Pathophysiology-based phenotyping in type 2 diabetes: A clinical classification tool


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Funding information
Danish Agency for Science, Grant/Award Number: 09-075724 09-067009; The Region of Southern Denmark; Novo Nordisk Foundation; Novo Nordisk A/S; Region of Southern Denmark; Danish Diabetes Association; Danish Health and Medicines Authority

Abstract
Background: Type 2 diabetes may be a more heterogeneous disease than previously thought. Better understanding of pathophysiological subphenotypes could lead to more individualized diabetes treatment. We examined the characteristics of different phenotypes among 5813 Danish patients with new clinically diagnosed type 2 diabetes.

Methods: We first identified all patients with rare subtypes of diabetes, latent autoimmune diabetes of adults (LADA), secondary diabetes, or glucocorticoid-associated diabetes. We then used the homeostatic assessment model to subphenotype all remaining patients into insulinopenic (high insulin sensitivity and low beta cell function), classical (low insulin sensitivity and low beta cell function), or hyperinsulinemic (low insulin sensitivity and high beta cell function) type 2 diabetes.

Results: Among 5813 patients diagnosed with incident type 2 diabetes in the community clinical setting, 0.4% had rare subtypes of diabetes, 2.8% had LADA, 0.7% had secondary diabetes, 2.4% had glucocorticoid-associated diabetes. We then used the homeostatic assessment model to subphenotype all remaining patients into insulinopenic (high insulin sensitivity and low beta cell function), classical (low insulin sensitivity and low beta cell function), or hyperinsulinemic (low insulin sensitivity and high beta cell function) type 2 diabetes.

Conclusions: Patients clinically diagnosed with type 2 diabetes are a heterogeneous group. In the future, targeted treatment based on pathophysiological characteristics rather than the current “one size fits all” approach may improve patient prognosis.

KEYWORDS
clinical diabetes, insulin sensitivity and resistance, insulin secretion, pathophysiology, individualized treatment, treatment guidelines

Abbreviations: DD2, Danish Centre for Strategic Research in Type 2 Diabetes; DNRP, Danish National Registry of Patients; FPG, fasting plasma glucose; GADA, glutamic acid decarboxylase antibodies; GLP-1, glucagon-like peptide 1; GP, general practitioner; IQR, interquartile range; IS, insulin sensitivity; LADA, latent autoimmune diabetes of adults; PR, prevalence ratio

†Professor Jens S. Christiansen, who supervised this research, died on 16 December 2015 before publication of this work.

Received: 4 April 2017 Revised: 10 February 2018 Accepted: 14 March 2018
DOI: 10.1002/dmrr.3005

https://doi.org/10.1002/dmrr.3005
1 | INTRODUCTION

Type 2 diabetes mellitus now affects 5% to 10% of the adult population in most countries, and its prevalence is rapidly increasing. Despite multifactorial interventions and expanding pharmacological treatment options, type 2 diabetes patients have greatly increased morbidity and mortality compared with individuals without diabetes. One reason may be that type 2 diabetes is a pathophysiologically more heterogeneous disease than previously thought and therefore requires more individualized treatment.

WHO classifies diabetes mellitus into 4 overall categories: type 1 diabetes, type 2 diabetes, "other specific forms of diabetes", and gestational diabetes. We hypothesize that patients with "other specific forms of diabetes" are frequently misclassified in everyday clinical practice as having type 2 diabetes. These patients are thus at risk of being treated on the basis of general type 2 diabetes treatment algorithms, rather than in accordance with the specific pathophysiology of their diabetes.

WHO defines type 2 diabetes as a disease characterized by varying degrees of insulin resistance and insulin deficiency, in which hyperglycemia develops when insulin secretory capacity cannot compensate for insulin resistance. Type 2 diabetes can develop at the 2 extremes of the continuum, with patients having either beta cell failure or insulin resistance as the principal pathophysiological defect. We hypothesize that subphenotyping based on estimation of insulin secretion and insulin sensitivity (IS) can be used to characterize this heterogeneity. Because most glucose-lowering agents target either IS or insulin secretion deficiency, subphenotyping may allow more individualized treatment with improved results.

We undertook this study to examine pathophysiological phenotypes among Danish patients with new clinically diagnosed type 2 diabetes. We first assessed the extent to which type 2 diabetes was accurately classified and then tested whether patients correctly diagnosed with WHO-defined type 2 diabetes could be further subphenotyped based on their estimated IS and insulin secretion. We also examined the association between different type 2 diabetes subphenotypes and important clinical characteristics present at the time of diagnosis, such as age, gender, waist circumference, and history of cardiovascular morbidity. Our ultimate goal was to provide clinicians with a rather simple clinical classification tool that could help them make diabetes treatment choices more individualized.

2 | MATERIALS AND METHODS

2.1 | Study population and data sources

This cross-sectional study was based on information from the "Danish Centre for Strategic Research in Type 2 Diabetes" (DD2) study, which has enrolled newly diagnosed type 2 diabetes patients via general practitioners (GPs) and hospital specialist outpatient clinics throughout Denmark since 2010. All patients aged ≥18 years with new clinically diagnosed type 2 diabetes in Denmark after 2009 are eligible to participate in the DD2 cohort. The patients are eligible regardless of treatment, including insulin, as long as the caregiver perceives the patient as having clinical type 2 diabetes. The DD2 project has enrolled on average approximately 1250 patients per year, ie, an estimated 5% of the approximately 25 000 new type 2 diabetes patients diagnosed annually in Denmark. At inclusion, participants undergo a detailed interview and clinical examination and provide blood and urine samples (fasting samples obtained in 77% of patients). These data are stored in a research database and biobank.

Participants eligible for our study consisted of the first 6,474 patients enrolled in the DD2 study cohort between 30 November 2010 and 29 June 2015. We excluded 660 patients with no available measurements of glutamic acid decarboxylase antibodies (GADA) (needed to exclude presence of type 1 diabetes with certainty) and 1 patient with type 1 diabetes. This left 5813 patients eligible for further phenotyping into either WHO-defined type 2 diabetes or other specific forms of diabetes (see Figure 1 flowchart). At the time of enrollment, 16.1% of patients in our study cohort had not yet begun to use glucose-lowering drugs, 78.3% were taking oral glucose-lowering agents, and 5.7% used insulin alone or in combination with glucose-lowering drugs. Median time from diagnosis to enrollment was 476 days (IQR 116, 1050) in the entire population, while it was 59 days (IQR 0, 612) in the drug-naive subpopulation. We used the Danish National Patient Registry to identify the presence of cardiovascular disease (CVD), based on hospital ICD-10 diagnostic codes for any CVD, including ischemic heart disease, cerebrovascular disease, peripheral vascular disease, and associated revascularization procedures.

All biochemical tests were performed in the ISO 15189 accredited laboratory at Center Hospital Lillebaelt, Region of Southern Denmark. We used the stored blood samples to measure antibodies against human glutamate decarboxylase 65-kDa isoform, using the AESKULISA GAD65 kit (AESKU Diagnostics, Wendelsheim, Germany). The kit has a sensitivity of 92% and a specificity of 98%, and a predictive value of a positive test of 85% in our population. Fasting C-peptide was analysed using the Roche C-Peptide assay (Roche Diagnostics, Mannheim, Germany). Fasting plasma glucose (FPG) was analysed using an enzymatic hexokinase method (Glucocquant Glucose/HK, Roche Diagnostics, Mannheim, Germany).

2.2 | Phenotypes of type 2 diabetes

We first identified patients with "other specific forms" of diabetes in the classification of diabetes mellitus described in the 2003 Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. The other forms included specific known causes of insulin resistance and/or beta cell failure leading to hyperglycemia, eg, rare subtypes of diabetes, latent autoimmune diabetes of adults (LADA), secondary diabetes (associated with pancreatic disease), and glucocorticoid-associated diabetes. Using data from the DNRP, the Danish National Health Service Prescription Registry, and the GAD antibody titers, we categorized these "other specific forms" as follows: (1) rare subtypes of diabetes (see supplemental material); (2) LADA, ie, GADA titer ≥20 IE/mL (international WHO units) and age > 30 years; (3) secondary diabetes, ie, with a history of pancreatitis. 

"Other specific forms of diabetes include specific known causes of insulin resistance and/or beta cell failure leading to hyperglycemia, eg, rare subtypes of diabetes, latent autoimmune diabetes of adults (LADA), secondary diabetes (associated with pancreatic disease), and glucocorticoid-associated diabetes. Using data from the DNRP, the Danish National Health Service Prescription Registry, and the GAD antibody titers, we categorized these "other specific forms" as follows: (1) rare subtypes of diabetes (see supplemental material); (2) LADA, ie, GADA titer ≥20 IE/mL (international WHO units) and age > 30 years; (3) secondary diabetes, ie, with a history of pancreatitis.

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or pancreas resection; and (4) glucocorticoid-associated diabetes, i.e., patients who redeemed prescriptions for oral glucocorticoids within 3 months prior to inclusion in the cohort.

2.3 | Subphenotypes of WHO-defined type 2 diabetes

The remaining 5445 patients were categorized as meeting WHO-defined criteria for "true" type 2 diabetes. We further subphenotyped these patients according to their beta cell function and IS (4285 patients with data available [see Figure 1]), into those with insulinopenic type 2 diabetes (high IS and low beta cell function), classical type 2 diabetes (low IS and low beta cell function), or hyperinsulinemic type 2 diabetes (low IS and high beta cell function). We used version 2 of the revised homeostatic assessment model (HOMA2) to estimate IS (HOMA2S) and beta cell function (HOMA2B) based on fasting C-peptide and plasma glucose values.17 High and low values for IS and beta cell function were defined as being above or below the median values for HOMA2S and HOMA2Beta in a non-diabetic background population sample selected from all residents (360,921) of 1 Danish county, as previously described.18 In brief, health registries were used to identify all persons aged 25 to 75 years in the county as of 31 December 2006, and those with diabetes were ascertained using a regional algorithm. Non-diabetic individuals were age- and gender-matched to the diabetic population. We used version 2 of the revised homeostatic assessment model (HOMA2) to estimate IS (HOMA2S) and beta cell function (HOMA2B) based on fasting C-peptide and plasma glucose values.17 High and low values for IS and beta cell function were defined as being above or below the median values for HOMA2S and HOMA2Beta in a non-diabetic background population sample selected from all residents (360,921) of 1 Danish county, as previously described.18 In brief, health registries were used to identify all persons aged 25 to 75 years in the county as of 31 December 2006, and those with diabetes were ascertained using a regional algorithm. Non-diabetic individuals were age- and gender-matched to the diabetic population. A random sample of non-diabetic subjects was then invited to contribute samples to a biobank. FPG was measured in 4980 subjects, from whom 120 persons within each age-decile (35-75 years of age) were randomly sampled. All 98 persons aged 25 to 35 years were included, yielding a total sample of 578 persons for whom C-peptide was measured. Among these 578 persons, 483 had normal glucose tolerance (defined as FPG ≤ 6.1 mmol/L). The sample of 483 persons was then used to calculate median HOMA values. The median BMI was 26 kg/m² in the background population sample, equal to the median BMI among Danish residents.19

2.4 | Statistical analyses

We calculated the prevalence with corresponding 95% confidence intervals (CIs), of the insulinopenic, classical, and hyperinsulinemic phenotypes in our type 2 diabetes population.

The robustness of our subphenotyping independent of the patients’ current pharmacological treatment was evaluated by separately examining the subphenotype distribution in the subcohort of patients who were naive to glucose-lowering drugs.

Within each subphenotype, median and quartiles were calculated for age and waist circumference, and the medians of the hyperinsulinemic and insulinopenic subphenotypes were compared with those of the classical subphenotype using the 2-sided Wilcoxon test. A level of P < 0.05 was considered statistically significant. Prevalence of CVD at inclusion in the DD2 cohort was calculated within each subphenotype, and the hyperinsulinemic and insulinopenic subphenotypes were compared with the classical subphenotype using prevalence ratios (PRs). For each patient, HOMA2Beta (y-axis) was plotted against HOMA2S (x-axis) to show the relation of beta cell function and IS among type 2 diabetes patients and among the non-diabetic background population. All analyses were performed using SAS version 9.4.

The study was approved by the Regional Ethical Committee on Health Research (record number S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035). All patients received oral and written information before signing an informed consent.
3  |  RESULTS

Among 5813 patients with newly diagnosed type 2 diabetes eligible for further phenotyping, 58.1% ([95% CI 56.9, 59.4], n = 3379) were men, and the median age was 62 years (interquartile range [IQR] 53-69 years). The median waist circumference was 106 cm (IQR 97-116 cm), and the median FPG level was 7.13 mmol/L (IQR 6.37-8.25 mmol/L). We found that 0.4% (n = 21) of the patients had rare subtypes of diabetes, 2.8% (n = 164) had LADA, 0.7% (n = 43) had secondary diabetes, and 2.4% (n = 140) had glucocorticoid-associated diabetes (Table 1). The remaining 93.7% ([95% CI 93.0, 94.3], n = 5445) of the patients who had been diagnosed with type 2 diabetes fulfilled the WHO criteria for type 2 diabetes.

For patients with WHO-defined type 2 diabetes, the results of our HOMA2 analysis based on FPG and fasting plasma C-peptide are shown in Figure 2. The figure presents the hyperbolic relation between the variables, HOMA2B (beta cell function) and HOMA2S (IS).20 For comparative purposes, Figure 3A presents the hyperbolic relation for the general population with normal glucose tolerance (FPG ≤ 6.1 mmol/L). As expected, values for patients meeting criteria for WHO-defined type 2 diabetes are located to the left and below the curve for the general population. Thus, for every value of IS, beta cell function in type 2 diabetes patients was lower than in the background population. There is some overlap (Figures 2 and 3A), however, indicating that some type 2 diabetes patients had FPG values below 6.1 mmol/L at enrollment in the DD2 study.

In Figure 2, median values for IS and beta cell function calculated from the background population separate the type 2 diabetes patients into 3 distinctly classified subphenotypes. One group (lower right) is characterized by normal to high IS but severely reduced beta cell function (insulinopenic type 2 diabetes). A second group is characterized by both insulin resistance and reduced beta cell function (classical type 2 diabetes). The third group is characterized by severe insulin resistance, but normal to high beta cell function (hyperinsulinemic type 2 diabetes). Figure 3B plots type 2 diabetes patients according to their FPG values. This shows that patients with classical type 2 diabetes had the highest FPG levels, while patients with insulinopenic and hyperinsulinemic type 2 diabetes had lower FPG values.

In our study cohort, classical type 2 diabetes was the most common (63.1%) of the 3 pathophysiologically determined subphenotypes of WHO-defined type 2 diabetes, while hyperinsulinemic type 2 diabetes (27.2%) and insulinopenic type 2 diabetes (9.7%) were less prevalent (Table 1). Compared with patients with classical type 2 diabetes, patients with insulinopenic type 2 diabetes were older (63.8 vs 61.9 years, P = 0.01), had a much smaller waist circumference (median 92.0 vs 105.0 cm, P < 0.0001), and tended to have a lower prevalence of previously diagnosed CVD (17.5% vs 20.5%, PR 0.85 [95% CI 0.68, 1.07]; Table 2). In contrast, patients with hyperinsulinemic type 2 diabetes had more pronounced central obesity (median 112.0 vs 105.0 cm, P < 0.0001) and substantially more CVD (26.5% vs 20.5%, PR 1.29 [95% CI 1.15, 1.46]) compared to patients with classical type 2 diabetes. Median Hba1c levels at enrollment were also significantly different among patients with hyperinsulinemic (6.33%) and insulinopenic type 2 diabetes (6.52%) compared to patients with classical type 2 diabetes (6.62%), although the absolute differences were modest. A family history of type 2 diabetes was found in 47.5% of hyperinsulinemic, 53.3% of insulinopenic, and 55.3% of classical type 2 diabetes patients.

Most type 2 diabetes patients included in our cohort had started glucose-lowering treatment before study enrollment and insulin treatment was more prevalent in insulinopenic type 2 diabetes patients.

### TABLE 1  Prevalence of pathophysiological phenotypes in 5,813 patients with new clinically diagnosed type 2 diabetes in Denmark, 2010-2015

<table>
<thead>
<tr>
<th>Pathophysiological Phenotypes</th>
<th>Number of Patients, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with &quot;other specific forms&quot; of diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>Rare subtypes</td>
<td>21.04 (0.2, 0.5)</td>
</tr>
<tr>
<td>LADA</td>
<td>164.28 (2.4, 3.2)</td>
</tr>
<tr>
<td>Secondary diabetes</td>
<td>43.07 (0.5, 1.0)</td>
</tr>
<tr>
<td>Glucocorticoid-associated diabetes</td>
<td>140.24 (2.0, 2.8)</td>
</tr>
<tr>
<td><strong>Patients with WHO-defined type 2 diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>Insulinopenic type 2 diabetes</td>
<td>411.96 (8.7, 10.5)</td>
</tr>
<tr>
<td>Classical type 2 diabetes</td>
<td>2713.63 (61.9, 64.8)</td>
</tr>
<tr>
<td>Hyperinsulinemic type 2 diabetes</td>
<td>1161.27 (25.8, 28.4)</td>
</tr>
</tbody>
</table>
However, we found a very similar subphenotype distribution among the 668 drug-naive patients, ie, 9.9% had insulinopenic, 62.0% had classical, and 28.1% had hyperinsulinemic type 2 diabetes. In drug-naive patients, the median HbA1c was marginally lower than in the whole population (6.30 [IQR 5.95, 6.71] vs 6.52 [IQR 6.14, 7.09]). However, the absolute values and intergroup differences in anthropometrics and CVD in the 3 different pathophysiological groups did not change materially when the analysis was restricted to drug-naive patients (Table 4).

4 | DISCUSSION

In this large study of patients newly diagnosed with type 2 diabetes by Danish GPs and hospital outpatient clinics, we identified several distinct pathophysiological phenotypes. Approximately 6% of the patients were clinically misclassified as type 2 diabetes patients, when they instead had secondary diabetes, glucocorticoid-associated diabetes, LADA, or rare subtypes of diabetes. Patients who met WHO-defined criteria for type 2 diabetes mostly had classical type 2 diabetes, but 1 subgroup of insulinopenic type 2 diabetes patients had completely normal IS, while another subgroup of hyperinsulinemic type 2 diabetes patients had normal to high beta cell function. In contrast to the 2 other subphenotypes, insulinopenic type 2 diabetes patients had a nearly normal waist circumference and (consistent with their high IS) a lower prevalence of CVD. In contrast, hyperinsulinemic type 2 diabetes patients had more abdominal obesity and a higher prevalence of CVD. These findings support the hypothesis that hyperinsulinemia is atherogenic. The prevalence of CVD was not associated with HbA1c at enrollment, as the hyperinsulinemic T2D patients had the lowest HbA1c. Even though insulinopenic type 2 diabetes patients had lower prevalence of CVD, it still remained higher than in the background population. National figures for the prevalence of myocardial infarction in 2015 was 2.5%, with an age and gender distribution approximated to our cohort. As the prevalence was 4.1% in insulinopenic type 2 diabetes patients, management of cardiovascular risk factors must still be considered important in this subphenotype.

Our study is novel as it, to our knowledge, is the first to propose a pathophysiologically based subphenotyping in the general type 2 diabetes population. The inherent heterogeneity of insulin resistance and beta cell function implied by the hyperbolic relationship in healthy subjects is not new. The existence of lean and obese healthy subjects with similar insulin resistance is also known. Nevertheless, in type 2 diabetes, such characterizations are scarce and have only focused on mean values—not the heterogeneity. Some studies have investigated the utility of C-peptide level in order to identify selected patients with an absolute need for insulin. These studies did not relate beta cell function to insulin resistance. Furthermore C-peptide measurements were not standardized which reduces the generalizability. This will also be true for HOMA2 unless an appropriate standardization against a healthy reference group is made, as done in our study.

A related paper from our department has characterized a clinic-based diabetes population, including type 1 diabetes, according to

![Figure 3](image-url)
Clinical characteristics of the 3 subphenotypes among patients meeting WHO-defined criteria for type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Insulinopenic Type 2 Diabetes (N = 411)</th>
<th>Classical Type 2 Diabetes (N = 2713)</th>
<th>Hyperinsulinemic Type 2 Diabetes (N = 1161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, IQR)</td>
<td>63.8 (55.3, 69.8)*</td>
<td>61.9 (53.3, 68.6)*</td>
<td>62.9 (53.8, 70.3)*</td>
</tr>
<tr>
<td>Men N, % (95% CI)</td>
<td>239, 58.2 (53.4, 62.9)</td>
<td>1625, 59.9 (58.1, 61.7)</td>
<td>639, 55.0 (52.2, 57.9)*</td>
</tr>
<tr>
<td>Waist (cm, IQR)</td>
<td>92.0 (85, 100)**</td>
<td>105.0 (97, 115)**</td>
<td>112.0 (102, 121)**</td>
</tr>
<tr>
<td>BMI (kg/cm², IQR)</td>
<td>25.3 (23.2, 28.7)**</td>
<td>30.1 (27.1, 34.0)</td>
<td>33.0 (29.3, 37.0)**</td>
</tr>
<tr>
<td>HbA1c (%, IQR)</td>
<td>6.52 (6.05, 7.00)**</td>
<td>6.62 (6.20, 7.20)</td>
<td>6.33 (6.05, 6.71)**</td>
</tr>
<tr>
<td>FPG (mmol/L, IQR)</td>
<td>6.51 (5.88, 7.38)**</td>
<td>7.63 (6.88, 8.75)</td>
<td>6.42 (5.88, 6.94)**</td>
</tr>
</tbody>
</table>

Previous cardiovascular disease (any) N, % (95% CI) 72, 17.5 (13.8, 21.2)b 556, 20.5 (19.0, 22.0) 308, 26.5 (24.0, 29.1)c
Previous myocardial infarction N, % (95% CI) 17, 4.1 (2.2, 6.1) 120, 4.4 (3.6, 5.2) 75, 6.5 (5.0, 7.9)d
Previous heart failure N, % (95% CI) 7, 1.7 (0.5, 3.0)e 90, 3.3 (2.6, 4.0) 71, 6.1 (4.7, 7.5)f
Previous cerebrovascular disease N, % (95% CI) 17, 4.1 (2.2, 6.1)g 175, 6.5 (5.5, 7.4) 78, 6.7 (5.3, 8.2)

All comparisons use classical type 2 diabetes as the reference group. HbA1c was available in 3543 and BMI in 2748 of 4285 patients.

C-peptide levels, age, and GADA. HbA1c was higher and other cardiovascular risk factors were decreased in patients with low C-peptide, regardless of age and GADA. These results are in line with the present study, although the proportion of patients with low C-peptide, which were characterized as clinically having type 2 diabetes, was not known.33

A second novel finding is the differences in cardiovascular morbidity between subphenotypes. Only few studies have investigated the association between measures of insulin resistance or beta cell function and CVD in type 2 diabetes. Some studies did not find an association between C-peptide and CVD,34-36 while others did.34 Insulin resistance, measured as HOMA-IR is associated with CVD, beyond known risk factors in persons without diabetes.37-41 This association has not been tested in unselected patients with type 2 diabetes, although insulin resistance is known to usually precede manifest diabetes by several years.42 The aim of the current cross-sectional investigation was not to examine whether insulin resistance causes CVD but first and foremost to establish a classification with pathophysiological and clinical relevance. Still, our data point to a role of insulin resistance in CVD. Obesity is also known to be associated with CVD and is possible a main mediator of the higher cardiovascular occurrence in hyperinsulinemic patients, although the association with obesity is complex in patients with type 2 diabetes.44,45 As the cause-and-effect directions in the pathophysiological pathways of obesity and IR are impossible to disentangle in a cross-sectional design, we cannot make inference if primary IR caused atherosclerosis in a time sequence, although evidence is present for a role of insulin resistance in CVD.41 On the other hand, intraabdominal fat deposition only explains 52% of the variation in insulin resistance,23 which in itself is an argument for measuring insulin resistance and not estimating it from obesity related measures, when pathophysiological treatment suggestions are made.

Misclassification of “other specific forms” of diabetes as type 2 diabetes has potential implications for treatment and subsequent outcomes, if affected patients are treated according to general type 2 diabetes treatment algorithms rather than receiving treatment based on specific causes of hyperglycemia.5 Other studies have found a higher prevalence of LADA in different European T2D populations than our 2.8%, with rates ranging from 2.8 to 9.3%.46-53 The main reason for the discrepancy is likely that our cohort enrolls unselected
TABLE 4  Clinical characteristics of the 3 subphenotypes among drug-naive patients meeting WHO-defined criteria for type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Insulinopenic Type 2 Diabetes</th>
<th>Classical Type 2 Diabetes</th>
<th>Hyperinsulinemic Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, IQR)</td>
<td>65.3 (57.9, 69.2)</td>
<td>65.0 (57.8, 71.2)</td>
<td>65.5 (56.3, 71.6)</td>
</tr>
<tr>
<td>Men N, % (95% CI)</td>
<td>35, 53.0 (41.0, 65.1)</td>
<td>235, 56.8 (52.0, 61.5)</td>
<td>97, 51.6 (44.4, 58.8)</td>
</tr>
<tr>
<td>Waist (cm, IQR)</td>
<td>90 (84, 99)***</td>
<td>102 (95, 112)</td>
<td>110 (101, 120)***</td>
</tr>
<tr>
<td>BMI (kg/m², IQR)</td>
<td>24.7 (23.1, 28.1)***</td>
<td>29.0 (26.5, 32.6)</td>
<td>33.1 (29.1, 37.0)***</td>
</tr>
<tr>
<td>HbA1c (%, IQR)</td>
<td>6.17 (5.86, 6.61)</td>
<td>6.30 (5.95, 6.71)</td>
<td>6.30 (5.90, 6.60)</td>
</tr>
<tr>
<td>FPG (mmol/L, IQR)</td>
<td>6.09 (5.74, 6.81)***</td>
<td>7.18 (6.64, 7.97)</td>
<td>6.49 (5.87, 7.06)***</td>
</tr>
<tr>
<td>Previous cardiovascular disease (any) N, % (95% CI)</td>
<td>8, 12.1 (4.2, 20.0)</td>
<td>80, 19.3 (15.5, 23.1)</td>
<td>47, 25.0 (18.8, 31.2)</td>
</tr>
<tr>
<td>Previous myocardial infarction N, % (95% CI)</td>
<td>1, 1.5 (0, 4.5)</td>
<td>18, 4.3 (2.4, 6.3)</td>
<td>11, 5.9 (2.5, 9.2)</td>
</tr>
<tr>
<td>Previous heart failure N, % (95% CI)</td>
<td>0, 0 (0, 0)</td>
<td>11, 2.7 (1.1, 4.2)</td>
<td>10, 5.3 (2.1, 8.5)</td>
</tr>
<tr>
<td>Previous cerebrovascular disease N, % (95% CI)</td>
<td>1, 1.5 (0, 4.5)</td>
<td>19, 4.6 (2.6, 6.6)</td>
<td>19, 10.1 (5.8, 14.4)</td>
</tr>
</tbody>
</table>

All comparisons use classical type 2 diabetes as the reference group. HbA1c was available in 527 and BMI in 393 of 668 patients.

PR 0.83 (95% CI 0.69, 1.00).
PR 0.63 (95% CI 0.32, 1.24).
PR 1.29 (95% CI 0.94, 1.78).
PR 0.35 (95% CI 0.05, 2.57).
PR 1.35 (95% CI 0.65, 2.79).
PR 2.00 (95% CI 0.87, 4.63).
PR 0.33 (95% CI 0.04, 2.43).
PR 2.20 (95% CI 1.19, 4.06).

***p < 0.0001.

Many studies were performed in a few selected clinics and/or among younger patient populations with greater disease severity, where the prevalence of LADA is likely to be higher. In community dwelling newly diagnosed type 2 diabetes patients resembling ours, the prevalence of LADA has been found to be comparable. Furthermore, GADA testing is not standardized across the referenced studies, making direct comparison between studies difficult. Other diabetes-related auto-antibodies could also define LADA but may only increase its prevalence marginally and at the same time increase the expense greatly.48-50 There is evidence that LADA patients may obtain best outcomes with initial insulin treatment, while sulfonylurea therapy is not recommended. As patients with secondary diabetes have low insulin and glucagon secretion and are at high risk of hypoglycemia, insulin and incretin-based drugs may be their best treatment option.55 Patients with glucocorticoid-associated diabetes often experience post-prandial hyperglycemia and may be treated with prandial insulin only, although GLP1 receptor agonists also seem to be effective.56 We acknowledge that we in the present study cannot prove that glucocorticoids were the direct cause of the diabetes, but only that they were associated. Steroid treatment is transient in many patients and formal phenotyping should be performed in case the diabetes persists after discontinuation. Patients with rare diseases that cause hyperglycemia should be treated individually, taking their specific underlying disease into consideration. Thus, general treatment guidelines are not applicable to patients with pathophysiologically diabetes phenotypes outside the traditional WHO type 2 diabetes definition.

Our findings are in line with a recent study showing that a proportion of prediabetic subjects develop type 2 diabetes despite having normal IS, due to a primary beta cell defect. These patients, designated as having insulinopenic type 2 diabetes, were not misclassified as type 1 diabetes or LADA patients in our study, as we excluded patients with autoimmune disease (GADA-positive patients) before we undertook extended phenotyping. Therefore, it seems likely that hyperglycemia develops in these patients only due to beta cell deficiency. The exact cause of the beta cell deficiency is not known. A high proportion of GADA-positive patients, ranging from 19 to 69%, have been shown to lose their anti-bodies over time, which could be a hypothetic explanation for GADA-negative insulinopenia. The majority of patients have been shown to lose their GADA positive status within 6 months.59

Our findings clearly indicate that type 2 diabetes is a heterogeneous disease with respect to pathophysiology, body composition, and cardiovascular complications. To properly classify newly diagnosed type 2 diabetes patients, we recommend measuring their fasting c-peptide, p-glucose, and GADA levels. Calculation of HOMA2 may be helpful in daily clinical practice because it is inexpensive, easy to perform, and correlates reasonably well with hyperinsulinemic clamp data. HOMA2S is a measure of IS in both peripheral and liver tissue, and our HOMA2S-based analysis showing that 10% of newly diagnosed type 2 diabetes patients had normal to increased IS appears to challenge much of the literature on type 2 diabetes pathophysiology. This could be due to the imprecision of the HOMA2 technique. However, the individual values obtained during hyperinsulinemic euglycemic clamp studies in type 2 diabetes patients also show that some patients have normal values for insulin-mediated glucose disposal, indicating normal IS. This is often overlooked in the literature. Moreover, a severe beta cell defect is a rather common finding in newly diagnosed type 2 diabetes patients, based on more sophisticated techniques than HOMA2.

Our study population consisted of patients treated at GPs or hospital outpatient clinics throughout Denmark and can be considered...
We also saw a higher proportion of insulinopenic patients who were treated with insulin (caregivers were not aware of the classification). Classical type 2 diabetes patients can be treated in accordance with present guidelines,5 ie, improvement of both insulin action and insulin secretion. The hyperbolic function (of normoglycemia) in this area has a tangent vector with a slope close to 45° inferring that the shortest route to normoglycemia will be equal and concomitant improvements in IS and beta cell function. Because hyperinsulinemic type 2 diabetes patients are severely insulin resistant and obese, treatment that improves insulin action seems most logical (Figure 3C), eg, bariatric surgery or GLP1 agonists.77

A very recent study has, by statistical cluster analysis, found that type 2 diabetes can be subdivided into 5 phenotypes with specific characteristics.78 These findings support our conclusion.

In conclusion, we found that patients diagnosed with type 2 diabetes in a community clinical setting were a heterogeneous group. In the future, a move away from the current “one size fits all” approach to more individualized treatment that is based on pathophysiological characteristics including FPG, serum C-peptide, and GADA may lead to improved outcomes for type 2 diabetes patients.

ACKNOWLEDGEMENTS

This study was supported by the Danish Agency for Science (grant nos. 09-067009 and 09-075724), the Danish Health and Medicines Authority, the Danish Diabetes Association, and the Region of Southern Denmark. The DD2 biobank was supported by an unrestricted donation from Novo Nordisk A/S. The partners of the DD2 project are listed on the website, https://dd2.nu. The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

DUALITY OF INTERESTS

Dr Olsen reports partial funding by a clinical research grant from the Novo Nordisk Foundation. Dr Henriksen reports grants from the Danish Agency for Science (grant nos. 09-067009 and 09-075724) for the conduct of the study. He is also a member of the MSD National Advisory Board. Dr Rungby reports personal fees from Novo Nordisk, Eli Lilly, Astra Zeneca, and Takeda outside the submitted work. Dr Toft Sorensen reports that the Department of Clinical Epidemiology, Aarhus University Hospital, receives funding for other studies from companies in the form of research grants to (and administered by) Aarhus University. None of those studies have any relation to the present study. Dr Beck-Nielsen reports grants from the Danish Agency for Science (grant nos. 09-067009 and 09-075724) and an unrestricted grant from Novo Nordisk for the conduct of this study, and personal lecture fees from Novo Nordisk, outside the submitted work. All other authors declare no competing interests.

The first preliminary study data were presented in abstract form at ADA 2014, 74th Scientific Sessions, San Francisco, California, June 13 to 17, 2014.
CONTRIBUTION STATEMENT

The executive committee of the DD2 study consists of H.B.N., J.R., J. S.C., H.T.S., and S.F., who collectively designed the study. Principal manager of the DD2 study was J.S.N. Study design, data collection, and data interpretation of the background population cohort were the responsibility of I.B. and A.A.N. Concept, data interpretation, and analysis were carried out by H.B.N., J.E.H., M.H.O., J.V.S., and T.B.O. S.P.U. and K.B. conducted the statistical analyses. J.V.S. and H.B.N. drafted the article, and H.T.S. and R.W.T. revised the draft. All authors participated in the critical revision of the intellectual content of the report and approved the final article version to be submitted.

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REFERENCES


SUPPORTING INFORMATION

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