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

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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, and 93.7% had WHO-defined type 2 diabetes. In the latter group, 9.7% had insulinopenic, 63.1% had classical, and 27.2% had hyperinsulinemic type 2 diabetes. Classical patients were obese (median waist 105 cm), and 20.5% had cardiovascular disease (CVD) at diagnosis, while insulinopenic patients were fairly lean (waist 92 cm) and 17.5% had CVD ($P = 0.14$ vs classical diabetes). Hyperinsulinemic patients were severely obese (waist 112 cm), and 25.5% had CVD ($P < 0.0001$ vs classical 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.

1 | INTRODUCTION

Type 2 diabetes mellitus now affects 5% to 10% of the adult population in most countries, and its prevalence is rapidly increasing.[1] Despite multifactorial interventions and expanding pharmacological treatment options, type 2 diabetes patients have greatly increased morbidity and mortality compared with individuals without diabetes.[2,3] 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.[4] 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.[5]

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.[4] 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.[6] 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.[7,8] We obtained supplementary patient data through linkage with several nationwide health databases, including the Danish National Patient Registry[9] and the Danish National Health Service Prescription Registry.[10]

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-naïve 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).[11] 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).[12] Fasting plasma glucose (FPG) was analysed using an enzymatic hexokinase method (Glucoquant 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.[4] The other forms included specific known causes of insulin resistance and/or beta cell failure leading to hyperglycemia, eg, rare subtypes of diabetes,[13] latent autoimmune diabetes of adults (LADA),[14] secondary diabetes (associated with pancreatic disease[15]), and glucocorticoid-associated diabetes.[16] 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, GADAtiter ≥20 IE/mL (international WHO units) and age > 30 years; (3) secondary diabetes, ie, with a history of pancreatitis

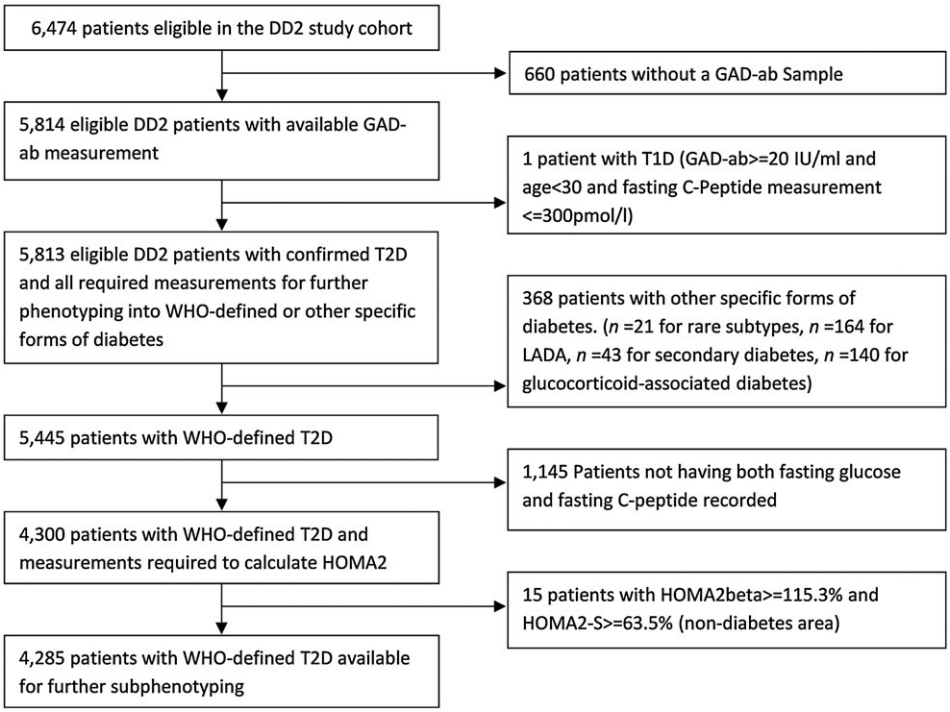

FIGURE 1 Study flowchart

or pancreas resection; and (4) glucocorticoid-associated diabetes, ie, 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-matched 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 $\leq$ 6.1 mmol/L). The sample of 483 persons was then used to calculate median HOMA values. The median BMI was 26 kg/m^2 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, HOMA2B (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

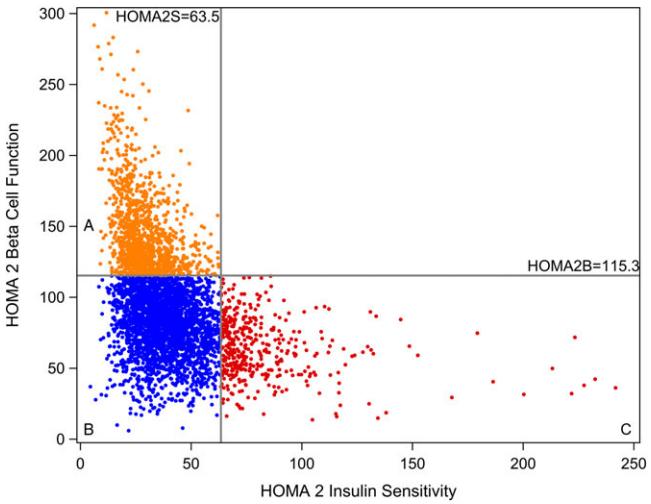

FIGURE 2 Plot of insulin sensitivity and beta cell function of patients meeting criteria for WHO-defined type 2 diabetes. Reference lines represent the median values of HOMA2 insulin sensitivity and HOMA2 beta cell function in the background population

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

Pathophysiological Phenotypes	Number of Patients, % (95% CI)
Patients with "other specific forms" of diabetes	
Rare subtypes	21, 0.4 (0.2, 0.5)
LADA	164, 2.8 (2.4, 3.2)
Secondary diabetes	43, 0.7 (0.5, 1.0)
Glucocorticoid-associated diabetes	140, 2.4 (2.0, 2.8)
Patients with WHO-defined type 2 diabetes	5,445, 93.8 (93.2, 94.5)
Insulinopenic type 2 diabetes	411, 9.6 (8.7, 10.5)
Classical type 2 diabetes	2,713, 63.3 (61.9, 64.8)
Hyperinsulinemic type 2 diabetes	1,161, 27.1 (25.8, 28.4)

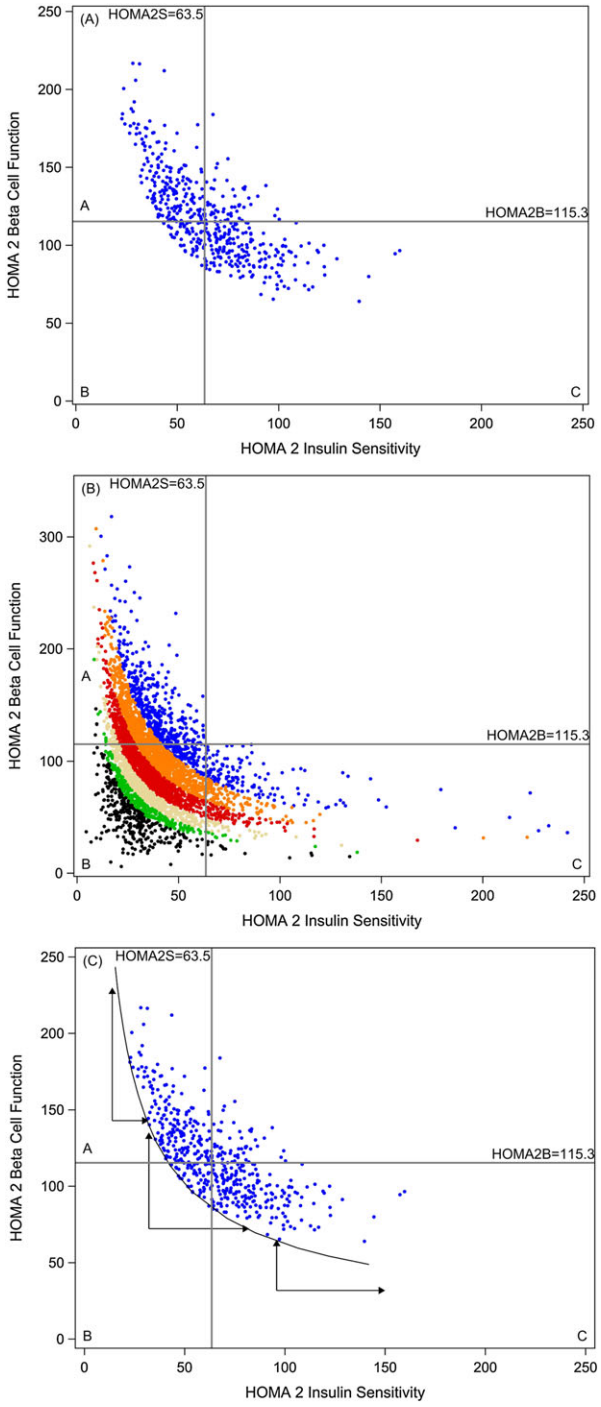

FIGURE 3 A, Plot of insulin sensitivity and beta cell function in the background population. B, Fasting plasma glucose intervals in the type 2 diabetes subphenotype groups. Blue: FPG < 6.1, Orange: 6.1 ≤ FPG < 7.0, brown: 7.0 ≤ FPG < 8.0, cream: 8.0 ≤ FPG < 9.0, green: 9.0 ≤ FPG < 10.0, black: 10.0 ≤ FPG. C, Plot of the background population with normoglycemia (FPG < 6.1). Three hypothetical patients with FPG = 8.5 mmol/L representing each of the 3 phenotypes are shown. Successful treatment of type 2 diabetes patients will bring a patient back into the area of normoglycemia. The path to normoglycemia through improved insulin sensitivity or beta cell function is shown for each of the patients. The shortest path to normoglycemia for the insulinopenic patient is to improve insulin secretion (or insulin treatment). For the hyperinsulinemic patient, the easiest way is to improve insulin action, whereas the classical T2D patient will benefit from improvement of both insulin action and secretion

(Table 3). 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-naïve 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.[21] 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.[22] 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.[20] The existence of lean and obese healthy subjects with similar insulin resistance is also known.[23] Nevertheless, in type 2 diabetes, such characterizations are scarce and have only focused on mean values—not the heterogeneity.[24-26] Some studies have investigated the utility of C-peptide level in order to identify selected patients with an absolute need for insulin.[27-32] 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

TABLE 2 Clinical characteristics of the 3 subphenotypes among patients meeting WHO-defined criteria for type 2 diabetes

	Insulinopenic Type 2 Diabetes (*N* = 411)	Classical Type 2 Diabetes (*N* = 2713)	Hyperinsulinemic Type 2 Diabetes (*N* = 1161)
Age (years, IQR)	63.8 (55.3, 69.8)*	61.9 (53.3, 68.6)	62.9 (53.8, 70.3)*
Men *N*, % (95% CI)	239, 58.2 (53.4, 62.9)	1625, 59.9 (58.1, 61.7)	639, 55.0 (52.2, 57.9)[a]
Waist (cm, IQR)	92.0 (85, 100)***	105.0 (97, 115)	112.0 (102, 121)***
BMI (kg/cm^2, IQR)	25.6 (23.2, 28.7)***	30.1 (27.1, 34.0)	33.0 (29.3, 37.0)***
HbA1c (%, IQR)	6.52 (6.05, 7.00)***	6.62 (6.20, 7.20)	6.33 (6.05, 6.71)***
FPG (mmol/L, IQR)	6.51 (5.88, 7.38)***	7.63 (6.88, 8.75)	6.42 (5.88, 6.94)***
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.

[a]) PR 0.92 (95% CI 0.87, 0.98).

[b]) PR 0.85 (95% CI 0.68, 1.07).

[c]) PR 1.29 (95% CI 1.15, 1.46).

[d]) PR 1.46 (95% CI 1.10, 1.93).

[e]) PR 0.51 (95% CI 0.24, 1.10).

[f]) PR 1.84 (95% CI 1.36, 2.50).

[g]) PR 0.64 (95% CI 0.39, 1.04).

*$P < 0.05$.

***$P < 0.0001$.

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.[36] 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[43] 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 enrols unselected

TABLE 3 Prevalence of glucose-lowering treatment in the cohort

	Insulinopenic Type 2 Diabetes (*N* = 411)	Classical Type 2 Diabetes (*N* = 2713)	Hyperinsulinemic Type 2 Diabetes (*N* = 1161)
Any antidiabetic treatment *N*, % (95% CI)	345, 83.9 (80.0, 87.4)	2299, 84.7 (83.3, 86.1)	973, 83.8 (81.6, 85.9)
Oral glucose-lowering treatment only *N*, % (95% CI)	287, 69.8 (65.1, 74.2)[a]	2166, 79.8 (78.3, 81.3)	932, 80.3 (77.9, 82.5)
Insulin treatment *N*, % (95% CI)	58, 14.1 (10.9, 17.9)[b]	133, 4.9 (4.1, 5.8)	41, 3.5 (2.5, 4.8)[c]

All comparisons use classical type 2 diabetes as the reference group.

[a]) PR 0.87 (95% CI 0.82, 0.93).

[b]) PR 2.88 (95% CI 2.15, 3.85).

[c]) PR 0.72 (95% CI 0.51, 1.02).

TABLE 4 Clinical characteristics of the 3 subphenotypes among drug-naive patients meeting WHO-defined criteria for type 2 diabetes

	Insulinopenic Type 2 Diabetes (*N* = 66)	Classical Type 2 Diabetes (*N* = 414)	Hyperinsulinemic Type 2 Diabetes (*N* = 188)
Age (years, IQR)	65.3 (57.9, 69.2)	65.0 (57.8, 71.2)	65.5 (56.3, 71.6)
Men *N*, % (95% CI)	35, 53.0 (41.0,65.1)	235, 56.8 (52.0, 61.5)	97, 51.6 (44.4, 58.8)[a]
Waist (cm, IQR)	90 (84, 99)***	102 (95, 112)	110 (101, 120)***
BMI (kg/cm^2, IQR)	24.7 (23.1, 28.1)***	29.0 (26.5, 32.6)	33.1 (29.1, 37.0)***
HbA1c (%, IQR)	6.17 (5.86, 6.61)	6.30 (5.95, 6.71)	6.30 (5.90, 6.60)
FPG (mmol/L, IQR)	6.09 (5.74, 6.81)***	7.18 (6.64, 7.97)	6.49 (5.87, 7.06)***
Previous cardiovascular disease (any) *N*, % (95% CI)	8, 12.1 (4.2, 20.0)[b]	80, 19.3 (15.5, 23.1)	47, 25.0 (18.8,31.2)[c]
Previous myocardial infarction *N*, % (95% CI)	1, 1.5 (0, 4.5)[d]	18, 4.3 (2.4, 6.3)	11, 5.9 (2.5, 9.2)[e]
Previous heart failure *N*, % (95% CI)	0, 0 (0, 0)	11, 2.7 (1.1, 4.2)	10, 5.3 (2.1, 8.5)[f]
Previous cerebrovascular disease *N*, % (95% CI)	1, 1.5 (0, 4.5)[g]	19, 4.6 (2.6, 6.6)	19, 10.1 (5.8, 14.4)[h]

All comparisons use classical type 2 diabetes as the reference group. Hba1c was available in 527 and BMI in 393 of 668 patients.

[a]) PR 0.83 (95% CI 0.69, 1.00).

[b]) PR 0.63 (95% CI 0.32, 1.24).

[c]) PR 1.29 (95% CI 0.94, 1.78).

[d]) PR 0.35 (95% CI 0.05, 2.57).

[e]) PR 1.35 (95% CI 0.65, 2.79).

[f]) PR 2.00 (95% CI 0.87, 4.63).

[g]) PR 0.33 (95% CI 0.04, 2.43).

[h]) PR 2.20 (95% CI 1.19, 4.06).

***$p < 0.0001$.

newly diagnosed patients. 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.[46,52-54] 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.[55] 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.[15] 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.[16] 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 pathophysiological 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.[56] 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,[57-60] 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.[61,62] HOMA2S is a measure of IS in both peripheral and liver tissue,[62] 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.[63] 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.[64] 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.[65]

Our study population consisted of patients treated at GPs or hospital outpatient clinics throughout Denmark and can be considered

fairly representative of the Danish type 2 diabetes population in earlier phases of the disease. In previous work, we found that baseline characteristics of the DD2 cohort were similar to baseline characteristics among all T2D patients in the Northern Region of Denmark at initiation of their first glucose-lowering therapy.[66]

Close to 80% of our study population had already started glucose-lowering drugs at enrollment, with 6% receiving insulin. Glucose-lowering drugs may affect both fasting c-peptide and FPG values, but not greatly,[62] as indicated by our findings of fairly identical HOMA2-based phenotype groups independent of ongoing treatment (Table 4). Drug-naïve patients in our cohort are a selected group, as illustrated by the slightly lower HbA1c and enrollment closer to diagnosis in this subgroup, but the robustness of the phenotype distribution and characteristics does not lead us to believe that pre-drug characterization of all patients will change the conclusions in the present work. Although our proposed phenotyping appears robust in a clinical setting, values for IS and beta cell function represent a continuum where there is overlap between the different groups. Therefore, final phenotyping always includes clinical judgement.

In this study, we classified our patients into characteristic pathophysiological phenotypes based on in vivo measurements. We know that formal genotyping would have given us a better basis for phenotyping[67] by permitting identification of the monogenetic forms of diabetes. The prevalence of monogenetic diabetes is only 1% to 2%, and a proportion of these will have impaired beta cell function.[68] A few insulinopenic type 2 diabetes patients will therefore have monogenic forms of diabetes. As genetic tests become readily available and inexpensive, genetic testing of patients with a family history of diabetes should therefore be implemented in the clinic.

Poor glycemic control has been linked to low levels of C-peptide.[33,69-71] In our study, we found that HbA1c and FPG were highest in patients with classical type 2 diabetes. When insulin resistance coexists with impaired beta cell function, a greater impact will be seen on glucose levels (Figure 3B). This emphasizes the importance of measuring IS and beta cell function in conjunction.

Treatment should ideally target the pathophysiological defect, and identification of subphenotypes enables the clinician to choose the most relevant treatment. The insulin secretion and sensitivity are part of a dependent continuum, but the extremes will differ greatly. Categorization of a continuum will always pose problems, especially around the dividing lines. Our categorization defines 2 phenotypes where the relative effect of improving beta cell function or IS, respectively, is limited. Specific glucose-lowering treatment (not insulin) might differ in their effect on the pathophysiological defect in different areas of the continuum adding further complexity to which cutoffs to choose. Insulinopenic type 2 diabetes patients may benefit from increased insulin values (eg, insulin treatment) as shown in Figure 3C, while a reduction in insulin resistance would have less effect or even potentially adverse effects, eg, ketoacidosis during SGLT-2 inhibitor treatment. The asymptotic nature of the hyperbolic function in the insulinopenic area (Figure 3C) infers that further improvements in IS will not bring the hyperglycemic patient to the normoglycemic area, whereas a small improvement in beta cell function will do so. In accordance with this, low beta cell function has been linked to decreased effect of several glucose-lowering treatments.[72-76] 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.

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DUALITY OF INTERESTS

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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

1. IDF Diabetes Atlas, Seventh Edition 2015. Available from www.diabetesatlas.org, accessed 4. january 2017.
2. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373(18):1720-1732.
3. Hansen MB, Jensen ML, Carstensen B. Causes of death among diabetic patients in Denmark. *Diabetologia*. 2012;55(2):294-302.
4. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;26(Suppl 1):S5-S20.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of diabetes. *Diabetologia*. 2015;58(3):429-442.
6. Beck-Nielsen H, Henriksen JE, Vaag A, Hother-Nielsen O. Pathophysiology of non-insulin-dependent diabetes mellitus (NIDDM). *Diabetes Res Clin Pract*. 1995;28(Suppl):S13-S25.
7. Beck-Nielsen H, Solomon TP, Lauridsen J, et al. The Danish Centre for Strategic Research in type 2 diabetes (DD2) study: expected outcome from the DD2 project and two intervention studies. *Clin Epidemiol*. 2012;4(Suppl 1):21-26.
8. Nielsen JS, Thomsen RW, Steffensen C, Christiansen JS. The Danish Centre for Strategic Research in type 2 diabetes (DD2) study: implementation of a nationwide patient enrollment system. *Clin Epidemiol*. 2012;4(Suppl 1):27-36.
9. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health*. 2011;39(7 Suppl):30-33.
10. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;39(7 Suppl):38-41.
11. Chen S, Willis J, Maclean C, et al. Sensitive non-isotopic assays for autoantibodies to IA-2 and to a combination of both IA-2 and GAD65. *Clin Chim Acta*. 2005;357(1):74-83.
12. Roche, COBAS Kit-insert C-peptide, REF 03184897 190, 2013-11, V 9.0 Dansk.
13. Huang J, Jones D, Luo B, et al. Iron overload and diabetes risk: a shift from glucose to fatty acid oxidation and increased hepatic glucose production in a mouse model of hereditary hemochromatosis. *Diabetes*. 2011;60(1):80-87.
14. Leslie RD. Predicting adult-onset autoimmune diabetes: clarity from complexity. *Diabetes*. 2010;59(2):330-331.
15. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol*. 2013;19(42):7276-7281.
16. van Raalte DH, Diamant M. Steroid diabetes: from mechanism to treatment? *Neth J Med*. 2014;72(2):62-72.
17. Hill NR, Levy JC, Matthews DR. Expansion of the homeostasis model assessment of beta-cell function and insulin resistance to enable clinical trial outcome modeling through the interactive adjustment of physiology and treatment effects: iHOMA2. *Diabetes Care*. 2013;36(8):2324-2330.
18. Nielsen AA, Christensen H, Lund ED, Christensen C, Brandslund I, Green A. Diabetes mortality differs between registers due to various disease definitions. *Dan Med J*. 2014;61(5):A4840.
19. Molsted S, Johnsen NF, Snorgaard O. Trends in leisure time physical activity, smoking, body mass index and alcohol consumption in Danish adults with and without diabetes: a repeat cross-sectional national survey covering the years 2000 to 2010. *Diabetes Res Clin Pract*. 2014 Aug;105(2):217-222.
20. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes*. 1993;42(11):1663-1672.
21. Reaven GM. Insulin resistance: the link between obesity and cardiovascular disease. *Med Clin North Am*. 2011;95(5):875-892.
22. Foundation TDH. https://hjerteforeningen.dk/alt-om-dit-hjerte/hjertetal/hjertetaldk/ 2. February, 2018.
23. Cnop M, Landchild MJ, Vidal J, et al. The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations : distinct metabolic effects of two fat compartments. *Diabetes*. 2002;51(4):1005-1015.
24. Amutha A, Ali MK, Unnikrishnan R, et al. Insulin sensitivity and secretion in youth onset type 2 diabetes with and without visceral adiposity. *Diabetes Res Clin Pract*. 2015;109(1):32-39.
25. Gujral UP, Narayan KM, Kahn SE, Kanaya AM. The relative associations of beta-cell function and insulin sensitivity with glycemic status and incident glycemic progression in migrant Asian Indians in the United States: the MASALA study. *J Diabetes Complications*. 2014;28(1):45-50.
26. Son JW, Park CY, Kim S, Lee HK, Lee YS. Changing clinical characteristics according to insulin resistance and insulin secretion in newly diagnosed type 2 diabetic patients in Korea. *Diabetes Metab J*. 2015;39(5):387-394.
27. Fujiwara D, Takahashi K, Suzuki T, et al. Postprandial serum C-peptide value is the optimal index to identify patients with non-obese type 2 diabetes who require multiple daily insulin injection: analysis of C-peptide values before and after short-term intensive insulin therapy. *J Diabetes Investig*. 2013;4(6):618-625.
28. Funakoshi S, Fujimoto S, Hamasaki A, et al. Utility of indices using C-peptide levels for indication of insulin therapy to achieve good glycemic control in Japanese patients with type 2 diabetes. *J Diabetes Investig*. 2011;2(4):297-303.
29. Hope SV, Jones AG, Goodchild E, et al. Urinary C-peptide creatinine ratio detects absolute insulin deficiency in type 2 diabetes. *Diabet Med*. 2013;30(11):1342-1348.
30. Hope SV, Knight BA, Shields BM, Hattersley AT, McDonald TJ, Jones AG. Random non-fasting C-peptide: bringing robust assessment of endogenous insulin secretion to the clinic. *Diabet Med*. 2016;33(11):1554-1558.
31. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. *Diabet Med*. 2013;30(7):803-817.
32. Munshi MN, Hayes M, Sternthal A, Ayres D. Use of serum c-peptide level to simplify diabetes treatment regimens in older adults. *Am J Med*. 2009;122(4):395-397.
33. Wod M, Yderstraede KB, Halekoh U, Beck-Nielsen H, Hojlund K. Metabolic risk profiles in diabetes stratified according to age at onset, islet autoimmunity and fasting C-peptide. *Diabetes Res Clin Pract*. 2017;134:62-71.
34. Bo S, Gentile L, Castiglione A, et al. C-peptide and the risk for incident complications and mortality in type 2 diabetic patients: a retrospective cohort study after a 14-year follow-up. *Eur J Endocrinol*. 2012;167(2):173-180.

35. Kim BY, Jung CH, Mok JO, Kang SK, Kim CH. Association between serum C-peptide levels and chronic microvascular complications in Korean type 2 diabetic patients. *Acta Diabetol*. 2012;49(1):9-15.
36. Pikkemaat M, Melander O, Molstad S, Garberg G, Bostrom KB. C-peptide concentration, mortality and vascular complications in people with type 2 diabetes. The Skaraborg diabetes register. *Diabet Med*. 2015;32(1):85-89.
37. Arnlov J, Ingelsson E, Sundstrom J, Lind L. Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation*. 2010;121(2):230-236.
38. Calori G, Lattuada G, Piemonti L, et al. Prevalence, metabolic features, and prognosis of metabolically healthy obese Italian individuals: the Cremona study. *Diabetes Care*. 2011;34(1):210-215.
39. Kuk JL, Ardern CI. Are metabolically normal but obese individuals at lower risk for all-cause mortality? *Diabetes Care*. 2009;32(12):2297-2299.
40. Meigs JB, Wilson PW, Fox CS, et al. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006;91(8):2906-2912.
41. Paneni F, Costantino S, Cosentino F. Insulin resistance, diabetes, and cardiovascular risk. *Curr Atheroscler Rep*. 2014;16(7):419.
42. Laakso M, Kuusisto J. Insulin resistance and hyperglycaemia in cardiovascular disease development. *Nat Rev Endocrinol*. 2014;10(5):293-302.
43. Mongraw-Chaffin ML, Peters SAE, Huxley RR, Woodward M. The sex-specific association between BMI and coronary heart disease: a systematic review and meta-analysis of 95 cohorts with 1.2 million participants. *Lancet Diabetes Endocrinol*. 2015;3(6):437-449.
44. Costanzo P, Cleland JG, Pellicori P, et al. The obesity paradox in type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. *Ann Intern Med*. 2015;162(9):610-618.
45. Zaccardi F, Dhalwani NN, Papamargaritis D, et al. Nonlinear association of BMI with all-cause and cardiovascular mortality in type 2 diabetes mellitus: a systematic review and meta-analysis of 414,587 participants in prospective studies. *Diabetologia*. 2017;60(2):240-248.
46. Bosi EP, Garancini MP, Poggiali F, Bonifacio E, Gallus G. Low prevalence of islet autoimmunity in adult diabetes and low predictive value of islet autoantibodies in the general adult population of northern Italy. *Diabetologia*. 1999;42(7):840-844.
47. Buzzetti R, Di Pietro S, Giaccari A, et al. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. *Diabetes Care*. 2007;30(4):932-938.
48. Genovese S, Bazzigaluppi E, Goncalves D, et al. Clinical phenotype and beta-cell autoimmunity in Italian patients with adult-onset diabetes. *Eur J Endocrinol*. 2006;154(3):441-447.
49. Hawa MI, Kolb H, Schloot N, et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: action LADA 7. *Diabetes Care*. 2013;36(4):908-913.
50. Tuomi T, Carlsson A, Li H, et al. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes*. 1999;48(1):150-157.
51. Turner R, Stratton I, Horton V, et al. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *UK Prospective Diabetes Study Group Lancet*. 1997;350(9087):1288-1293.
52. Zinman B, Kahn SE, Haffner SM, O'Neill MC, Heise MA, Freed MI. Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. *Diabetes*. 2004;53(12):3193-3200.
53. Davies H, Brophy S, Fielding A, et al. Latent autoimmune diabetes in adults (LADA) in South Wales: incidence and characterization. *Diabet Med*. 2008;25(11):1354-1357.
54. Maddaloni E, Lessan N, Al Tikriti A, Buzzetti R, Pozzilli P, Barakat MT. Latent autoimmune diabetes in adults in the United Arab Emirates: clinical features and factors related to insulin-requirement. *PLoS one*. 2015;10(8):e0131837.
55. Brophy S, Davies H, Mannan S, Brunt H, Williams R. Interventions for latent autoimmune diabetes (LADA) in adults. *Cochrane Database Syst Rev* 2011(9):CD006165.
56. Morimoto A, Tatsumi Y, Deura K, et al. Impact of impaired insulin secretion and insulin resistance on the incidence of type 2 diabetes mellitus in a Japanese population: the Saku study. *Diabetologia*. 2013;56(8):1671-1679.
57. Barker JM, Barriga KJ, Yu L, et al. Prediction of autoantibody positivity and progression to type 1 diabetes: diabetes autoimmunity study in the young (DAISY). *J Clin Endocrinol Metab*. 2004;89(8):3896-3902.
58. Borg H, Gottsater A, Fernlund P, Sundkvist G. A 12-year prospective study of the relationship between islet antibodies and beta-cell function at and after the diagnosis in patients with adult-onset diabetes. *Diabetes*. 2002;51(6):1754-1762.
59. Huang G, Yin M, Xiang Y, et al. Persistence of glutamic acid decarboxylase antibody (GADA) is associated with clinical characteristics of latent autoimmune diabetes in adults: a prospective study with 3-year follow-up. *Diabetes Metab Res Rev*. 2016;32(6):615-622.
60. Liu L, Li X, Xiang Y, et al. Latent autoimmune diabetes in adults with low-titer GAD antibodies: similar disease progression with type 2 diabetes: a nationwide, multicenter prospective study (LADA China study 3). *Diabetes Care*. 2015;38(1):16-21.
61. Sarafidis PA, Lasaridis AN, Nilsson PM, et al. Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. *J Hum Hypertens*. 2007;21(9):709-716.
62. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487-1495.
63. Halban PA, Polonsky KS, Bowden DW, et al. beta-cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. *J Clin Endocrinol Metab*. 2014;99(6):1983-1992.
64. Vind BF, Birk JB, Vienberg SG, et al. Hyperglycaemia normalises insulin action on glucose metabolism but not the impaired activation of AKT and glycogen synthase in the skeletal muscle of patients with type 2 diabetes. *Diabetologia*. 2012;55(5):1435-1445.
65. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia*. 2003;46(1):3-19.
66. Thomsen RW, Baggesen LM, Svensson E, et al. Early glycaemic control among patients with type 2 diabetes and initial glucose-lowering treatment: a 13-year population-based cohort study. *Diabetes Obes Metab*. 2015;17(8):771-780.
67. McCarthy MI, Hattersley AT. Learning from molecular genetics: novel insights arising from the definition of genes for monogenic and type 2 diabetes. *Diabetes*. 2008;57(11):2889-2898.
68. Anik A, Catli G, Abaci A, Bober E. Maturity-onset diabetes of the young (MODY): an update. *J Pediatr Endocrinol Metab*. 2015;28(3-4):251-263.
69. Bacha F, Pyle L, Nadeau K, et al. Determinants of glycemic control in youth with type 2 diabetes at randomization in the TODAY study. *Pediatr Diabetes*. 2012;13(5):376-383.
70. Kuhtreiber WM, Washer SL, Hsu E, et al. Low levels of C-peptide have clinical significance for established type 1 diabetes. *Diabet Med*. 2015;32(10):1346-1353.
71. Saisho Y, Kou K, Tanaka K, et al. Association between beta cell function and future glycemic control in patients with type 2 diabetes. *Endocr J*. 2013;60(4):517-523.
72. Bluher M, Lubben G, Paschke R. Analysis of the relationship between the Pro12Ala variant in the PPAR-gamma2 gene and the response rate to therapy with pioglitazone in patients with type 2 diabetes. *Diabetes Care*. 2003;26(3):825-831.
73. Jones AG, McDonald TJ, Shields BM, et al. Markers of beta-cell failure predict poor glycemic response to GLP-1 receptor agonist therapy in type 2 diabetes. *Diabetes Care*. 2016;39(2):250-257.

74. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. *UK Prospective Diabetes Study (UKPDS) Group Diabet Med*. 1998;15(4):297-303.
75. Thong KY, McDonald TJ, Hattersley AT, et al. The association between postprandial urinary C-peptide creatinine ratio and the treatment response to liraglutide: a multi-centre observational study. *Diabet Med*. 2014;31(4):403-411.
76. Aarts EO, Janssen J, Janssen IM, Berends FJ, Telting D, de Boer H. Preoperative fasting plasma C-peptide level may help to predict diabetes outcome after gastric bypass surgery. *Obes Surg*. 2013;23(7):867-873.
77. Kishimoto M, Noda M. Effects of Exenatide in a morbidly obese patient with type 2 diabetes. *Diabetes Ther*. 2014;5(1):323-332.
78. Ahlqvist E, Storm P, Karajamaki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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