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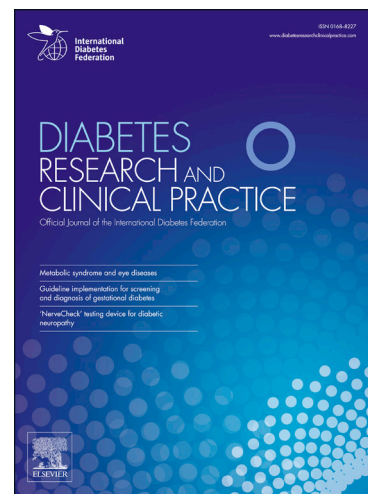
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Metabolic risk profiles in diabetes stratified according to age at onset, islet autoimmunity and fasting C-peptide

Mette Wod¹, Knud B. Yderstræde¹, Ulrich Halekoh², Henning Beck-Nielsen¹, Kurt Højlund^{1,3}

¹Department of Endocrinology, Odense University Hospital, DK-5000 Odense, Denmark

²Department of Epidemiology, Biostatistics and Biodemography, University of Southern Denmark, DK-5000 Odense, Denmark.

³Section of Molecular Diabetes & Metabolism, Institute of Clinical Research and Institute of Molecular Medicine, University of Southern Denmark, DK-5000 Odense, Denmark

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Corresponding author:

Kurt Højlund, MD, PhD, DMSc

Department of Endocrinology, Odense University Hospital,

Klørvænget 6, DK-5000 Odense, Denmark

Phone: +45 25320648, e-mail address: kurt.hoejlund@rsyd.dk

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Abstract

Objective: Islet autoimmunity, age at onset and time to insulin treatment are often used to define subgroups of diabetes. However, the latter criterion is not clinically useful. Here, we examined whether an unbiased stratification of diabetes according to age at onset, fasting C-peptide and GAD autoantibodies (GADab) defines groups with differences in glycaemic control and markers of cardiometabolic risk.

Design and methods: A cohort of 4,374 adults with relatively newly diagnosed diabetes referred to a Danish hospital during 1997-2012 was stratified according to age at onset above or below 30 years, fasting C-peptide above or below 300 pmol/l (CPEP_{high} or CPEP_{low}), and presence or absence of GADab (GAD_{pos} or GAD_{neg}). HbA_{1c}, BMI, blood pressure (BP), lipid profile, alanine aminotransferase (ALT) and creatinine were evaluated.

Results: GADab were present in 13% of the cohort. Age at onset was not associated with major differences between groups. Patients with insulin deficient diabetes (CPEP_{low}; n=503) had higher HbA_{1c} but otherwise lower cardiometabolic risk (lower BMI, BP, LDL, triacylglycerol, and ALT, and higher HDL) than both patients with latent autoimmune diabetes of adults (LADA defined as GAD_{pos}CPEP_{high}; n=327) and patients with type 2 diabetes (GAD_{neg}CPEP_{high}; n=3,544). Patients with LADA defined an intermediate group with higher HbA_{1c} but otherwise lower cardiometabolic risk than patients with type 2 diabetes.

Conclusions: Our results demonstrate that fasting C-peptide and GADab status, but not age at onset, define groups of patients with diabetes with clinically relevant differences in glycaemic control and cardiometabolic risk.

Introduction

In clinical practice, a major purpose of classifying diabetes into different types is to provide optimal treatment of hyperglycaemia, dyslipidaemia and hypertension to prevent complications. Approximately 10% of adults with apparent type 2 diabetes have markers of islet autoimmunity as seen in type 1 diabetes [1-4]. This subgroup, which is proposed to represent the second most common form of adult-onset diabetes, has been defined as latent autoimmune diabetes in adults (LADA) [3, 5]. The pathophysiological mechanisms underlying LADA are less well defined than those of type 1 diabetes and type 2 diabetes [3, 4, 6]. This includes controversy about the relative roles of autoimmune-mediated destruction of pancreatic β -cells as seen in type 1 diabetes, and of insulin resistance, central obesity, hypertension, dyslipidaemia, and with time, failure of the β -cell function as seen in type 2 diabetes [3, 4]. Moreover, a family history of diabetes and risk factors for type 2 diabetes, such as age, obesity and lack of physical activity are also predictive of LADA [5, 7-9]. Thus, LADA shares biochemical, phenotypic and as shown recently even genetic characteristics with both type 1 diabetes and type 2 diabetes [6, 10-12].

Currently proposed criteria for LADA include the presence of islet autoantibodies, age at onset >30 years and treatment without insulin for at least 6 months after diagnosis [4]. However, both the age at onset and time to insulin criteria have been questioned [3, 6, 13, 14]. Thus, the age of onset criteria is arbitrary as suggested by the presence of LADA in childhood and youth [15, 16], and time to insulin initiation cannot be applied, because clinicians with access to a GAD antibody (GADab) assay will tend to start insulin therapy in GADab positive patients [13]. C-peptide provides an important measure of residual endogenous insulin secretion, and can be used to assist diabetes classification and the need for insulin treatment [17]. Moreover, recent studies indicate that initial levels of fasting C-peptide predict failure of β -cell function in autoimmune diabetes [18], and

is superior to age at onset and BMI in discrimination between autoimmune and non-autoimmune diabetes [19].

Although most studies are small, differ in the criteria for LADA, and compares LADA with either type 1 diabetes or type 2 diabetes [20], there is evidence to suggest that the prevalence of metabolic syndrome and levels of cardiometabolic risk factors such as obesity, hypertension and dyslipidaemia are lower in LADA compared to type 2 diabetes [5, 8, 21-24], but higher than in type 1 diabetes in some [22, 25], but not all studies [1, 8]. Moreover, patients with LADA appear to have a worse glycaemic control than in type 2 diabetes [22-24, 26, 27]. However, currently there is no consensus regarding the optimal treatment of LADA [20], and, in particular, there is a lack of knowledge whether cardiometabolic risk factors such as hypertension, obesity and dyslipidaemia should be targeted more or less aggressively than in type 2 diabetes. In fact, there is a further need for differentiation of diabetes to facilitate individualised care and precision medicine [28, 29].

The aim of the present study was to test the hypothesis that an unbiased stratification of adult-onset diabetes according to age at onset (18-30 years or >30 years), and measurement of fasting C-peptide and GADab at first hospital admission for diabetes can be used to define subgroups of patients with clinically relevant differences in levels of glycaemia and markers of cardiometabolic risk such as measures of BMI, BP (blood pressure), lipid profile and liver enzymes.

Methods

Study population

In this cohort study, we included data on all consecutive patients with relatively newly diagnosed diabetes mellitus referred to the Department of Endocrinology at Odense University Hospital (OUH), Denmark in the period 1997-2012. Since 1997 it has been standard procedure to test all patients admitted for the first time with diabetes to our hospital for GADab and fasting serum C-peptide levels to point out patients with possible autoimmunity-based destruction of their pancreatic beta cells, and hence a rapid progression to insulin dependence.

For the last twenty years, a fasting serum C-peptide <300 pmol/l has been used as a cut-off value suggestive of insulin deficient diabetes and hence for starting insulin therapy in our clinic [30, 31].

Moreover, the majority of patients with diabetes diagnosed with GADab positivity (GAD_{pos}) at our clinic is started on insulin treatment independent of fasting C-peptide levels. Therefore, time to insulin initiation cannot be used to define LADA in our clinic [13].

The Danish Data Protection Agency and The Regional Scientific Ethical Committees for Southern Denmark approved the study.

Data Linkage

In the present study, we retrieved data on the first available set (age of test) of GADab status, fasting serum C-peptide and HbA_{1c} , and concomitant (taken within three months from the analysis of the GADab test) measures of HDL cholesterol, LDL cholesterol, triacylglycerol (TG), creatinine, alanine aminotransferase (ALT), leucocytes and C-reactive protein (CRP) from a local database at our Hospital. Except for data on GADab, fasting C-peptide and HbA_{1c} , all other biochemical data from patients with concomitant evidence of bacterial infection ($CRP \geq 50$ mg/l and leucocyte count $\geq 11 \times 10^9/l$) were excluded from data analysis because bacterial infections could influence the

results. Data on BMI, systolic and diastolic BP (SBP and DBP) closest to the GADab test and year of onset of diabetes were retrieved from a local Diabetes Database (www.fddb-produktion.dk), which is used by our clinicians as well as general practitioners referring patients with diabetes to our clinic. If only the year and not the exact date was known, age of onset was set as June 30 in the year of onset.

Assays

Blood samples were analysed using standardised assays to measure HbA_{1c}, HDL-cholesterol, LDL-cholesterol, TG, creatinine, ALT, leucocytes and CRP. Fasting serum C-peptide was measured by a non-competitive time-resolved immunofluorometric assay (TR-IFMA; Wallac Oy, Turku, Finland) as previously described (27). From 2001 to 2012, GADab were measured using the Glutamic Acid Decarboxylase (GAD) Autoantibody RIA kit (RSR, Cardiff, United Kingdom) measuring units per ml with 95% specificity and 84% sensitivity. Units are RSR arbitrary units and one RSR kit unit per ml is equivalent to 25 units per ml of 97/550 (WHO units), which was considered positive. From 1997-2001 GADab was measured and defined as negative or clear positive at Statens Serum Institut (SSI), Denmark, using the GAD II Antikörper ImmunoRadioMetrischer Assay (IRMA) from ELIAS Medizintechnik GMBH, Freiburg, Germany.

Stratification of diabetes

Diabetes was diagnosed according to the existing WHO criteria in the period 1997-2012. To investigate in an unbiased manner whether age at onset, fasting C-peptide and presence of GADab can be used to define groups with different levels of glycaemia (HbA_{1c}) and markers of cardiometabolic risk, here defined as BMI, HDL, LDL, TG, ALT, as well as SBP and DBP, we

stratified patients with diabetes into 8 groups according to age at onset above or below 30 years ($AGE < 30$ or $AGE > 30$) as suggested for LADA (4), presence or absence of GADab (GAD_{pos} or GAD_{neg}), and fasting serum C-peptide above or below 300 pmol/l ($CPEP_{high}$ or $CPEP_{low}$) (Fig. 1).

Approach

A 4-step approach was used to examine whether age at onset, GADab status and fasting C-peptide could be used to identify groups of patients with diabetes with clinically relevant differences in glycaemic control and other markers of cardiometabolic risk. Step 1: In groups with similar status of fasting C-peptide and GADab, we examined the influence of age at onset below ($AGE < 30$) or above ($AGE > 30$) 30 years of age. Based on the results in Step 1, we decided to merge groups with similar status of age at onset. Step 2: In the resulting groups with similar GADab status, we examined the influence of fasting C-peptide above ($CPEP_{high}$) or below ($CPEP_{low}$) 300 pmol/l. Step 3: In groups with similar status of fasting C-peptide, we examined the influence of the presence (GAD_{pos}) or absence (GAD_{neg}) of GADab. Based on the results in Step 2 and 3, we decided to merge groups with fasting C-peptide below 300 pmol/l ($CPEP_{low}$). Step 4: The resulting three groups were then compared for clinically relevant differences in glycaemic control and other markers of cardiometabolic risk. For each step, groups were merged if no more than 3 markers of cardiometabolic risk including HbA1c differed.

Statistical Analyses

Statistical analyses were performed using STATA Version 12 and R Version 3.1.1. Multivariate linear regression analysis was used to test for differences in means for each variable between groups. The analyses were adjusted for sex in Step 1 (where the groups are stratified by age at onset) and adjusted for age at test and sex in Step 2,3 and 4. Levels of TG, creatinine and ALT

showed skewed distribution. Thus, these data were transformed using the natural logarithm. Moreover, a sensitivity analyses were performed in the multivariate linear regression analysis to test whether participants that had GADab tested on the assay used from 1997-2001 had any major impact on the results. Model assumptions were checked by residual plots and quantile-quantile plots of residuals and found to be met.

In a model including the variables HbA_{1c}, BMI, HDL, TG and DBP, we tested whether the means of the respective variables were different between two groups using the test of 'no-regression' in a logistic regression of the binary group indicator on all five variables [32]. This test does not depend on a normality assumption of the covariates as Hotelling's T₂ test. A *p*-value of <0.05 was considered statistically significant. Descriptive statistics are presented as mean (SD) and median (IQR) where appropriate.

Results

Diabetes stratified according to age at onset, GADab status and fasting C-peptide

A total of 5,671 adults (≥ 18 years) patients with diabetes were tested for GADab in the period 1997-2012 (Fig. 1). Of these, 905 patients were excluded due to missing data on age at onset and 392 patients were excluded due to the absence of a fasting C-peptide. Thus, data from 4,374 patients were eligible for final stratification according to age at onset and status of fasting C-peptide and GADab for further analyses of clinical and cardiometabolic characteristics in these 8 groups (Table 1). Of these 557 (13%) were GADab positive. The vast majority of patients with diabetes (Gr. 8) were AGE >30 and GAD_{neg}CPEP_{high} (77.8%) followed by patients (Gr. 6) that were AGE >30 and GAD_{pos}CPEP_{high} (6.4%) with the other groups representing between 1-5% of the study cohort.

Stratification according to age at onset

First (Step 1), we examined whether age at onset (AGE <30 versus AGE >30) contributed to relevant discrimination between glycaemic control and other markers cardiometabolic risk in groups with the similar status of fasting C-peptide and GADab (Table 1). Except for slightly lower SBP in younger GAD_{pos}CPEP_{low} patients ($p < 0.05$), there were no significant differences in markers of cardiometabolic risk between the younger and the older GAD_{pos}CPEP_{low} patients (Gr. 1 versus Gr. 5). Similarly, the only differences between the younger and the older GAD_{pos}CPEP_{high} patients (Gr. 2 versus Gr. 6) were higher SBP ($p < 0.001$) and DBP ($p < 0.01$) in the older group.

The only significant difference in markers of cardiometabolic risk between the younger and the older GAD_{neg}CPEP_{low} patients (Gr. 3 versus Gr. 7) was higher HbA1c ($p < 0.01$) in the younger group. In contrast, the younger GAD_{neg}CPEP_{high} patients (Gr. 4) had higher BMI ($p < 0.001$), TG ($p < 0.01$) and ALT ($p < 0.001$) and lower HDL ($p < 0.001$), but also lower SBP and creatinine (all

$p < 0.001$) than the older $GAD_{pos}CPEP_{high}$ patients (Gr. 8). These differences between the two groups of patients assumed to have type 2 diabetes were to be expected based on the more pronounced role of obesity in the development of type 2 diabetes at early ages, and when further adjusting for BMI (data not shown), SBP and TG were no longer significantly different between the two groups. Sensitivity analyses excluding individuals that had GADab tested on the assay used from 1997-2001 had no impact on the results other than SBP were no longer significantly different when comparing the younger $GAD_{pos}CPEP_{low}$ with the older $GAD_{pos}CPEP_{low}$.

Taken together, age at onset ($AGE < 30$ versus $AGE > 30$) was not useful to point out major differences between groups with otherwise similar status of fasting C-peptide and GADab. A model including the variables HbA_{1c} , BMI, HDL, TG and DBP further supported the lack of significant differences between the younger and older groups with otherwise similar status of fasting C-peptide and GADab ($GAD_{pos}CPEP_{low}$; $p = 0.14$, $GAD_{pos}CPEP_{high}$; $p = 0.16$, and $GAD_{neg}/CPEP_{low}$; $p = 0.52$, except for the above-mentioned well-explained differences between younger and older patients with $GAD_{neg}CPEP_{high}$ ($p < 0.001$). For further analyses, we, therefore, decided to compare the following 4 groups independent of age at onset; $GAD_{pos}CPEP_{low}$ patients (Gr. I), $GAD_{pos}CPEP_{high}$ patients (Gr. II), $GAD_{neg}CPEP_{low}$ patients (Gr. III) and $GAD_{pos}CPEP_{high}$ patients (Group IV).

Stratification according to fasting C-peptide

To investigate whether fasting C-peptide is a useful discrimination tool with respect to glycaemic control and other markers of cardiometabolic risk (Step 2), we compared the groups with the same GADab status (I-IV) defined above (Table 2). The $GAD_{pos}CPEP_{low}$ patients (Gr. I) had lower BMI, LDL, TG and ALT and higher HbA_{1c} and HDL than the $GAD_{pos}CPEP_{high}$ patients (Gr. II). When comparing the $GAD_{neg}CPEP_{low}$ patients (Gr. III) with the $GAD_{neg}CPEP_{high}$ patients (Gr. IV), the

group with lower fasting C-peptide had lower BMI, SBP, DBP, LDL, TG, ALT and creatinine and higher HbA_{1c} and HDL. This showed that fasting C-peptide no matter age at onset and GADab status was indeed useful to distinguish groups of patients with diabetes with respect to levels of glycaemia and other markers of cardiometabolic risk.

Stratification according to GADab

Next (Step 3), we examined whether GADab status also influenced glycaemic control and other markers of cardiometabolic risk in patients with diabetes with the same status of fasting C-peptide independent of age at onset (Table 2). When comparing GAD_{pos}CPEP_{low} patients (Gr. I) to GAD_{neg}CPEP_{low} patients (Gr. III), no noteworthy differences were observed except from slightly higher HDL and slightly lower TG in the GAD_{pos}CPEP_{low} group. These findings indicate that in patients with diabetes with lower fasting C-peptide (CPEP_{low}) (Gr. I+III), neither age at onset nor GADab status contribute much to discriminate with respect to glycaemic control or markers of cardiometabolic risk. This was supported by the absence of a significant difference between the GAD_{neg}CPEP_{low} group and the GAD_{pos}CPEP_{low} group ($p=0.37$), when using a model including the variables HbA_{1c}, BMI, HDL, TG and DBP. Thus, the groups with lower fasting C-peptide were merged for the following analyses (see below). However, when comparing GAD_{pos}CPEP_{high} patients (Gr. II) with GAD_{neg}CPEP_{high} patients (Gr. IV), a number of differences were observed (Table 2). Thus, the GAD_{pos}CPEP_{high} patients (Gr. II) had lower BMI, SBP, TG and ALT, and higher HDL and HbA_{1c}. This showed that GADab status can predict glycaemic control and other markers of cardiometabolic risk in patients with diabetes with fasting C-peptide above 300 pmol/l independent of age at onset.

Based on Step 1-3, three groups were defined for further analyses: A heterogeneous group of patients ($n=503$) with low fasting C-peptide below 300 pmol/l independent of age at onset and

GADab status, hereafter called insulin deficient diabetes (IDD), a group of GADab positive patients (n=327) with fasting C-peptide above 300 pmol/l independent of age at onset, hereafter called LADA, and a group of GADab negative patients (n=3,544) with fasting C-peptide above 300 pmol/l no matter age at onset ($GAD_{neg}CPEP_{high}$) expected to be patients with type 2 diabetes (Table 3). Sensitivity analyses excluding individuals that had GADab tested on the assay used from 1997-2001 did not impact the results.

Metabolic risk profiles of patients with IDD, LADA and type 2 diabetes

Patients with LADA were diagnosed with diabetes ~6 years earlier than patients with type 2 diabetes, but ~7 years later than patients with IDD (both $p < 0.001$). The other differences between the patients with LADA and the patients with type 2 diabetes are listed above (Table 3). The patients with LADA had higher BMI, DBP, LDL, TG, and ALT, and lower HbA_{1c} and HDL levels compared with the patients with IDD (Table 3). The differences between patients with IDD and patients with type 2 diabetes were even more pronounced for each parameter than those pointed out for the patients with LADA above (Table 3).

Discussion

In this cohort study of 4,374 consecutive individuals, we showed that both fasting C-peptide and GADab status measured at first hospital admission with diabetes, but only to a minor extent age at onset segregates adult patients with relatively newly diagnosed diabetes into groups with clinically relevant differences in metabolic risk profiles.

The differences in HbA_{1c} and markers of cardiometabolic risk between the patients defined as patients with LADA, IDD and type 2 diabetes are quite similar to the differences reported between patients with LADA and type 1 diabetes and type 2 diabetes in other studies [5, 8, 21-27, 33]. Thus, patients with LADA defined an intermediate group with higher HbA_{1c} but otherwise lower cardiometabolic risk than patients with type 2 diabetes. In line, a recent study on metabolites also found LADA to be an intermediate group of type 1 diabetes and type 2 diabetes [34]. However, in contrast to other studies, we also included patients with diabetes with age at onset between 18-30 years and used a fasting C-peptide >300 pmol at first hospital admission with diabetes as a measure of residual insulin production [17]. Thus, in most other studies, these differences were demonstrated only in cohorts of patients older than 30 years using 6-12 months of treatment without insulin as criterion for LADA [1, 8, 21-27, 33, 35]. However, in a study including individuals with age above 20 years, no differences were found between patients with LADA and patients with type 2 diabetes not treated with insulin [36]. These patient subgroups were, however, much smaller than the LADA and type 2 diabetes subgroups in our study, and the average age of onset was above 65 years [36]. Thus, the lack of differences in their study could be explained by less power and older age at onset.

Although previous studies have indicated the presence of LADA in childhood and youth [15, 16], our data extend these findings by showing that LADA with residual insulin secretion (GAD_{pos}CPEP_{high}) also exists in early adulthood (18-30 years of age). Thus, they presented with similar high levels of fasting C-peptide as older GAD_{pos}CPEP_{high} patients. This is in line with the

findings of Bakhtadtze *et al*[37] that uses common variants in *TCF7L2* to differentiate autoimmune from non-autoimmune diabetes in young and middle-aged patients with diabetes. As previously suggested [2, 3, 14, 38], these results question the age at onset criteria for LADA, and suggest that in GADab positive patients, it is the residual insulin secretion that matters, whether measured by fasting C-peptide or time to insulin treatment. This is important to recognise, since there is evidence to suggest that patients with LADA may benefit from early insulin treatment to preserve beta cell function and achieve good glycaemic control [39, 40].

Before tests for islet autoantibodies were clinically available, grouping of patients with diabetes was often based mainly on the analysis of C-peptide or clinical phenotype [17, 41]. Nevertheless, it has been known for decades that islet autoantibodies and low fasting C-peptide often predict insulin requirement in patients with diabetes [42, 43]. Recent studies, indicate that clinicians with access to tests for islet auto-antibodies in a clinical setting tend to start insulin therapy in GADab positive patients with diabetes independent of residual insulin secretion [13, 20]. Using analysis of both GADab and fasting C-peptide in a clinical setting, we demonstrate that cardiovascular risk factors other than HbA_{1c} were lower in patients with LADA compared to patients with type 2 diabetes. On the other hand, patients with LADA had higher levels of these cardiometabolic risk factors than patients with IDD. There is currently no consensus regarding the optimal treatment of LADA [20]. However, while the prognosis of patients with LADA may be better than in patients with type 2 diabetes in terms of macrovascular disease, our data suggest that patients with LADA may benefit from a more aggressive targeting of dyslipidaemia and hypertension than patients with type 1 diabetes and IDD in general.

The patients with LADA had slightly higher HbA_{1c} than patients with type 2 diabetes. This is in agreement with most [22-24, 26, 27], but not all [33] recent studies of patients with LADA versus patients with type 2 diabetes with age at onset >30 years. According to a recent large follow-

up study of LADA and type 2 diabetes [26] this does not seem to be caused by an earlier unmet need for insulin therapy. Thus, patients with LADA had worse glycaemic control despite a longer time on insulin therapy [26]. However, of concern, a recent study demonstrated that mortality in patients with LADA was as high as in patients with type 2 diabetes, and that this could be ascribed to a higher HbA_{1c} rather than BMI or lifestyle factors [24]. We observed no significant differences in HbA_{1c} or markers of cardiometabolic risk other than BMI between the younger and the older LADA cohorts. Thus, our data suggest the possibility that the reported increased mortality may not be confined to patients with LADA with age at onset > 30 years. This lend further support to the notion that age of onset is a very arbitrary criterion for LADA [2, 3, 14, 38]. Consistent with previous studies of LADA [20], these results emphasize the need for better recommendations for treatment of hyperglycaemia and other markers of cardiometabolic risk than hitherto thought. Our findings also indicate that this is equally important for patients diagnosed with autoimmune diabetes in the early adulthood despite residual beta cell function and hence lack of need for insulin therapy.

An important novel finding was that an unbiased stratification according to age at onset, and measurements of islet autoimmunity and fasting C-peptide at first hospital admission with diabetes segregated individuals with a low residual beta cell function (IDD) into a single group with apparently similar markers of cardiometabolic risk independent of age at onset and GADab. Thus, a fasting C-peptide below 300 pmol/l defined a group of insulin deficient patients with diabetes (IDD) with higher HbA_{1c} but also lower levels of other cardiometabolic risk factors than both autoimmune and non-autoimmune patients with diabetes with residual insulin secretion. In some [22, 25], but not all studies [1, 8, 33], similar differences between patients with LADA and type 1 diabetes have been reported. However, again, the novel finding is that these differences were not restricted to patients with an age of onset above 30 years. Patients with IDD had slightly worse glycaemic control than both LADA and patients with type 2 diabetes, and, therefore, potentially

worse prognosis in terms of microvascular diseases. This suggests that treatment of patients with diabetes with a low endogenous insulin secretion, independent of its aetiology, should focus more on the glycaemic control than on other markers of cardiovascular risk. The older group with IDD was quite large, comprising 5% of the study cohort. This suggests that this group includes not only patients with classical type 1 diabetes with other islet autoantibodies than GADab [1], but most likely also a large group of patients with secondary causes of diabetes with loss of residual beta cell function due to e.g. pancreatitis, pancreatic cancer and other pancreatic diseases. Overall, our results provide evidence that in addition to GADab, measurement of fasting C-peptide at an appropriate time after diagnosis in a clinical setting is valuable in pointing out patients with an earlier need for insulin therapy and perhaps less need for targeting dyslipidaemia and hypertension. However, larger prospective studies are needed to provide firm evidence for this, in particular in the older patients with IDD.

In neither GAD_{pos} nor CPEP_{low} subgroups, age of onset above or below 30 years pointed out major differences between groups except for those to be expected by increasing age such as BP. For patients with type 2 diabetes, we observed that BMI, TG, ALT was higher and HDL was lower, whereas DBP, SBP and creatinine were lower in younger patients with type 2 diabetes. This was expected as BMI and consequently fatty liver are believed to play an important role in the pathogenesis of type 2 diabetes in younger individuals [44]. Our data suggest that the younger patients with type 2 diabetes should be offered similar aggressive treatment with respect to both glycaemic control and dyslipidaemia as older patients with type 2 diabetes. The higher BMI and reduced levels of HDL in the younger patients with type 2 diabetes suggest the possibility that they may to a higher extent benefit from lifestyle recommendations such as diet and exercise than the rather disappointing results reported for patients with type 2 diabetes 45-75 years of age [45].

A strength of this study is that it is one of the largest study of glycaemic control and cardiovascular risk factors in a population of consecutive patients with relatively newly diagnosed diabetes. To our knowledge, it is also the first study that investigates the stratification of adult-onset diabetes according to age at onset, fasting C-peptide and presence of GADab at first hospital admission in a clinical setting including patients with onset during early adulthood. The limitations include a high proportion of missing values for markers of cardiometabolic risk. In addition, we lack information about glucose-, lipid-, and BP-lowering medication including treatment with insulin and follow-up data on cardiovascular disease. The high frequency (13%) of GADab positivity indicates a selection bias of patients with diabetes referred to our hospital. This probably reflects a higher need for insulin treatment than seen in the primary care sector. This selection bias also explains a high fraction of patients with IDD, although this may in fact have helped us to point out relevant differences. While previous studies have reported that measurement of other islet autoantibodies seems to add little value to GADab in the diagnosis of LADA [1], we cannot exclude the possibility that analysis of other antibodies (e.g. islet antigen-2 antibody (IA-2A), insulin autoantibody (IAA) and zinc transporter 8 (ZnT8)) in particular among the GADab negative patients with IDD could have influenced the results. Sensitivity analysis showed that it virtually had no impact on the results when including patients that had GADab measured on a different assay from 1997-2001, thus these patients could be included in the analyses.

In summary, our results demonstrate that an unbiased stratification according to age of onset, presence of GADab and fasting C-peptide segregates patients with newly diagnosed adult-onset diabetes into three major groups with clinically relevant differences in glycaemic control and markers of cardiometabolic risk. While age of onset seems of less importance, both GADab status and fasting C-peptide contributed significantly to this segregation of patients with diabetes.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contributions

MW, HB-N, KY and KH were responsible for the conception and design of the study. MW performed the data collection, the analysis and interpretation of data and wrote the manuscript. UH contributed to the analysis of the data, and KH contributed to the analysis and interpretation of the results, and drafting of the manuscript. MW, KY, UH, HB-N and KH revised the manuscript and approved the final version. KH is responsible for the integrity of the work as a whole.

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Figure legends

Figure 1 - Flowchart showing the stratification of patients with adult-onset (>18 years) diabetes according to age of onset above or below 30 years, presence (GAD_{pos}) or absence (GAD_{neg}) of GADab, and fasting C-peptide (CPEP) below ($CPEP_{low}$) or above ($CPEP_{high}$) 300 pmol/l at their first admission with diabetes to Odense University Hospital, Denmark

Table 1 - Clinical and biochemical characteristics of the study cohort

	<i>n</i>	AGE<30 GAD _{pos} CPEP _{low} (Gr. 1)	AGE<30 GAD _{pos} CPEP _{high} (Gr. 2)	AGE<30 GAD _{neg} CPEP _{low} (Gr. 3)	AGE<30 GAD _{neg} CPEP _{high} (Gr. 4)	AGE>30 GAD _{pos} CPEP _{low} (Gr. 5)	AGE>30 GAD _{pos} CPEP _{high} (Gr. 6)	AGE>30 GAD _{neg} CPEP _{low} (Gr. 7)	AGE>30 GAD _{neg} CPEP _{high} (Gr. 8)
<i>n(m/f)</i>	4,374	93(60/33)	48(26/22)	55(39/16)	141(62/79)	137(68/69)	279(149/130)	218(146/72)	3,403(1,971/1,432)
Age at onset (years)	4,374	23.6±3.8	24.4(3.5)	23.8±3.3	25.5±3.4	44.2±11.1	52.5±12.4	51.2±12.2	55.4±12.0
Age at test (years)	3,508	30.9±11.5	26.2(7.5)	33.8±13.7	30.1±9.4	50.6±13.7	55.8±13.2	57.5±12.8	59.1±12.5
BMI (kg/m ²)	3,502	24.5±4.1	27.7(5.3)	24.2±4.6	33.9±9	24.8±3.6	29.6±6.6	24.8±5.3	31.4±6.7***
SBP (mmHg)	3,277	126±15	124(11)	131±18	129±14	132±21*	136±17***	134±22	139±20***
DBP (mmHg)	3,277	77±9	76(8)	79±10	81±11	79±12	82±11*	78±12	82±11
C-peptide (pmol/l)	4,374	117(22-185)	500(408-812)	120(44-196)	1,051(672-1,588)	146(55-217)	793(489-1,230)	189(128-235)	1,080(753-1,504)
HbA _{1c} (%)	4,259	9.2±2.3	8.2(2.2)	10.6±3.3	8.4±2.3	9.8±2.7	8.8±2.2	9.3±2.7*	8.4±2.0
HbA _{1c} (mmol/mol)	4,259	76.8±25.3	65.9(24.5)	92.2±36.2	68.2±24.6	83.2±29.8	72.8±23.8	78.5±29.8	67.9±21.8
HDL (mmol/l)	3,292	1.5±0.5	1.2(0.4)	1.4±0.4	1.1±0.4	1.6±0.5	1.3±0.4	1.5±0.6	1.3±0.4***
LDL (mmol/l)	3,177	2.5±0.8	2.7(0.8)	2.7±0.7	2.9±1.0	2.6±0.8	2.8±1.0	2.4±1.0	2.7±1.0
TG (mmol/l)	3,295	1.09(0.76-1.31)	1.81(1.30-2.57)	1.2(0.77-2.15)	2.1(1.44-3.00)	0.99(0.73-1.22)	1.56(1.13-2.38)	1.16(0.80-1.66)	1.8(1.77-2.65)**
ALT (U/l)	3,182	21(15-29)	27(16-41)	22(15-27)	35(20-63)	19(15-27)	27(19-41)	21(16-30)	29(20-44)***
Creatinine (μmol/l)	3,387	86(76-94)	83(69-89)	81(67-97)	79(70-89)	80(65-92)	84(74-96)	82(68-96)	87(76-100)***

Patients with adult-onset (<18 years) diabetes stratified into 8 groups (Gr.1 – Gr. 8) according to age of onset below (AGE<30) or above (AGE>30) 30 years, serum fasting C-peptide below (CPEP_{low}) or above (CPEP_{high}) 300 pmol/l, and the presence (GAD_{pos}) or absence (GAD_{neg}) of anti-GAD antibodies. Data are mean +/- SD or median (IQR). **p*<0.05, ***p*<0.01 and ****p*<0.001 vs AGE<30 in the group with the same CPEP and GAD status.

Table 2 - Clinical and biochemical characteristics of segregated groups (I-IV) of the study cohort

	<i>n</i>	GAD _{pos} CPEP _{low} (Gr. I)	GAD _{pos} CPEP _{high} (Gr. II)	GAD _{neg} CPEP _{low} (Gr. III)	GAD _{neg} CPEP _{high} (Gr. IV)
<i>n(m/f)</i>		230(128/122)	327(175/152)	273(185/88)	3,544(2,033/1,511)
Age at onset (years)	4,374	35.9±13.5	48.4±15.3	45.7±15.6	54.2±13.1
Age at test (years)	4,374	42.6±16.1	51.4±16.3	52.7±16.1	57.9±13.6
BMI (kg/m ²)	3,502	24.7±3.8 ^{***}	29.3±6.4 ^{†††}	24.6±5.2	31.5±6.8 ^{†††}
SBP (mmHg)	3,277	129±19	134±17 [†]	133±22	138±19 [†]
DBP (mmHg)	3,277	78±11	81±10	79±11	82±11 ^{†††}
C-peptide (pmol/l)	4,374	130(29-204)	745(469-1,207)	173(100-230)	1,079(752-1,511)
HbA _{1c} (%)	4,259	9.5±2.6 ^{***}	8.7±2.2 [†]	9.6±2.9	8.4±2.0 ^{†††}
HbA _{1c} (mmol/mol)	4,259	80.6±28.2	71.8±24.0	81.3±31.6	67.9±21.9
HDL (mmol/l)	3,292	1.6±0.5 ^{***}	1.3±0.4 ^{†††}	1.5±0.5 [#]	1.2±0.4 ^{†††}
LDL (mmol/l)	3,177	2.6±0.8 [*]	2.8±1.0	2.5±1.0	2.8±1.0 ^{††}
TG (mmol/l)	3,295	1(0.73-1.26) ^{***}	1.58(1.16-2.40) ^{†††}	1.20(0.80-1.68) [#]	1.80(1.27-2.66) ^{†††}
ALT (U/l)	3,182	20(15-28) ^{***}	27(19-41) ^{††}	22(16-29)	29(20-44) ^{†††}
Creatinine (μmol/l)	3,387	82(70-92)	84(73-94)	82(68-97)	87(76-100) [†]

Patients with adult-onset diabetes were segregated into four groups according to serum fasting C-peptide below (CPEP_{low}) or above (CPEP_{high}) 300 pmol/l, and the presence (GAD_{pos}) or absence (GAD_{neg}) of anti-GAD antibodies. Data are mean +/- SD or median (IQR).

p*<0.05, *p*<0.01 and ****p*<0.001 GAD_{pos}CPEP_{low} vs. GAD_{pos}CPEP_{high}.

†*p*<0.05, ††*p*<0.01 †††*p*<0.001 GAD_{neg}CPEP_{high} vs. GAD_{neg}CPEP_{low}.

†*p*<0.05, ††*p*<0.01 and †††*p*<0.001 GAD_{pos}CPEP_{high} vs. GAD_{neg}CPEP_{high}.

#*p*<0.05 GAD_{neg}CPEP_{low} vs GAD_{pos}CPEP_{low}.

Table 3 - Clinical and biochemical characteristics of segregated groups of the study cohort

	<i>n</i>	IDD	LADA	T2D
n(m/f)	4,374	503(313/190)	327(175/152)	3,544(2,033/1,511)
Age at onset (years)	4,374	41.2±15.4	48.4±15.3	54.2±13.1
Age at test (years)	4,374	48.1±16.8	51.4±16.3	57.9±13.6
BMI (kg/m ²)	3,502	24.7±4.6 ^{***}	29.3±6.4 ^{†††}	31.5±6.8 [‡]
SBP (mmHg)	3,277	131±20	134±17 [†]	138±19 [‡]
DBP (mmHg)	3,277	79±11 [*]	81±10	82±11 [‡]
C-peptide (pmol/l)	4,374	158(64-222)	745(469-1,207)	1,079(752-1,511)
HbA _{1c} (%)	4,259	9.6±2.8 ^{***}	8.7±2.2 [†]	8.4±2 [‡]
HbA _{1c} (mmol/mol)	4,259	81±30.1	71.8±24	67.9±21.9
HDL (mmol/l)	3,292	1.5±0.5 ^{***}	1.3±0.4 ^{†††}	1.2±0.4 [‡]
LDL (mmol/l)	3,177	2.5±0.9 ^{**}	2.8±1.0	2.8±1.0 [‡]
TG (mmol/l)	3,295	1.08(0.77-1.51) ^{***}	1.58(1.16-2.40) ^{††}	1.8(1.27-2.66) [‡]
ALT (U/l)	3,182	21(15-29) ^{***}	27(19-41) ^{††}	29(20-44) [‡]
Creatinine (μmol/l)	3,387	82(69-95)	84(73-94)	87(76-100)

Patients with adult-onset diabetes were segregated into three major groups. Insulin deficient diabetes (IDD) patients with fasting C-peptide below 300 pmol/l independent of GADab, patients with LADA with GADab positivity and fasting C-peptide above 300 pmol/l, and type 2 diabetes (T2D) patients with absence of GADab and fasting C-peptide above 300 pmol/l. Data are mean +/- SD or median (IQR).

* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ for IDD vs LADA;

[†] $p < 0.05$, ^{††} $p < 0.01$ and ^{†††} $p < 0.001$ for LADA vs T2D;

[‡] $p < 0.001$ for T2D vs IDD.

Highlights

- Method for stratifying diabetes into groups with differences in cardiometabolic is proposed.
- Age at onset is not useful in stratifying diabetes into these groups.
- Fasting C-peptide and GADab define groups with relevant differences in cardiometabolic risk.
- Groups are defined as insulin deficient diabetes, LADA and type 2 diabetes mellitus.

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FIG. 1.

