Pathophysiological based phenotyping in type 2 diabetes - a clinical tool

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- **Type 2 diabetes (T2D) can be considered a syndrome with several different pathophysiological mechanisms leading to hyperglycemia.**
- **We investigated the prevalence of different pathophysiological phenotypes among newly diagnosed T2D patients in Denmark.**

Methods

In a Danish national cohort study (DD2) we investigated 1047 incident T2D patients, who was newly-diagnosed accordig to the WHO criteria based on clinical judgement by general practitioners and outpatient clinics. Specific phenotypes were classified into the following five hierarchical groups: Rare subtypes of diabetes, latent autoimmune diabetes (LADA), secondary diabetes, steroid-associated diabetes and WHO defined T2D patients (**Table 1**). The homeostatic assessment model (HOMA2) model was used to assess insulin sensitivity (HOMA2S) and beta cell function (HOMA2B) and used to sub-classify the WHO defined patinets (**Table 1**).

Results

Median age of our newly-diagnosed T2D patients was 61 years (range 21-95 years). We calculated the prevalence with corresponding 95% confidence intervals (95%-CI) of the defined phenotypes (**Table 2**). Within each WHO defined phenotype the median and quartiles were calculated for age and waist circumference as well as prevalence and 95%-CI of men and previous cardiovascular disease (**Table 3**).

Phenotype	Definition
Rare sub-types	Patients with haemocromatosis, cystic fibrosis, Cushings disease, acromegaly, pheochromacytoma, glucagonoma, somatostatinoma, Downs syndrome, Friederichs ataxia.
GAD positives	GAD antibody titer ≥20 IE/ml and not T1D
Secondary diabetes	Recent history of pancreatitis, pancreatectomy or pancreas amylase > 65U/l, and GAD negativity
Steroid induced diabetes	Oral glucocorticoid treatment within 3 months prior to inclusion
Insulinopenic T2D	HOMA2B < 78.45% HOMA2S ≥ 105.50%
Classic T2D	HOMA2B < 78.45% HOMA2S < 105.50%
Hyoperinsulinemic T2D	HOMA2B ≥ 78.45% HOMA2S < 105.50%

TABLE 1: Definition of phenotypes

Phenotype	Prevalence n, % (95% CI)
Rare sub-types	6, 0.6% (0.1-1.0)
GAD positives	31, 3.0% (1.9-4.0)
Secondary Diabetes	41, 3.9% (2.7-5.1)
Possible steroid induced diabetes	23, 2.2% (1.3-3.1
WHO defined T2D patients	
Insulinopenic T2D	126, 12.0% (10.1-14.0)
Classical T2D	556, 53.1% (50.1-56.1)
Hyperinsulinemic T2D	264, 25.2% (22.6-27.8)

TABLE 2: Prevalence of phentotypes among newly diagnosed T2D.

Prevalence, n, % (95%-CI)	Insulinopenic T2D (n=126)	Classical T2D (n=556)	Hyperinsulinemic T2D (n=264)
Waist (cm)	95.0 (86-103)[1]	106.0 (98-116)	113.5 (101-122)[1]
Age (years)	63.0 (55-67)[2]	60.0 (52-66)	61.0 (54-69)[3]
Men	83, 65.9% (57.6-74.2)	313, 56.3% (52.2-60.4)	143, 54.2% (48.1-60.2)
Previous Myocardial infarction	5, 4.0% (0.6-7.4)	27, 4.9% (3.1-6.6)	28, 10.6% (6.9-14.3)
Previous heart failure	1, 0.8% (0.0-2.3)	13, 2.3% (1.1-3.6)	15, 5.7% (2.9-8.5)
Previous cerebrovascular disease	2, 1.6% (0.0-3.8)	36, 6.5% (4.4-8.5)	21, 8.0% (4.7-11.2)

TABLE 3: Prevalence's and clinical characterization of the three sub-phenotypes of "WHO defined T2D patients". Measures are median (interquartile range) if not otherwise stated. [1]p<0.0001, [2]p=0.027, [3]p=0.018, when medians were compared by two-sided Wilcoxon test with classical T2D as a reference.

Conclusion

- **We conclude that T2D is a heterogeneous disease, which can be divided into specific pathophysiological phenotypes of great clinical implication.**

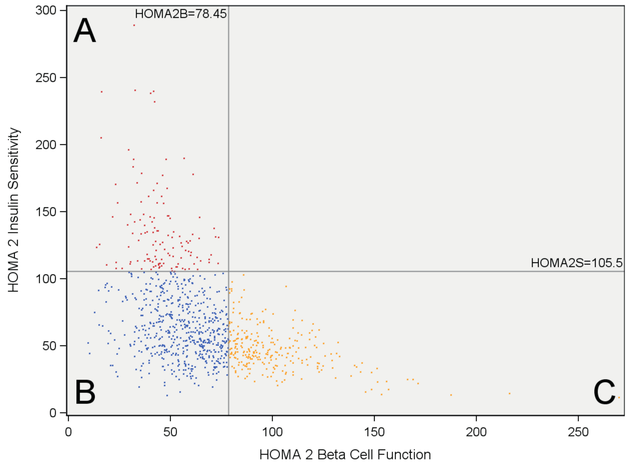

FIGURE 1: Plot of insulin sensitivity and beta cell function of patients with WHO-defined T2D – with reference lines for the median values of HOMA2 insulin sensitivity and HOMA2 beta cell function from the background population

Perspective

The subphenotyping presented here may potentially lead to a more causal treatment of T2D, thereby improving treatment effect and prognosis for the patients.