SUPPLEMENTARY METHODS

Inclusion and exclusion criteria

The initial retrieval of patients and the definition of patient cohorts with ambiguous diabetes type, type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM) is displayed in Supplementary Fig. 1. Patients attending this hospital more than once during the index year were only analysed based on their latest admission. Patients aged younger than 18 years and patients with T2DM without insulin therapy ($n=5$, 4.0% of the random sample). In seven cases (1.9% of 372 eligible patients), essential information was lacking, and these patients were not included in the present analysis. After excluding patients, in whom a definite clinical diagnosis of T1DM ($n=51$) or T2DM ($n=32$) could be made on clinical grounds, and of seven patients with incomplete documentation, clinical data of the remaining 115 patients (6.3% of all patients with diabetes mellitus) were compared to those with definite T1DM or T2DM (same diabetes type coded upon admission and at discharge).

Discriminating features characterizing T1DM vs. T2DM

There are typical differences between subjects with T1DM and T2DM regarding the presence of obesity (low vs. high body mass index [1]) and features belonging to the insulin resistance syndrome (high triglycerides and low high-density lipoprotein cholesterol, arterial hypertension, need for higher insulin doses in T2DM) [2], age at onset (usually higher in T2DM [3]), insulin requirement shortly after diagnosis [3], proneness to severe hypoglycaemic and ketoacidosis episodes (typical for T1DM [3,4]), family history for T2DM (pointing to a genetic risk for T2DM [5,6]), and laboratory indicators of the autoimmune destruction of endocrine pancreatic β-cells (glutamic acid decarboxylase [3,7] and other autoantibodies against β-cell antigens [8]) and the resulting deficiency in insulin production (low fasting or stimulated concentrations of connecting peptide [9,10]) in T1DM. T1DM subjects may have other associated autoimmune diseases like thyroiditis [11,12], type A gastritis [12,13], vitiligo [14], and other, more rare autoimmune conditions [15,16]. In addition, T1DM subjects typically have more fluctuations (higher coefficient of variation) in their plasma glucose profiles from day to day, whereas the variation is less pronounced in T2DM patients [17,18].

Sample size

In the absence of data regarding patients with diabetes mellitus of an ambiguous type, the present study has to be regarded a pilot study, the sample size was mainly based on the number of patients for whom the definition of an ambiguous diabetes type applied during the entire year 2014 in the institution, where data were collected.

Phenotypic similarities between "ambiguous diabetes type" and T1DM

Based on a history of changing the diagnosis from T2DM to T1DM, it is no surprise that clinical and laboratory characteristics of our patients with "ambiguous diabetes type" are more similar to those with T1DM, possibly with the exception of body measures indicating obesity and its consequences, where there are overlapping features with T2DM, in line with experiences from Korea [19,20].

Diabetes type score

Based on the results of the multivariate regression analysis, a score was developed that assigned three levels to each variable based on the range of values observed (for details, see Supplementary Table 2). The score related to each level of all variables took into account the weight that this variable had in the multivariate regression model (based on the output parameter β from the multivariate regression analysis and the mean value of that variable for the total population encompassing patients with T1DM and T2DM). The system was designed such that a higher score indicated a higher risk for T2DM. The resulting score was divided by 14 on purely empirical grounds to approximate results near 1 for T1DM subjects and near 2 for T2DM subjects, in order to allow comparison to the results of multivariate regression analysis. This score displayed a distribution similar to the output variable of multivariate regression analysis (Fig. 1C, Supplementary Fig. 2A) and was significantly correlated with the output variable of multivariate regression analysis (Supplementary Fig. 2B).

Useful parameters to discriminate T1DM and T2DM

Some of them are clinical characteristics related to obesity and its consequences (insulin resistance [21], facets of the insulin resistance syndrome [22,23]) like total daily insulin dosage (individual insulin resistance [24], diabetic dyslipidaemia [22]), and hypertension (use of multiple anti-hypertensive drugs [22,25]). Other parameters that might help distinguish between T1DM and T2DM are related to the degree of impairment in endogenous insulin secretion and the consequences

hereof. A higher risk of ketoacidosis [26,27] and (severe) hypoglycaemia [28,29] in T1DM as compared to T2DM. Only a few parameters are directly related to the aetiology and pathophysiology of either T1DM or T2DM, like β-cell auto-antibodies [7] and low C-peptide concentrations [9] speaking in favour of T1DM, or a family history of T2DM attesting of a genetic predisposition to develop T2DM in a substantial proportion of first-degree relatives [30].

Supplementary references

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