1c, diabetes duration, migration background and treatment center, people with increased liver enzymes were more likely to have hypertension (OR: 1.48, 95% CI:1.31-1.68) and dyslipidemia (OR 1.75, 95% CI: 1.54-2.00) and more likely to have had a myocardial infarction and to have end stage renal disease (OR were 1.5 and 1.6, respectively, Table 2), but there was no association with the prevalence of history of stroke or major amputations (Table 2).

Subgroup comparison between patients with increased ALT and normal ALT.

Two (or more) ALT measurements per patient were available in a subgroup of 2335 patients (25%). ALT was increased at least twice in 686 (29%) of these patients. Patients with increased ALT were older, had a higher BMI and waist circumference, had a higher HbA1c and a more adverse lipid profile (Table 3, supplemental material). After adjustment for age, sex, HbA1c, diabetes duration, migration background and treatment center in linear and logistic regression models, patients with ALT were more likely to have hypertension (OR 1.58, 95% CI: 1.26-1.97) and dyslipidemia (OR 1.89, 95% CI: 1.51-2.37), to be older and have a higher HbA1c and BMI (Table 4, supplemental material), but there were no differences in prevalence of

myocardial infarction, stroke, major amputation or end stage renal disease (Table 4, supplemental material).

When comparing the group of patients who were included based on the criteria above (see methods section) and the availability of liver enzyme measurements (n=9226) with those who fulfilled all inclusion criteria but had no liver enzyme measurements available (n= 22849), the patients with available liver enzyme measurements were younger, had a higher proportion of people with migration background, had a higher BMI and waist circumference, higher HbA1c and daily insulin doses, lower triglyceride levels and lower blood pressure (Table 5, supplemental material). The prevalences of MCI, stroke, end stage renal disease were not different, but the prevalence of hypertension and dyslipidemia was higher in the patients in whom liver enzymes have been reported (Table 5, supplemental material).

The comparison between patients from centers in which liver enzymes were measured in >50% of the patients (n= 5073, 55%) and those coming from centers with less frequent liver enzyme measurements (n=4153, 45%) showed that patients from centers with frequent liver enzyme measurements had a longer duration of diabetes, a higher proportion with migration background, higher HbA1c and systolic blood pressure (Table 6, supplemental material). When analyzing only data from centers that measure frequently, the proportion of patients with increased liver enzymes was 19.4%, which is similar to the proportion reported in the total dataset (19.8%). The prevalence of MCI, stroke and major amputation did not differ, but there was a higher prevalence of end stage renal disease and hypertension in patients treated at centers with frequent measurement of liver enzymes (Table 6, supplemental material).

Discussion

In this report we describe the prevalence of increased liver enzymes in a multicenter audit of 45519 adults with T1DM in routine clinical care. After exclusion of people with health factors known to influence hepatic function, liver enzyme measurements were available in 29% of the patients. Of these, 20% had increased liver enzymes during the course of routine clinical follow up. Elevation of liver enzymes was associated with worse glycemic control, less favorable cardiovascular risk profile and a higher prevalence of diabetes late complications (myocardial infarction and end stage renal failure).

For reports such as this to be useful to practicing clinicians, it is essential to put them in context. The prevalence of increased liver enzymes observed here compares to estimates of 10-21% in the general population [15-17] and 12% to 71% in Type 2 diabetes [18-21]. Comparing the results from our study with data from the general population is difficult because the latter will, for example, include individuals with undiagnosed liver pathologies, or individuals consuming alcohol in excess of the recommended levels. In contrast, we have excluded from our analyses people with known liver pathologies and excessive alcohol consumption. Further, people with an established diagnosis of T1DM are more likely to be taking statin therapy by virtue of the awareness of diabetes physicians of the cardiovascular risk.

A smaller observational study in approximately 900 patients with T2DM and T1DM noted that increased ALT was increased in 2-35% of T1DM and 4-51% in T2DM, depending on the cut-off used [22]. In their subgroup with patients with T1DM applying the same lower ALT threshold as we have used in our subgroup analysis, the

35% of patients had increased ALT was 35%, which is a higher proportion than in our cohort [22].

Another issue that arises in the analyses of large datasets is that no clear consensus exists as to where to set the cut-off thresholds for increased liver enzymes in T1DM, such that the proportion of people with increased measurements depends on the diagnostic threshold applied. We have used different diagnostic criteria within the same DPV dataset, one applying national liver association guidelines and one using lower ALT cut-off but in two measurements as suggested elsewhere [12]. Using these two approaches the proportions of patients with elevated liver enzymes changes from 20 to 29%. However, the association with poorer glycemic control and less favorable cardiovascular risk profile (dyslipidemia and hypertension) was consistent in both analyses, whereas the association with diabetes complications (myocardial infarction and end stage renal disease) was only significant in the analysis applying the higher liver enzyme cut off thresholds of the national guidelines. This would suggest that a lower ALT cut-off has the potential to identify patients with higher cardiovascular risk at an earlier stage.

In the present cross sectional analysis in people with T1DM in the DPV registry, the group with increased liver enzymes had a more adverse cardiovascular risk profile with a high prevalence of hypertension and dyslipidemia and worse glycemic control than those with normal liver enzymes. Patients with elevated liver enzymes were also more obese, suggesting a higher level of insulin resistance. Notably, the odds ratios for myocardial infarction and end stage renal disease were 1.5 and 1.6, respectively, when compared with the patients with normal liver enzymes and after adjustment for age, HbA1c and other factors. This is in line with observations from a large,

population-based, longitudinal study that suggested an association between elevated GGT levels and all-cause and cardiovascular mortality in men [23] , and from smaller clinic-based reports in people with T1DM in whom NAFLD was associated with an increased incidence of chronic kidney disease [24] and with a greater prevalence of retinopathy and nephropathy [25].

Given the audit-style nature of this report it is not possible to determine whether the increased rates of diabetes complications in the patients with T1DM who have increased liver enzymes are a consequence of shared conventional risk factors (hypertension, dyslipidemia, hyperglycemia), or whether the increased liver enzymes represent an independent risk marker in this situation. The former seems more likely. Further, longitudinal observational studies will be needed to better understand the relationship between increased liver enzymes and comorbidities and complications in people with T1DM and to determine the diagnostic thresholds for increased liver enzymes clinically relevant for people with T1DM.

Although the DPV has the potential to provide insight into routine clinical practice by virtue of its size, our study has obvious limitations. First, the real-world character of a clinical database is apparent in the 29% of patients in whom liver enzyme measurements were available. This heterogeneity of clinical practice between centers has the potential to introduce bias into our dataset. Patients who did not have their liver enzymes reported were younger, leaner, had a better diabetes control and lower prevalence of hypertension and dyslipidemia, which may have contributed to an individual clinician's decision not to measure liver enzymes.

The additional comparison made between patients from centers that measure liver enzymes in over 50% of their patients and patient from centers that measure in less

than 50% of patients confirmed that patients from centers with frequent liver enzyme measurements had a longer diabetes duration, worse diabetes control, more likely to have a migration background and had a higher prevalence of hypertension and end stage renal disease, which altogether may have contributed to local clinical routine standards more in favor of a risk factor assessment including liver enzymes.

Conclusion.

In this clinical audit in adults with T1DM, elevated liver enzymes on routine clinical assessment were associated with a less favorable cardiovascular risk profile and poorer glycemic control. We consider these observations worthy of reporting as they may, if supported by future longitudinal studies from other groups, provide an additional factor in the cardiovascular risk stratification of people with T1DM.

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Uni-Klinik Innere Medizin, Kirchheim-Noertingen Innere, Limburg Innere Medizin, Hildesheim Kinderarztpraxis, Trostberg Innere, Wangen Oberschwabenklinik Innere Medizin, Saaldorf-Surheim Diabetespraxis, Heilbronn Innere Klinik, Innsbruck Universitaetsklinik Innere, Gelsenkirchen Kinderklinik Marienhospital, Marktredwitz Innere Medizin, Murnau am Staffelsee - diabetol. SPP, Stolberg Kinderklinik, Berlin Endokrinologikum, Deggendorf Medizinische Klinik II, Erfurt Kinderklinik, Rastatt Kreiskrankenhaus Innere, Braunfels-Wetzlar Innere, Ludwigshafen diabetol. SPP, Osterkappeln Innere, Wittenberg Innere Medizin, Wien Uni-Kinderklinik, M¸nster Clemens-Hospital Innere, Linz Krankenhaus Barmherzige Schwestern Kardiologie Abt. Int. II, Wetzlar Schwerpunkt-Praxis, Plauen Vogtlandklinikum, Berlin Evang. Krankenhaus Koenigin Elisabeth, Rostock Universitaet Innere Medizin, Oldenburg Schwerpunktpraxis, Bottrop Knappschaftskrankenhaus Innere, Innsbruck Universitaetskinderklinik, Berlin Virchow-Kinderklinik, Rosenheim Schwerpunktpraxis, Koblenz Kemperhof 1. Med. Klinik, Magdeburg Uni-Kinderklinik, Bremen - Kinderklinik Nord, Herdecke Kinderklinik, Linz AKH - 2. Med, Goeppingen Kinderklinik am Eichert, Mannheim Uni-Kinderklinik, Hanau St. Vincenz - Innere, Heidelberg Uni-Kinderklinik, Wien Uni Innere Med III, Asbach Kamillus-Klinik Innere, Krefeld Innere Klinik, Augsburg Kinderklinik Zentralklinikum, Luxembourg - Centre Hospitalier, Wilhelmshaven St. Willehad Innere, Recklinghausen Dialysezentrum Innere, Schwerin Innere Medizin, Wiesbaden Kinderklinik DKD, Dortmund-St. Josefshospital Innere, Mannheim Uniklinik Innere Medizin, Sinsheim Innere, Stade Kinderklinik, Muenster paediat. Schwerpunktpraxis, Bielefeld Kinderklinik Gilead, Berlin St. Josephskrankenhaus Innere, Berlin Vivantes Hellersdorf Innere, Bocholt Kinderklinik, Graz Universitaets-Kinderklinik, Hinrichsegen-Bruckm¸hl Diabetikerjugendhaus, Moedling Kinderklinik, Berlin DRK-Kliniken, Hameln Kinderklinik, Herford Klinikum Kinder & Jugendliche, Kaiserslautern-Westpfalzklinikum Kinderklinik, Berchtesgaden CJD, Dornbirn Kinderklinik, Moers Kinderklinik, Osnabrueck Christliches Kinderhospital, Tuebingen Uni-Kinderklinik, Coesfeld Kinderklinik, Ottobeuren Kreiskrankenhaus, Ravensburg Kinderklink St. Nikolaus, Oberhausen Kinderpraxis, Aurich Kinderklinik, Erlangen Uni Innere Medizin, Kempen Heilig Geist - Innere, Kirchen DRK Krankenhaus Kinderklinik, Koblenz Kinderklinik Kemperhof, Mainz Uni-Kinderklinik, Heidenheim Kinderklinik, Trier Kinderklinik der Borromaeerinnen, Berchtesgaden MVZ Innere Med, Berlin Klinik St. Hedwig Innere, Hamburg Endokrinologikum, Lindenfels Luisenkrankenhaus Innere 2, Muenster Uni-Kinderklinik, Gera Kinderklinik, Hamburg-Nord Kinder-MVZ, Heide Kinderklinik, Lienz Diabetesschwerpunktpraxis fuer Kinder und Jugendliche, Muenchen-Schwabing Kinderklinik, Wiesbaden Horst-Schmidt-Kinderkliniken, Berlin Schlosspark-Klinik Innere, Eutin St.-Elisabeth Innere, Garmisch-Partenkirchen Kinderklinik, Hagen Kinderklinik, Hildesheim GmbH - Innere, Krefeld Kinderklinik, Koeln Kinderklinik Amsterdamerstrasse, M¸nchen-Gauting Kinderarztzentrum, Neunkirchen Marienhausklinik Kohlhof Kinderklinik, Reutlingen Kinderarztpraxis, Schwaebisch Hall Diakonie Kinderklinik, Stuttgart Bethesda Agaplesion, Weingarten Kinderarztpraxis, Wilhelmshaven Reinhard-Nieter-Kinderklinik, Aachen - Innere RWTH, Augsburg Innere, Bad Mergentheim - Gemeinschaftspraxis DM-dorf Althausen, Bonn Uni-Kinderklinik, Dortmund Medizinische Kliniken Nord, Kiel Staedtische Kinderklinik, Lappersdorf Kinderarztpraxis, Ludwigsburg Innere Medizin, Ludwigsburg Kinderklinik, Moers - St. Josefskrankenhaus Innere, Oberhausen Kinderklinik, Scheidegg Reha-Kinderklinik Maximilian, Suhl Kinderklinik, Ulm Schwerpunktpraxis Bahnhofsplatz, Waldshut Kinderpraxis, Bad

Orb Spessart Klinik Reha, Darmstadt Kinderklinik Prinz. Margaret, Essen Diabetes-Schwerpunktpraxis, Frankenthal Kinderarztpraxis, Freiburg Kinder-MVZ, Gieflen Uni-Kinderklinik, Haren Kinderarztpraxis, Heidenheim Arztpraxis Allgemeinmed, Kassel Klinikum Kinder- und Jugendmedizin, Koeln Uni-Kinderklinik, M¸hlacker Enzkreiskliniken Innere, Sylt Rehaklinik, Waldshut-Tiengen Kinderpraxis Biberbau, Wien SMZ Ost Donauspital, Worms Kinderklinik, Wuppertal Kinderklinik, Aachen - Uni-Kinderklinik RWTH, Bad Driburg / Bad Hermannsborn Innere, Bremen Zentralkrankenhaus Kinderklinik, Duesseldorf Uni-Kinderklinik, Freiburg Uni-Kinderklinik, Goeppingen Innere Medizin, Hannover Kinderklinik auf der Bult, Iserlohn Innere Medizin, Lilienthal Diabeteszentrum, Magdeburg Staedtisches Klinikum Innere, Moenchengladbach Kinderklinik Rheydt Elisabethkrankenhaus, M¸nchen Schwerpunktpraxis, Neuwied Kinderklinik Elisabeth, Offenbach/Main Kinderklinik, Oldenburg Kinderklinik, Oschersleben MEDIGREIF Bˆrdekrankenhaus, Pfullendorf Innere Medizin, Rastatt Gemeinschaftspraxis, Regensburg Kinderklinik St. Hedwig, Rendsburg Kinderklinik, Rotenburg/W¸mme Agaplesion Diakonieklinikum Kinderabteilung, Spaichingen Innere, St. Pˆlten Kinderklinik, Ulm Uni-Kinderklinik, Wels Innere, Aue Helios Kinderklink, Bad Hersfeld Kinderklinik, Bad Koesen Kinder-Rehaklinik, Bad Lauterberg Diabeteszentrum Innere, Bad Salzungen Kinderklinik, Bayreuth Innere Medizin, Berlin Parkklinik Weissensee, Bochum Universitaetskinderklinik St. Josef, Bremerhaven Kinderklinik, Coesfeld/Duelmen Innere Med., Datteln Vestische Kinderklinik, Duisburg-St.Johannes Helios, Eisleben Lutherstadt Helios-Klinik, Erlangen Uni-Kinderklinik, Feldkirch Kinderklinik, Hamburg Kinderklinik Wilhelmstift, Hamm Kinderklinik, Hanau Kinderklinik, Hannover Kinderklinik MHH, Heringsdorf Inselklinik, Hof Kinderklinik, Itzehoe Kinderklinik, Kaiserslautern Kinderarztpraxis, Kempten Oberallgaeu Kinderklinik, Leverkusen Kinderklinik, Linz Landes-Kinderklinik, L¸beck Uni-Kinderklinik, Marburg - UKGM Endokrinologie & Diabetes, Minden Kinderklinik, Mutterstadt Kinderarztpraxis, Muenchen Kinderarztpraxis diabet. SPP, M¸nchen von Haunersche Kinderklinik, Nauen Havellandklinik, N¸rnberg Cnopfsche Kinderklinik, Oberhausen St.Clemens Hospitale Sterkrade, Oy-Mittelberg Hochgebirgsklinik Kinder-Reha, Pforzheim Kinderklinik, Prenzlau Krankenhaus Innere, Rheine Mathiasspital Kinderklinik, Saarbruecken Kinderklinik Winterberg, Salzburg Kinderklinik, Schweinfurt Kinderklinik, Siegen Kinderklinik, Ulm Endokrinologikum, Weiden Kinderklinik, Weisswasser Kreiskrankenhaus, Wernberg-Koeblitz SPP, Wien Wilhelminenspital 5. Med. Abteilung,

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Legends to Figures

Figure 1.
Flow chart of patient inclusion and exclusion for the final analysis.
DPV, Diabetes Prospective Documentation; ALT, alanine-aminotransferase; AST, aspartate-aminotransferase; GGT, gamma-glutamyl transferase.

Legends to Tables.

Table 1.
Anthropometric, clinical and laboratory characteristics of patients with T1DM with increased ALT, AST and/or GGT compared with patients with normal ALT, AST and GGT and prevalence of diabetes late complications and comorbidities (un-adjusted percentages).
Data are presented as median (Q1, Q3). P-values for subgroup comparisons for continuous variables are derived from non-parametric testing applying Wilcoxon tests and from χ^2 tests for binominally distributed variables. P values adjusted for multiple comparisons using the Holm method.
T1DM, type 1 diabetes mellitus; BMI, body mass index; HbA1c, glycated Hemoglobin A1c; BP, blood pressure; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, gamma-glutamyl-transferase; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high density lipoprotein cholesterol;

Table 2.
Comparison of prevalence of comorbidities and complications by means of logistic regression models (with adjustment for age, sex, diabetes duration, migration background, HbA1c and treatment center) and comparison of age, BMI, insulin doses and HbA1c using linear regression models (*) (with adjustement for age, sex, diabetes duration, migration background, HbA1c and treatment center) between patients with increased and with normal liver enzymes.
Data are presented as means ± standard error of the means and adjusted p-values. OR, odds ratios with 95% CI, confidence intervals. BMI, body mass index; HbA1c, glycated Hemoglobin A1c;

Figure 1.

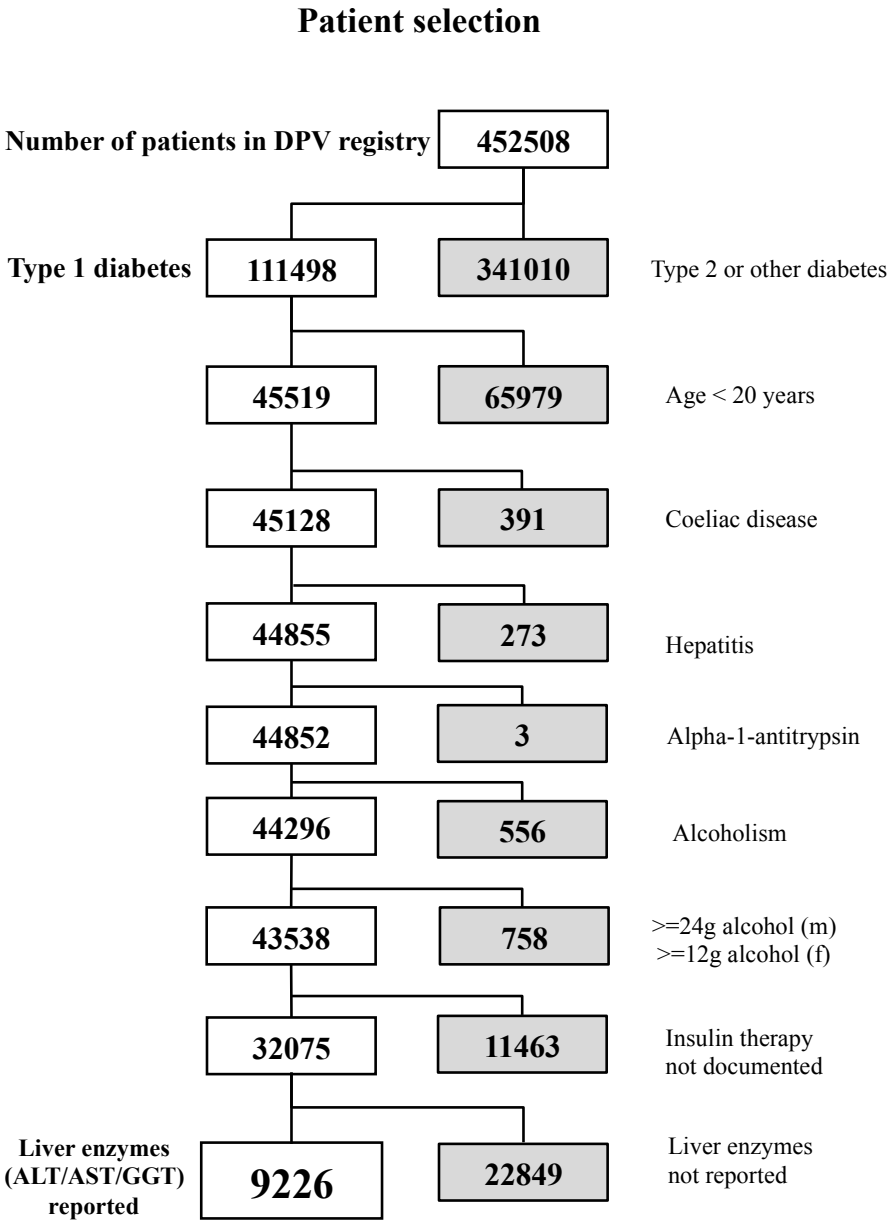
Patient selection
Number of patients in DPV registry
452508
Type 1 diabetes
111498
341010
Type 2 or other diabetes
45519
65979
Age < 20 years
45128
391
Coeliac disease
44855
273
Hepatitis
44852
3
Alpha-1-antitrypsin
44296
556
Alcoholism
43538
758
>=24g alcohol (m)
>=12g alcohol (f)
32075
11463
Insulin therapy
not documented
Liver enzymes
(ALT/AST/GGT)
reported
9226
22849
Liver enzymes
not reported

Table 1.

	Datasets	Total cohort	Increased Liver enzymes	Normal Liver enzymes	p-value
N	9226		1824	7402	
Female (%)	9226	46	49	45	0.2
Age (yrs)	9226	42.2 (27.1, 56.7)	49.4 (36.0, 61.9)	40.0 (25.7, 54.9)	<0.000001
Migration background (%)	9226	4.0	3.6	4.2	1.0
Duration of T1DM (yrs)	9226	15.0 (7.1, 25.9)	15.6 (6.5, 28.8)	14.8 (7.3, 25.4)	1.0
BMI (kg/m^2)	9155	25.0 (22.5, 28.2)	25.7 (22.8, 29.9)	24.8 (22.5, 27.9)	<0.000001
BMI>= 30kg/m^2 (%)	9155	17	25	15	
Waist circumference (cm)	2198	92 (84, 101)	94 (87, 107)	91 (84, 100)	0.0005
HbA1c (%)	9119	7.9 (7.0, 9.1)	8.1 (7.1, 9.8)	7.8 (6.9, 9.0)	<0.000001
HbA1c (mmol/mol)		62 (53, 76)	65 (54, 83)	62 (52, 75)	
HbA1c <=7.5% (%)		40	34	42	
HbA1c > 9.0% (%)		33	32	24	
Insulin dosis (IU/kg/day)	9226	0.62 (0.46, 0.82)	0.62 (0.46, 0.83)	0.62 (0.46, 0.82)	1.0
Diabetes therapy	9226				
Conventional insulin therapy		15%	19%	15%	0.0006
Intensified insulin therapy		56%	60%	55%	0.002
Insulin pump		29%	21%	30%	<0.00001
BP systolic/diastolic (mmHg)	9008	126 (119, 138) /76 (70, 80)	130 (120, 140) /76 (70, 80)	125 (119, 137) /76 (70, 80)	<0.0001/ 1.0
Total cholesterol (mg/dl)	8409	190 (164, 218)	197 (165, 228)	189 (163, 216)	<0.00001
LDL-cholesterol (mg/dl)	7930	107 (85, 132)	110 (84, 140)	106 (85, 130)	0.02
HDL-cholesterol (mg/dl)	8034	58 (46, 72)	54 (41, 69)	59 (48, 73)	<0.00001
Triglycerides (mg/dl)	8252	100 (71, 149)	124 (85, 194)	95 (69, 140)	<0.00001
ALT (U/l)	8681	20 (15, 29)	38 (25, 58)	19 (14, 24)	<0.00001
AST (U/l)	6717	21 (17, 28)	34 (24, 49)	20 (16, 24)	<0.00001
GGT (U/l)	8432	20 (14, 34)	64 (39, 105)	18 (13, 25)	<0.00001
No alcohol consumption		81%	85%	81%	0.02
Alcohol consumption g/day (in those consuming alcohol)	925	5 (3, 10)	6 (3, 11)	5 (2,10)	0.2
Myocardial infarction (%)	9226	3.9	6.4	3.2	<0.00001
Stroke (%)	9226	2.8	4.1	2.5	0.004
Major amputation (%)	9226	0.7	1.4	0.5	0.001
End stage renal disease (%)	9015	2.7	4.1	2.3	0.0004
Hypertension (%)	9082	47	59	44	<0.00001
Dyslipidemia (%)	8671	63	78	60	<0.00001

Table 2.

	Increased Liver enzymes	Normal Liver enzymes	Adj. p value	Odds Ratio (95% CI)
Hypertension (%)	57.3±2.1	47.5±1.7	<0.0001	1.48 (1.31-1.68)
Dyslipidaemia (%)	73.7±1.3	61.5±1.0	<0.0001	1.75 (1.54-2.00)
Myocardial infarction (%)	2.7± 0.4	1.8±0.2	0.002	1.49 (1.17-1.91)
Stroke (%)	1.78±0.3	1.5±0.2	0.28	1.17 (0.88-1.60)
Major amputation (%)	0.66±0.16	0.33±0.07	0.23	1.99 (0.07-57
End stage renal disease (%)	3.0±0.5	1.9±0.2	0.004	1.59 (1.17-2.17)
Age *	39.5±0.8	35.5±0.7	<0.0001	
BMI *	26.4±0.1	25.2±0.1	<0.0001	
Insulin dosis (IU/kg/day) *	0.74±0.01	0.71±0.01	<0.0001	
HbA1c (%)*	8.2±0.1	7.9±0.1	<0.0001	

Table 3.

Subgroup analysis of patients in whom ALT was increased above 30 U/l in males and 19 U/l in females on at least two occasions.

Anthropometric, clinical and laboratory characteristics of the patients with T1DM with increased and normal ALT.

Data are presented as median (Q1, Q3). P-values for subgroup comparisons for continuous variables are derived from non-parametric testing applying Wilcoxon tests and from χ^2 tests for binominally distributed variables. P values adjusted for multiple comparisons using the Holm method.

T1DM, type 1 diabetes mellitus; BMI, body mass index; HbA1c, glycated Hemoglobin A1c; BP, blood pressure; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, gamma-glutamyl-transferase; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high density lipoprotein cholesterol;

Patients with >= 2 ALT measurements available	Increased ALT (>=twice)	Normal ALT	p-value	Total subgroup
N	686	1649	<0.00001	2335
Female (%)	56	42		46
Age (yrs)	46.1 (31.6, 57.9)	41.0 (26.5, 55.8)	<0.002	42.8 (28.2-56.5)
Migration background	3.0	1.5	0.78	2.5
Duration of T1DM (yrs)	15.9 (6.5, 27.7)	15.9 (7.8, 26.4)	1.0	15.9 (7.5-26.7)
BMI (kg/m^2)	26.4 (23.5, 29.9)	25.0 (22.6, 28.0)	<0.00001	25.3 (22.9-28.6)
Waist circumference (cm)	94 (87, 101)	92 (85, 99)	0.15	92 (86-99)
Insulin dosis (IU/kg/ day)	0.62 (0.47-0.81)	0.62 (0.48-0.81)	1.0	0.62 (0.48-0.81)
HbA1c (%)	8.2 (7.3, 9.8)	7.8 (7.0, 8.9)	<0.000001	7.9 (7.1-9.0)
HbA1c (mmol/mol)	66 (56, 83)	62 (53, 73)		63 (54-75)
BP systolic/diastolic (mmHg)	125 (120, 137) /78 (70, 80)	125 (118, 134) /75 (70, 80)	0.9/0.9	125 (119-135)/ 76 (70-80)
Total cholesterol (mg/dl)	200 (172, 228)	185 (162, 212)	<0.000001	189 (164-217)
LDL-cholesterol (mg/dl)	112 (87, 136)	102 (82, 125)	<0.000001	104 (83-128)
HDL-cholesterol (mg/dl)	57 (46, 74)	59 (48, 72)	1.0	59 (47-73)
Triglycerides (mg/dl)	108 (74, 162)	95 (70, 138)	<0.000001	98 (70-147)
ALT U/l	33 (25, 45)	17 (14, 22)	<0.000001	20 (16-28)
AST U/l	29 (23, 39)	20 (16, 24)	<0.000001	21 (17-28)
GGT U/l	27 (16, 46)	17 (13, 26)	<0.000001	19 (13-32)
Myocardial infarction (%)	3.0	4.5	1.0	4.1
Stroke (%)	2.6	2.5	1.0	2.5
Major amputation (%)	1.0	1.0	1.0	1.0
End stage renal disease (%)	3.0	3.6	1.0	3.4
Hypertension (%)	57	47	0.0008	50
Dyslipidemia (%)	76	61	<0.000001	65

Table 4.

Subgroup analysis of patients in whom ALT was increased above 30 U/l in males and 19 U/l in females on at least two occasions.

Comparison of prevalence of comorbidities and complications by means logistic regression models (with adjustment for age, sex, diabetes duration, migration background, HbA1c and treatment center) and of age, BMI, insulin doses and HbA1c using linear regression models (*) (with adjustement for age, sex, diabetes duration, migration background, HbA1c and treatment center) between patients with increased and with normal ALT.

Data are presented as means ± standard error of the means and adjusted p-values.

BMI, body mass index; glycated Hemoglobin A1c;

Patients with >= 2 ALT measurements available	Increased ALT (>= twice)	Normal ALT	Adj. p value	Odds Ratio (95% CI)
Hypertension (%)	60.6±3.0	49.4±2.6	<0.0001	1.58 (1.26-1.97)
Dyslipidaemia (%)	77.9±2.0	65.0±1.9	<0.0001	1.89 (1.51-2.37)
Myocardial infarction (%)	2.4± 0.6	2.9±0.6	0.37	0.80 (0.50-1.29)
Stroke (%)	1.1±12	0.8±9.8	0.43	1.27 (0.70-2.33)
Major amputation (%)	0.74±0.3	0.69 ±0.2	0.89	1.08 (0.003-418)
End stage renal disease (%)	2.2±0.5	2.7±0.4	0.58	0.81 (0.025-25.9)
Age *	40.6±1.3	38.1±1.2	<0.0001	
BMI *	26.5±0.2	25.1±0.2	<0.0001	
Insulin dosis (IU/kg/day) *	0.71±0.02	0.70±0.02	0.59	
HbA1c (%)*	8.4±0.1	7.8±0.1	<0.0001	

Table 5.
Anthropometric, clinical and laboratory characteristics of the total cohort of patients with T1DM in whom liver enzymes were measured compared with patients in whom no liver enzyme measurements were available.
T1DM, type 1 diabetes mellitus; BMI, body mass index; HbA1c, glycated Hemoglobin A1c; BP, blood pressure; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high density lipoprotein cholesterol;

Data are presented as median (Q1, Q3). P-values for subgroup comparisons for continuous variables are derived from non-parametric testing applying Wilcoxon tests and from χ^2 tests for binominally distributed variables. P values adjusted for multiple comparisons using the Holm method.

Comparison patients with liver enzyme measurements available/ not available	**Liver enzymes measured**	**Liver enzymes not measured**	**p-value**
N	9226	22849	
Female (%)	46	47	1.0
Age (yrs)	42.2 (27.0, 56.1)	43.6 (28.4, 58.0)	<0.0001
Migration background	4.0%	1.9%	<0.0001
Duration of T1DM (yrs)	15.0 (7.1, 25.9)	15.0 (6.7, 26.7)	1.0
BMI (kg/m^2)	25.0 (22.5, 28.2)	24.8 (22.3, 28.0)	<0.002
Waist circumference (cm)	92 (84, 101)	89 (81, 98)	<0.00001
HbA1c (%)	7.9 (7.0, 9.1)	7.7 (6.8, 9.1)	<0.00001
HbA1c (mmol/mol)	62 (53, 76)	61 (51, 76)	
Insulin dosis (IU/kg/day)	0.62 (0.46, 0.82)	0.61 (0.45, 0.81)	0.004
BP systolic/diastolic (mmHg)	126 (119, 138) /76 (70, 80)	128 (120, 140) /78 (70, 80)	0.0002/ 0.001
Total cholesterol (mg/dl)	190 (164, 218)	190 (163, 220)	1.0
LDL-cholesterol (mg/dl)	107 (85, 132)	106 (82, 131)	0.1
HDL-cholesterol (mg/dl)	58 (46, 72)	57 (45, 72)	0.1
Triglycerides (mg/dl)	100 (71, 149)	106 (74, 159)	<0.0001
No alcohol consumption	81%	82%	1.0
Alcohol consumption g/day (in those consuming alcohol)	5 (3, 10)	5 (3,10)	1.0
Myocardial infarction (%)	3.9	3.7	1.0
Stroke (%)	2.8	2.7	1.0
Major amputation (%)	0.7	0.7	1.0
End stage renal disease (%)	2.7	3.2	0.1
Hypertension (%)	47	41	<0.000001
Dyslipidemia (%)	63	66	<0.005

Table 6.

Anthropometric, clinical and laboratory characteristics of the patients with T1DM in centers where liver enzymes were measured in at least 50% of the patients (83 of the 270 centres) compared with patients from centers that measure less frequently.

T1DM, type 1 diabetes mellitus; BMI, body mass index; HbA1c, glycated Hemoglobin A1c; BP, blood pressure; LDL-cholesterol, low-density lipoprotein cholesterol; HDL-cholesterol, high density lipoprotein cholesterol;

Data are presented as median (Q1, Q3). P-values for subgroup comparisons for continuous variables are derived from non-parametric testing applying Wilcoxon tests and from χ^2 tests for binominally distributed variables. P values adjusted for multiple comparisons using the Holm method.

	Patients from centres with >=50% patients liver enzymes measured	Patients from centres with <50% patients liver enzymes measured	p-value
N	5073	4153	
Female (%)	47	45	0.9
Age (yrs)	41.8 (27.1, 56.1)	42.6 (27.1, 57.4)	1.0
Migration background	5.6%	2.0%	<0.000001
Duration of T1DM (yrs)	16.0 (7.6, 28.0)	13.9 (6.5, 24.0)	<0.000001
BMI (kg/m^2)	25.0 (22.5, 28.3)	24.9 (22.4, 28.2)	1.0
Waist circumference (cm)	92 (85, 101)	90 (82, 99)	0.06
HbA1c (%)	8.0 (7.1, 9.2)	7.6 (6.8, 9.0)	<0.000001
HbA1c (mmol/mol)	63 (54, 78)	60 (51, 74)	<0.000001
BP systolic/diastolic (mmHg)	125 (118, 137) /75 (70, 80)	128 (120, 139) /76 (70, 80)	0.006/0.1
Total cholesterol (mg/dl)	189 (162, 217)	191 (165, 219)	0.2
LDL-cholesterol (mg/dl)	106 (83, 132)	108 (87, 132)	0.1
HDL-cholesterol (mg/dl)	58 (47, 72)	58 (46, 72)	1.0
Triglycerides (mg/dl)	99 (71, 149)	101 (72, 149)	1.0
Heart attack	3.6%	4.2%	1.0
Stroke	2.7%	3.0%	1.0
Major amputation	0.8%	0.7%	1.0
End stage renal disease	3.3%	1.9%	0.0004
Hypertension	49%	44%	0.0003
Dyslipidemia	63%	63%	1.0