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Diabetes mellitus and autoimmune hepatitis: Demographical and clinical description of a relatively rare phenotype.

Running title: Diabetes and autoimmune hepatitis

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Abstract

Aims: We studied demographic, metabolic, and clinical characteristics of patients with diabetes and autoimmune hepatitis (AIH) from the German/Austrian DPV registry.

Methods: 139 patients with diabetes and AIH were analyzed and compared to 437728 patients with diabetes without AIH.

Results: The prevalence of AIH in patients with T1DM (44.8/100,000) seems higher than in the general population, the prevalence of AIH in patients with T2DM (23.6/100,000) does not seem to be increased. Patients with T2DM and AIH had a shorter duration of diabetes ($p=0.007$) and a higher proportion of females ($p<0.001$) compared to T2DM without AIH. Patients with diabetes (T1DM or T2DM) and AIH required higher insulin doses ($p<0.001$ resp. $p=0.03$) and showed increased liver enzymes (aspartate transaminase, alanine transaminase, gamma-glutamyltransferase) compared to diabetes patients without (all $p<0.001$). We detected a lower percentage of patients treated with oral antidiabetic drugs ($p=0.01$) and a higher percentage of patients treated by insulin in patients with T2DM and AIH ($p<0.001$) compared to patients with T2DM alone. We observed a higher incidence of autoimmune thyroid disease (AIT) in patients with diabetes (T1DM or T2DM) and AIH ($p<0.001$) compared to diabetes patients without AIH.

Conclusions: AIH seems more frequent in patients with T1DM. Patients with diabetes and AIH require intensification of antidiabetic therapy and seem to have a higher prevalence of AIT.

Key words: type 1 diabetes - type 2 diabetes - autoimmune thyroid disease - clinical outcome - diabetes treatment

1. Introduction

The pathogenesis of type 1 diabetes mellitus (T1DM) is characterized by autoimmune destruction of beta cells in the pancreas [1]. Being an autoimmune disorder, T1DM is associated with other immune-mediated diseases, such as autoimmune thyroid disease (AIT) [2], celiac disease [3, 4], and Addison's disease [5], suggesting a common genetic susceptibility [6].

Up to now, only a few case reports have been published on patients with T1DM and autoimmune hepatitis (AIH) [6, 7, 8]. Hovinga et al. described the case of a 12-year-old girl with T1DM who developed AIH. Interestingly, human leucocyte antigen typing of the girl showed DRB1*03 heterozygosity, which has been associated with both AIH and T1DM suggesting that perhaps similar pathogenic pathways are involved in different autoimmune conditions, including T1DM and AIH [6]. This assumption is supported by the fact that a relationship between celiac disease and AIH has been reported [9, 10]. The pathomechanistic relationship between AIH and other autoimmune processes, however, has only been poorly investigated so far [8].

On the other hand, also patients with type 2 diabetes mellitus (T2DM) have been found to express autoimmune characteristics, including the presence of autoantibodies against pancreatic beta cells and self-reactive T-cells [11]. Accordingly, associations have been observed between psoriasis and T2DM, and rheumatoid arthritis and T2DM [12, 13].

Analysing the relationships between T2DM and autoimmune diseases, Hemminki et al. found 15,103 patients with T2DM among 757,368 patients with autoimmune diseases. An overall SIR (Standardized incidence ratio) of 1.66 for T2DM was calculated. T2DM risks were clearly increased after 27 of 32 autoimmune diseases; the highest SIR were calculated for chorea minor (8.00), autoimmune hepatitis (5.75), and Addison's disease (2.63) [11]. To the best of our knowledge, studies investigating a possible link between T2DM and AIH, however, have not been published yet.

As AIH is treated with corticosteroids [14, 15, 16], the question arises whether glycemic control of patients with diabetes and AIH deteriorates and in turn results in higher HbA1c-values. It could further be possible that patients with T2DM and AIH undergoing treatment with corticosteroids require an intensification of their anti-hyperglycemic treatment with a shift from oral antidiabetic drugs towards insulin treatment. Finally, it would be interesting to know whether the frequency of other immune-mediated diseases, such as AIT and celiac disease, is increased in patients with diabetes and comorbid AIH.

Studies describing a larger group of patients with diabetes (T1DM or T2DM) and comorbid AIH, however, have not been published so far. We therefore aimed to study demographic, metabolic, and clinical characteristics in a sufficiently large cohort of patients with diabetes and AIH and compare them to patients with diabetes without AIH.

2. Research Design and Methods

2.1. Data Source

The standardized, multicenter, prospective, computer-based diabetes data acquisition system DPV (www.d-p-v.eu) was used in this study. The DPV initiative currently comprises 451 diabetes care centers from Germany, Austria, Switzerland, and Luxembourg using the DPV software for standardized documentation of diabetes diagnosis and patient care. The electronic health record contains demographic data, type and onset of diabetes, data on metabolic control and treatment regimen, and information on comorbidities. The locally documented information is transmitted twice a year anonymously to Ulm, Germany, for central analyses and quality assurance [17, 18]. If necessary, centers are requested to correct inconsistent data. All plausible data are then aggregated into a cumulative database. The DPV initiative was approved by the ethics committee of the University of Ulm and the data documentation by the local review boards. Until September 2016, demographic and clinical data of 452,493 patients with any type of diabetes were recorded in the database.

2.2. Subjects

For the present study, patients with T1DM, T2DM or other specific types of diabetes (type 3 diabetes mellitus (T3DM)) were considered. The database was searched for the

additional lifetime diagnosis of AIH by ICD-10 code (k75.4) and specific German search terms considering different spellings (e.g. “autoimmun hepatitis“, “autoimmune hepatitis“, “autoimunhepatitis“, “autoimunehepatitis“). The final study population comprised 437,728 pediatric and adult patients with diabetes without AIH and 139 patients with AIH from 411 German, 37 Austrian, 2 Swiss, and 1 Luxembourgian centers. For each patient included, data from the last documented visit were studied.

2.3. Variables analyzed

. We analyzed demographic data (age, sex, body-mass-index (BMI), duration of diabetes), glycemic control (HbA1c,), insulin dose in units/kg as well as treatment regimen. In T1DM, treatment regimen was classified as conventional insulin therapy (1-3 insulin injections/day), intensive insulin treatment (4-8 insulin injections/day) insulin pump therapy (9 insulin injections/day), and additional administration of oral antidiabetic drugs (OAD). In T2DM, anti-hyperglycemic treatment was categorized by insulin only, insulin and OAD, OAD only, and lifestyle modification only. Additionally, we analyzed liver enzymes (aspartate transaminase, alanine transaminase, gamma-glutamyltransferase) and in T1DM diabetes autoantibodies (islet cell antibodies, insulin autoantibodies, glutamic acid decarboxylase, protein tyrosine phosphatase). Finally, our analysis also evaluated the frequency of documented celiac disease (diagnosis confirmed by small-bowel biopsy) or AIT.

To adjust for differences between laboratory methods, the multiple of the mean method was applied to mathematically standardize HbA1c measurements to the Diabetes Control and Complications Trial (DCCT) reference range (20.7–42.6 mmol/mol) [19].

2.4. Statistics

Data analysis was performed using SAS 9.4 (SAS Institute, Cary, NC). Results were presented as median with quartiles or proportion. We compared patients with either T1DM or T2DM and AIH to patients with T1DM or T2DM without AIH. Wilcoxon-test was used for continuous variables and χ^2-test for binary variables. P-values were corrected for multiple comparisons using FDR algorithm (false discovery rate). To account for potential confounding effects such as age, sex and duration of diabetes, multivariable regression models were created to compare diabetes-related outcome variables between groups. Linear regression was used for continuous variables, logistic regression for binary data. Between-within method was applied to calculate denominator degrees of freedom. Restricted maximum likelihood was used as estimation technique in linear regression and maximum likelihood for logistic regression. Results are given as adjusted means with standard error of the mean (SEM). Two-sided p-values < 0.05 were defined as statistically significant.

3. Results

Table 1 summarizes the frequency of AIH by type of diabetes in the entire cohort, with significant difference among groups ($p<0.001$). The majority of patients with T3DM and AIH had uncommon forms of immune-mediated diabetes and diabetes caused by drugs i.e. corticosteroids (table 2).

Information on the type of AIH was available only in 38/139 patients (29 patients type 1 AIH, 9 patients type 2 AIH) after specific request at the participating centers. Analyses stratified by type of AIH were therefore not possible.

Comparisons of demographics (age, sex, duration of diabetes) are shown in tables 3 and 4. The patients with T2DM and AIH had a significantly shorter duration of diabetes than the patients with T2DM without AIH ($p=0.007$). Furthermore, the group of patients with T2DM and AIH had a higher percentage of female patients when compared to the group of patients with T2DM without AIH ($p<0.001$). T1DM patients with or without AIH did not differ with regard to age, sex and diabetes duration.

Demographically adjusted comparisons of metabolic and clinical variables are summarized in tables 3 and 4. Patients with diabetes (T1DM or T2DM) and AIH required significantly higher insulin doses ($p<0.001$ resp. $p=0.03$) and showed higher levels of liver enzymes than patients with diabetes without AIH (both $p <0.001$). In

comparison to patients with T2DM without AIH, we detected a lower percentage of patients treated by oral antidiabetic drugs ($p=0.01$) and a higher percentage of patients treated by insulin only ($p<0.001$) in patients with T2DM and AIH. Finally, we observed a higher frequency of AIT in patients with diabetes (T1DM or T2DM) and AIH when compared to patients with T1DM or T2DM without AIH (p-values both <0.001). In T1DM with or without AIH, metabolic control and type of diabetes treatment regimen did not differ significantly. Nutritional status assessed by BMI or BMI-SDS were comparable between diabetes patients (T1DM or T2DM) with or without AIH.

Group comparisons of patients with T3DM were not possible due to the limited number of subjects with AIH in this subgroup (n=15).

4. Discussion

To the best of our knowledge, this is the first study comparing demographic, metabolic, and clinical characteristics between patients with diabetes and AIH and patients with diabetes without AIH.

Epidemiological data on AIH are rather scarce and heterogeneous, as the prevalence of AIH differs in various geographic regions, between different age groups, and between Type 1 AIH and Type 2 AIH [20-23]. As pointed out by Kim et al., prevalence estimates of AIH therefore range widely from 4 to 42.9 cases per 100,000 persons [23]. Therefore, conclusions from comparisons between data have to be drawn very carefully. Only two studies have assessed the population-based prevalence of AIH in Europe detecting a prevalence of 16.9/100,000 and 24.5/100,000 respectively [21, 24]. The prevalence of AIH in our group of patients with T1DM was 44.8/100,000 and 23.6/100,000 in the group of patients with T2DM. It therefore seems that the prevalence of AIH is increased in patients with T1DM pointing towards a possible autoimmunological link between these two diseases. The prevalence of AIH in patients with T2DM seems to be similar to the prevalence in the general population possibly pointing towards the fact that these two diseases are not associated. Up to now, however, a possible relationship between T1DM and AIH has been poorly investigated, mainly restricted to immunological aspects [1, 25-28].

One focus of our analysis was to compare the frequency of AIT and celiac disease in these two groups, as T1DM and AIH are both associated with AIT and celiac disease [2-4, 25, 27, 29-31]. In our analysis, patients with diabetes (T1DM and T2DM) and AIH did not differ from patients without AIH with respect to the rate of celiac disease. By contrast, p atients with T1DM and AIH or with T2DM and AIH demonstrated a higher frequency of AIT compared to patients with diabetes without AIH. As classified by Neufeld et al., patients with AIT, insulin-requiring diabetes, and at least one other autoimmune disease fulfill the definition of Autoimmune Polyglandular Syndrome Type III A (APS III A) in the absence of Addison's disease [32], so that our group of patients with AIT, T1DM, and AIH can be diagnosed to have APS III A. Addison's disease was not diagnosed in any of these patients. Autoimmune Polyglandular Syndrome is considered to be a rare form of autoimmune disorder [33, 34]. The exact prevalence of APS III is unknown as epidemiological data are limited [35]. In a study with 461 children with T1DM, however, Ben-Skowronek et al. detected APS III in 14.5% of their patients [36]. Reports on patients with AIH as part of APS III are limited to two case-reports in adults [10, 37].

Interestingly, patients with T2DM and AIH also showed a higher prevalence of AIT as compared to patients with T2DM without AIH. Studies or reports on patients with T2DM, AIH, and AIT are lacking so far. However, patients with T2DM have also been found to express autoimmune characteristics, including the presence of autoantibodies against pancreatic beta cells and self-reactive T-cells [11]. Furthermore, the association between T2DM, AIH, and AIT is also explained by the established association between AIH and AIT [29] which does not exclude patients with T2DM.

When comparing glycemic control (assessed by HbA1c), we did not find differences between patients with diabetes (T1DM or T2DM) with or without AIH. In order to achieve comparable HbA1c-values, however, patients with diabetes (T1DM or T2DM) with AIH required higher insulin doses. The necessity to intensify antidiabetic therapy in patients with diabetes and AIH is further illustrated by the fact that the proportion of patients treated with insulin only was higher in the group of patients with T2DM and AIH, and accordingly the rate of patients being treated with oral antidiabetic drugs only was lower in this group.

The necessity to intensify antidiabetic treatment in patients with diabetes and AIH can be explained by the use of corticosteroids in the management of AIH [14-16]. Corticosteroids are known to cause postprandial hyperglycemia. Part of the mechanism of hyperglycemia involves peripheral insulin resistance, which leads to an increase in insulin requirement [38, 39]. Additionally, corticosteroids increase hepatic glucose production [40]. Diabetes caused by treatment with corticosteroids is classified as T3DM. The prevalence of T3DM in patients with AIH being treated with corticosteroids is unknown [41]. In our analysis of 139 patients with AIH and diabetes, we found 7 patients with T3DM as a consequence of steroid treatment. Matsumoto et al. analyzed 118 adult patients with AIH and found diabetes in 29 (24.5%) patients, one of these having T1DM. 21 (72.4%) of the patients with diabetes received corticosteroids [41]. Otherwise, data on the occurrence of diabetes in patients with AIH undergoing treatment with corticosteroids are lacking. Furthermore, insulin resistance and consecutive hyperglycemia can be a consequence of inflammation in patients with AIH. In inflammatory disorders, pro-inflammatory cytokines can cause insulin resistance in adipose tissue, skeletal muscle, and liver by inhibiting insulin signal transduction [42,

43]. Finally, hyperglycemia and diabetes can be a complication of chronic liver diseases [44, 45].

The strength of this study is that we were able to examine a sufficient number of patients with diabetes and AIH. To our best knowledge, this is the first report on demographic, metabolic, and clinical characteristics of patients with diabetes and AIH. A potential limitation of our study is the fact that we did not have sufficient data concerning the type of AIH, even after request at the participating centers. Further analyses separated by type of AIH would be of great interest but were not possible. Furthermore, our study is based on data and diagnoses from a registry. Detailed data on the diagnostic criteria concerning the diagnosis of AIH, such as histology, severity, or fibrosis, are therefore not available to us. Similarly, comprehensive data on the treatment of AIH (e.g. type of medication, dosages, duration of treatment) and clinical course (e.g. remission, relapses) are not available in the DPV registry. However, we were able to elicit that 53% of the patients with diabetes and AIH were treated with corticosteroids. Of these patients, 14% of casesused corticosteroids already at the onset of diabetes.

In conclusion, the results of our analyses show that AIH seems to be more frequent in patients with T1DM. Furthermore, patients with diabetes (T1DM or T2DM) and AIH require an intensification of their antidiabetic therapy. Finally, patients with diabetes (T1DM or T2DM) and AIH seem to have a higher prevalence of AIT. Patients with T1DM, AIH, and AIT represent APS III A, a rare autoimmune disorder which has been less studied so far.

Duality of Interest: No potential conflicts of interest relevant to this article were reported. The authors have no competing interests to declare.

Author Contributions: GdS created tables and wrote and edited the manuscript. NP edited the manuscript. MB, RD, UF, DM, NH, IE, HB, DW, MF, and BS researched data and reviewed the manuscript. RH conceptualized the study and reviewed the manuscript. RH is the guarantor 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. All authors have approved the final article.

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Table 1: Frequency of AIH among different diabetes subtypes

Type of diabetes	**Total No. of patients**	**Patients with AIH (n/%)**		
		< 18 yrs.	**≥ 18 yrs.**	**Total**
Type 1 diabetes	111,547	29 (0.05)	21 (0.04)	50 (0.04)
Type 2 diabetes	313,916	1 (0.08)	73 (0.02)	74 (0.02)
Type 3 diabetes	12,404	5 (0.23)	10 (0.10)	15 (0.12)
Total	437,867	35 (0.06)	104 (0.03)	139 (0.03)

AIH: autoimmune hepatitis. The total frequency of AIH among different types of diabetes was statistically significant ($p<0.001$).

Table 2: Patients with T3DM and autoimmune hepatitis

Diagnosis	Patients
Mutation in the insulin-receptor gene	1
Berardinelli-Seip syndrome	1
Uncommon forms of immune-mediated diabetes	15
Diabetes caused by corticosteroids	7
Diabetes after transplantation/malignancy	2

(Multiple entries possible)

Table 3: Demographical, clinical, and metabolic comparison of patients with T1DM with or without AIH.

Parameter	T1DM		p-value
	No AIH	AIH	
No. of patients	111,497	50	
Age [years]	17.73 (14.33-36.74)	17.26 (13.73-44.75)	0.92
< 18 years	53%	58%	0.75
Male patients	53%	40%	0.25
Duration of diabetes [years]	6.96 (2.76-13.49)	8.04 (3.32-13.61)	0.80
BMI [kg/m^2]	23.09±0.01	22.84±0.66	0.71
BMI-SDS	0.107±0.003	0.062±0.150	0.77
HbA1c [mmol/mol]	67.03±0.07	64.86±3.16	0.49
Insulin dose [units/kg][1]	0.79±0.00	1.06±0.05	<0.001
Aspartate Transaminase [U/l]	25.59±0.14	143.88±6.04	<0.001
Alanine Transaminase [U/l]	22.86±0.14	98.45±6.30	<0.001
Gamma-Glutamyltransferase [U/l]	25.37±0.26	203.11±10.81	<0.001
Conventional insulin therapy, %	13%	11%	0.62
Intensive insulin treatment, %	59%	58%	0.86
Insulin pump therapy, %	28%	31%	0.70
Additional OAD therapy, %	2%	3%	0.90
Islet Cell Antibodies, %	60%	25%	0.07

Insulin Autoantibodies, %	67%	49%	0.34
Glutamic Acid Decarboxylase, %	59%	66%	0.69
Protein Tyrosine Phosphatase, %	52%	14%	0.08
Coeliac disease, %	2%	3%	0.45
Thyroid disease, %	10%	36%	<0.001

T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; AIH: autoimmune hepatitis Except for age, sex and duration of diabetes, values are adjusted means ± SEM. Adjustments were made for age, sex, and diabetes duration. T1DM: type 1 diabetes mellitus; AIH: autoimmune hepatitis; BMI: body-mass-index; OAD: oral antidiabetic drugs.

Table 4: Demographical, clinical, and metabolic comparison of patients with T2DM with or without AIH.

Parameter	T2DM		p-value
	No AIH	AIH	
No. of patients	313,842	74	
Age [years]	70.07 (60.32-77.67)	67.06 (57.73-74.40)	0.05
< 18 years	1%	0.4%	0.26
Male patients	52%	18%	<0.001
Duration of diabetes [years]	8.22 (2.79-14.82)	5.93 (1.23-9.78)	0.007
BMI [kg/m^2]	30.70±0.01	30.46±0.76	0.75
HbA1c [mmol/mol]	59.51±0.04	62.31±2.61	0.28
Insulin dose [units/kg][1]	0.59±0.00	0.74±0.06	0.03
Aspartate Transaminase [U/l]	32.88±0.17	72.26.±6.94	<0.001
Alanine Transaminase [U/l]	33.55±0.16	90.57±6.80	<0.001
Gamma-Glutamyltransferase [U/l]	72.42±0.40	231.96±17.78	<0.001
Insulin only, %	28%	53%	<0.001
Insulin plus OAD, %	20%	13%	0.15
OAD only, %	25%	13%	0.01
Lifestyle modification, %	27%	21%	0.67
Coeliac disease, %	0.2%	1.4%	0.05
Thyroid disease, %	5%	21%	<0.001

Except for age, sex and diabetes duration, values are adjusted means ± SEM. Adjustments were made for age, sex and diabetes duration. T2DM: type 2 diabetes mellitus; AIH: autoimmune hepatitis; BMI: body-mass-index; OAD: oral antidiabetic drugs, [1]for patients with insulin therapy.