Reclassification of diabetes type in pediatric patients initially classified as type 2 diabetes mellitus: 15 years follow-up using routine data from the German/Austrian DPV database

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A B S T R A C T

Objective: To examine change of diagnosis in patients from the German/Austrian multicenter DPV (Diabetes Patienten Verlaufsdokumentation) database initially classified as type 2 diabetes.

Methods: Patients aged <20 years at onset, diagnosed between 1995 and 2010 were followed for at least 6 months. Chi-square/Wilcoxon tests were performed to compare patient groups according to diabetes type after reclassification.

Results: From 580 study patients, 60 (10.3%) were reclassified, on average 2.4 years after initial diagnosis as follows: 23 (38.3%) as type 1 diabetes; 9 (15%) as maturity onset diabetes of the young (MODY); 20 (33.3%) as “other specific diabetes forms” and 8 (13.3%) as “remission” of type 2 diabetes. Patients reclassified to type 1 were significantly younger (13.5 ± 2.9 versus 14.0 ± 2.6; p = 0.027) and more often β-cell antibody positive at disease onset (80.0% versus 31.2%; p = 0.002), while patients reclassified as MODY had significantly lower BMI-SDS values than 520 patients with confirmed type 2 diabetes (2.5 ± 1.1 versus 0.9 ± 1.1; p < 0.001). The latter were also considerably more obese than patients in “remission” and those reclassified to “other specific diabetes forms”.

Conclusion: About 10% of patients in the DPV database, initially diagnosed as type 2 diabetes, were retrospectively reclassified.

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1. Introduction

Children and adolescents are increasingly diagnosed with type 2 diabetes mellitus [1]. Despite guidelines for classification, similarities and overlap between type 2 diabetes and other diabetes forms sometimes make a revision of the initial diagnosis necessary [2,3]. For example, children and adolescents with the more prevalent type 1 diabetes are increasingly
becoming obese [4,5] and a good number of those with type 2 diabetes are antibody positive [6–8]. Thus, in some cases, distinguishing between diabetes types at initial diagnosis can be challenging and misclassification can result. Success of disease management and effectiveness of prevention strategies are however highly reliant on accuracy of diagnosis.

The aim of this study is therefore to analyze routinely collected data from the standardized, prospective DPV (Diabetes Patienten Verlaufsdokumentation) database of patients with a diagnosis of type 2 diabetes and to examine how they differ clinically from those for whom this initial diagnosis was later revised.

2. Patients and methods

Patients were selected from the DPV database, a nationwide register for patients with diabetes in Germany/Austria. DPV participating centers send standardized, prospectively documented, anonymized data twice a year for central analysis to Ulm, Germany. Inconsistencies and implausible data are reported back for verification and correction. DPV data is used for benchmarking and clinical research. Presently (March 2010) the DPV database comprises diabetes related data of 207,784 patients with 1,500,542 appointments from 330 DPV participating centers.

2.1. Inclusion criteria

Patients with an initial diagnosis of type 2 diabetes, aged ≤20 years at disease onset, registered in DPV from 1995 to 2009, were included. These patients had been observed for at least 6 months. In order to minimize the possibility of data entry errors, the diagnosis “type 2 diabetes” had to have been transmitted from the treatment facility to the DPV data center at least twice for each included patient.

2.2. Diabetes classification

Diabetes specialists at DPV participating health facilities assign patient’s diabetes type according to national guidelines, consistent with WHO/ADA diagnosis criteria [8–10]. In case of diagnosis change (e.g. based on clinical course, immunologic or genetic test findings), this is documented and sent to the DPV data center with the next biannual data transmission.

In this study, patients classified as “remission” were patients whose initial diagnosis of type 2 diabetes was annulled as their clinical features no longer met the criteria for assigning a diagnosis of type 2 or another diabetes type. Patients labeled “other specific diabetes forms” were initially diagnosed and documented as type 2 diabetes, then later reclassified, based on evidence of genetic cause or syndromes. Type 1 diabetes patients were classified as type 2 patients at initial diagnosis and later reclassified when their clinical course met the classification of type 1 diabetes according to guidelines [8,9]. Immunological evaluation (β-cell autoimmunity: ICA, GAD, IA2, IAA; thyroid autoimmunity: TG, TPO) of DPV patients registered between 1990 and 2008 has been recently described [11]. Antibodies were measured in specific accredited laboratories in Germany and Austria, who participate in diabetes antibody standardization workshops [12,13]. DPV centers use the respective local cutoff values for the diagnosis of antibody positivity.

Statistical programming using SAS V9.2, NC was conducted. To compare clinical parameters among groups, Wilcoxon tests were performed for continuous variables and χ² analysis for percentages. Significance was given at p < 0.05.

3. Results

Type 2 diabetes was initially diagnosed in 580 subjects with disease onset prior to the age of 20 years. In 60 patients (10.3%), this initial diagnosis was revised on average 2.4 years later as follows: N = 23 patients (4%) were reclassified as type 1 diabetes; for N = 20 patients (3.6%) diagnosis was changed to “other specific diabetes forms” and N = 9 patients (1.6%) were reclassified to MODY: HNF4A-MODY (N = 1), GCK-MODY (N = 2), HNF1A-MODY (N = 5), MODY-X (N = 1). N = 8 patients (1.4%) were reclassified to “remission” of type 2 diabetes, i.e. were no longer considered diabetic based on their metabolic state. The initial diagnosis of type 2 diabetes was confirmed for N = 520 patients (89.7%).

Compared to patients who maintained the diagnosis of type 2 diabetes, patients reclassified to ‘remission phase’ were significantly slimmer, though on average overweight. These patients were neither β-cell nor thyroid-antibody positive and none presented with any degree of diabetic ketoacidosis (DKA) at diagnosis. Other clinical parameters did not significantly differ between both patient groups (Table 1).

In contrast, patients whose diagnoses changed to type 1 diabetes were significantly younger, significantly slimmer and significantly more often β-cell antibody positive at disease onset than subjects with confirmed type 2 diabetes. No significant differences were found with respect to sex, A1C, blood glucose, pH at onset or thyroid antibody positivity (Table 1).

Patients reclassified as MODY were likewise significantly slimmer than patients with a confirmed diagnosis of type 2 but were otherwise clinically similar, i.e. sex, A1C, pH at onset, β-cell- and thyroid antibody positivity did not differ between both groups (Table 1).

The diagnoses of patients reclassified to “other specific diabetes forms” (N = 20) included the following: Prader–Willi syndrome (N = 4), cystic fibrosis (N = 2), pancreatic disease (N = 2), insulin receptor mutation (N = 2), Ulrich–Turner syndrome (N = 2), malignancy/transplantation (N = 2), Trisomy 21 (N = 1), Alström syndrome (N = 1), cortisone treatment (N = 1), endocrinopathy (N = 1), Bardet–Biedl syndrome (N = 1) and mitochondrial diabetes (N = 1). 40% of these patients were male and age at disease onset ranged from 10.2 years to 18.6 years; A1C values ranged from 6.0% to 11.7% and range of BMI-SDS was −3.2 to 4.1. No patient in this group had any degree of ketoacidosis. Four out of nine patients examined were β-cell antibody positive and one no patient was positive for thyroid antibodies at initial diagnosis.

4. Discussion

Type 2 diabetes, rarely reported before the 1990 in pediatric patients, is now said to affect about 8–45% of patients (with
Table 1

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Type 2 diabetes confirmed diagnosis (N = 520)</th>
<th>All patients with revised diagnosis (N = 60)</th>
<th>Type 2 diabetes &gt; “remission phase” (N = 8)</th>
<th>Type 2 diabetes ≥ type 1 diabetes (N = 23)</th>
<th>Type 2 diabetes ≥ MODY (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>35.4</td>
<td>40.0 (p = 0.511)</td>
<td>12.5 (p = 0.173)</td>
<td>47.8 (p = 0.236)</td>
<td>44.4 (p = 0.587)</td>
</tr>
<tr>
<td>Age at disease onset (years)</td>
<td>14.8 ± 2.5</td>
<td>14.0 ± 2.6 (p = 0.027)</td>
<td>14.6 ± 3.0 (p = 0.816)</td>
<td>13.5 ± 2.9 (p = 0.026)</td>
<td>13.5 ± 2.0 (p = 1.801)</td>
</tr>
<tr>
<td>Follow-up before reclassification (years)</td>
<td>-</td>
<td>2.4 (p = 0.848)</td>
<td>2.4 (p = 0.962)</td>
<td>2.5 (p = 0.911)</td>
<td>2.3 (p = 0.990)</td>
</tr>
<tr>
<td>A1C at diagnosis (%)</td>
<td>7.7 ± 2.3</td>
<td>8.4 ± 2.4 (p = 0.016)</td>
<td>6.6 ± 1.2 (p = 0.268)</td>
<td>8.2 ± 2.4 (p = 0.254)</td>
<td>8.6 ± 3.3 (p = 0.598)</td>
</tr>
<tr>
<td>BMI-SDS at diagnosis</td>
<td>2.5 ± 1.1</td>
<td>1.5 ± 1.6 (p &lt; 0.001)</td>
<td>1.1 ± 2.4 (p = 0.050)</td>
<td>1.7 ± 1.1 (p &lt; 0.001)</td>
<td>0.9 ± 1.1 (p &lt; 0.001)</td>
</tr>
<tr>
<td>Blood glucose level at diagnosis (mg/dl)</td>
<td>180.9 ± 101.8</td>
<td>192.2 ± 134.5</td>
<td>112.7 ± 23.5</td>
<td>176 ± 93.4</td>
<td>218.8 ± 80.9</td>
</tr>
<tr>
<td>Thyroid antibody positive (%)</td>
<td>9.7</td>
<td>13.3 (p = 0.672)</td>
<td>0 (p = 0.624)</td>
<td>8.3 (p = 0.797)</td>
<td>28.6 (p = 0.145)</td>
</tr>
<tr>
<td>β-Cell antibody positive (%)</td>
<td>31.7</td>
<td>46.7 (p = 0.127)</td>
<td>0 (p = 0.167)</td>
<td>80.0 (p = 0.002)</td>
<td>28.6 (p = 0.828)</td>
</tr>
<tr>
<td>pH &lt; 7.3 at diagnosis (%)</td>
<td>1.9</td>
<td>0 (p = 0.279)</td>
<td>0 (p = 0.692)</td>
<td>0 (p = 0.502)</td>
<td>0 (p = 0.674)</td>
</tr>
</tbody>
</table>

Comparisons of patients groups (all patients with revised diagnoses; patients in “remission” of type 2 diabetes; type 1 diabetes and MODY) are made with the group of patients with a confirmed diagnosis type 2 diabetes (N = 520). The follow-up period before diagnosis change is compared only among patients whose diagnoses were revised (N = 60) and the respective new classification. Significant p-values are depicted in bold letters to the right of the table.

Overweight in pediatric patients with type 1 diabetes, who have clinical symptoms resembling type 2 diabetes, can mislead from the right classification. Similar to certain studies [18], type 2 diabetes patients in this study who were reclassified to type 1 diabetes were on average overweight. The fact that the majority of these patients were β-cell antibody positive at initial diagnosis underlines the challenge of an accurate initial diagnosis, given the change of the traditional clinical picture: on the one hand type 1 patients are becoming more frequently overweight [4] and on the other hand patients with type 2 are becoming more often antibody positive [6,7]. The pathophysiology of autoimmunity in type 2 diabetes still remains unclear [20] and the danger of misclassification is sharpened by the fact that response to treatment often determines if additional testing should be performed. This risk is perpetuated given that some aspects of the disease only become evident as patients grow older.

Patients reclassified from type 2 to MODY in this study were significantly slimmer. The majority were HNF1A-MODY followed by GCK-MODY. Occasional difficulties may be encountered in differentiating between HNF1A-MODY, GCK-MODY and diabetes type 2 with atypical symptoms, as certain patients’ characteristics (age, sex, BMI, prevalence of hypertension and macrovascular complication) have been found to be comparable [21]. Though expensive and laborious, genetic testing to identify pathogenic mutations is highly relevant for assigning proper treatment options.

Patients reclassified as “remission” of type 2 diabetes were comparably less overweight at diagnosis than type 2 diabetes. They may have responded well to lifestyle intervention which positively influenced their BMI, insulin sensitivity and metabolic control, leading to remission of diabetes. They may have clinical “pre-diabetes” and still be at risk of developing diabetes at a later age and should thus be monitored.

Severely obese patients, whose clinical phenotype of type 2 diabetes remained unchanged over time, were clinically comparable to pediatric patients with type 2 diabetes from other multicenter studies [22].

ethnic disparities] [14–16]. The concurrent rise in obesity among pediatric patients has been put in causal association with this phenomenon, which is viewed with a high degree of interest within the medical community and in the media. The diagnosis of type 2 diabetes in ever younger patients can however be challenging, as similarities of symptoms with other forms of diabetes could mislead from the right diagnosis. This similarity of symptoms portrays an overlap between type 1 and type 2 diabetes and is referred to as type 1.5 diabetes or double diabetes [17–19]. Nowadays, with more readily available immunologic/genetic testing and increasing insight into the pathophysiology and clinical course of the disease, it is not uncommon that patients previously classified as type 2 diabetes are reclassified as having other diabetes types, e.g. MODY or other monogenic types. In certain cases, monogenic diabetes forms are only diagnosed upon referral for molecular testing, months or years after an initial diagnosis has been assigned. Prior to this, patients may be misclassified as type 2 diabetes based on the clinical picture at initial presentation. In other cases, additional testing of a pediatric patient, initially classified as type 2 diabetes, is prompted by diagnosis of an adult relative with a genetic diabetes form.

In this study we examined if and how patients initially classified as type 2 diabetes, documented in the DPV database, were reclassified over the last 15 years. One third of all reclassified patients fell in the group denoted by “other specific forms”. These patients had genetically determined diabetes forms and syndromes and usually do not develop DKA. They may have been misclassified due to similar clinical features with type 2 diabetes at initial presentation, prior to referral for genetic or other testing. Misclassification in this group may also have come about due to the fact that some patients (or parents of minors) only consent to genetic testing after a good and trusting relationship has been established with the health care provider. This is usually the case when they have received satisfactory care in a particular facility over some time.
5. **Strength and weakness of this study**

Multicenter data, used in this longitudinal analysis, was collected using the standardized DPV software. The aim was to analyze a large number of pediatric patients for change of initial type 2 diabetes diagnosis. Considering that data collected over a period of 15 years was analyzed and that additional diagnostic criteria for maturity onset diabetes of the young (MODY) has recently been introduced in best practice guidelines [23], it is possible that in certain cases, patients whose diagnoses changed to MODY were patients who no long met an earlier valid classification. Additionally, given the nature of the database and the fact that data is collated from many different centers, consistency in diagnoses at different health facilities cannot be verified. It is also possible that in some cases, data on which a diagnosis was based was not fully documented in the database. For example, β-cell antibody positivity is unaccounted for in 20% of patients whose diagnosis changed from type 2 to type 1. Nonetheless, diagnoses were assigned by diabetes specialists, who use valid national guidelines, comparable to WHO/ADA classifications. Thus, the possibility of diagnostic inconsistencies is very marginal. It was also not evident if some of the 60 patient for the whom initial diagnosis of type 2 diabetes was revised were actually initially misdiagnosed or if any were only wrongly documented during data entry. However, considering that only patients who had been followed for at least 6 months and for whom the diagnosis “type 2 diabetes” was transmitted at least twice from the treatment facility to the DPV data center were included and the fact that diabetes classification was revised on average 2.4 years later, it is more likely that patients who were reclassified were actually initially misdiagnosed rather than just incorrectly documented. Moreover, inconsistencies and implausible data are reported back to DPV participating centers for verification and correction shortly after each transmission.

6. **Conclusion**

About 10% of pediatric patients with type 2 diabetes were initially misdiagnosed. This may have been due to overlapping clinical phenotypes which have been observed in pediatric patients at disease onset [18,19]. The difficulty of correct classification at onset in youth highlights the importance of considering the possibility of misdiagnosis when analyzing the prevalence and incidence of type 2 diabetes in pediatric patients. Similar difficulties in classification are encountered between type 2 diabetes and late autoimmune diabetes (LADA) in adults [24]. Optimally, patients reclassified to “remission” of type 2 diabetes should still be monitored, as diabetes may reappear at a later age.

There is still no gold standard for diabetes classification in pediatric patients [19]. Classification, however, has implications for treatment, associated outcomes, future complications and prevention.

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**Conflict of interest**

The authors declare that they have no conflict of interest.

**REFERENCES**


