

## Diabetes phenotypes: Beyond IDDM vs NIDDM

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An older nosology of diabetes distinguished two major groups, the “insulin-dependent” and “non-insulin-dependent.” Some argued that this was no more a definition of real subgroups than would be characterization of cases of pneumonia as those responding or not responding to a given antibiotic. A myriad of factors leading to hyperglycemia have been delineated, including islet autoimmunity, insulin secretory defects, resistance to insulin action, and obesity, but efforts to better characterize diabetes phenotypes have not been widely accepted. We currently term diabetes as type 1 and type 2, with recognition of the former as an autoimmune disease directed at the  $\beta$ -cell. Type 2 diabetes is, however, a complex disease in which both insulin resistance and insulin deficiency play roles. To be worthwhile, novel approaches to phenotyping type 2 diabetes would provide improvement both in therapeutic decision making and in assessing risk of diabetes-related complications.

In a complex study published last year, Ahlqvist and colleagues analyzed diabetes characteristics of a large Swedish cohort, with replication in three other Scandinavian groups, using C-peptide and glucose measurement to assess insulin deficiency and resistance (<sup>1</sup>). Insulin secretion and insulin resistance were based on the Homeostasis Model (HOMA)2 B and IR indices, respectively. Among diabetic persons not having evidence of islet autoimmunity, four subgroups were distinguished using cluster analysis (1). The first group was termed severe insulin deficiency diabetes (SIDD), characterized at onset by relatively young age, 56.7 years old, relatively low BMI, 28.9 kg/m<sup>2</sup>, insulin secretion approximately half of normal(<sup>2</sup>), and poor metabolic control, with HbA1c around 11.5% (1). The second group, termed severe insulin resistance (SIRD), had mean age 65.3, BMI 33.9, greater insulin resistance, insulin secretion approximately 50% above normal (2), and better metabolic control, with HbA1c around 7.1% (1). The third group, mild obesity-related diabetes (MOD), had mean age 49.0, BMI 35.7, insulin resistance similar to that of SIDD, and HbA1c around 7.4%; the first three groups each accounted for approximately 20% of the total (1). The fourth group, termed mild age-related (MARD), accounted for approximately 40% of the total, was less insulin resistant than the other three, had lower insulin secretion than all but those with SIDD, with mean age at onset 67.4, BMI 27.9, and HbA1c 6.7%(1). The characteristics of the four groups are shown in the Table. Using similar methodology, Zou et al report roughly similar prevalences of the respective groups in representative Chinese and US populations (<sup>3</sup>), and Dennis et al

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(<sup>4</sup>) recently reported similar prevalences in participants in the A Diabetes Outcome Progression Trial (ADOPT) and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial.

Do these four subtypes of type 2 diabetes offer sufficient information to warrant their adoption? Dennis et al assessed response to glucose-lowering treatments and concluded that more insulin-resistant persons had better response to thiazolidinediones, while those with greater degrees of insulin deficiency responded better to sulfonylureas (4). In the same study, the subtype assignment was less indicative of risk of worsening renal function than was the baseline level of renal function, and younger age at diagnosis explained glycemic worsening to a similar degree as subtype grouping (4). Rather than the subtypes representing separate forms of type 2 diabetes, they may represent different stages and modes of progression in the natural history of the disease. The wide confidence limits shown in the Table further suggest the difficulty the clinician might encounter in endeavoring to apply the criteria in an individual patient. These studies do, however, allow us to put in perspective the tremendous variability in clinical presentations of type 2 diabetes. It is intriguing to think that lipid-based measurements may allow easier clinical ascertainment of insulin resistance (<sup>5,6</sup>). Similarly to the analysis of Dennis et al showing that use of thiazolidinediones might be particularly appropriate for patients with HOMA2-based insulin resistance in ADOPT and in RECORD (4), Zonszein and coworkers used the triglyceride-HDL ratio as an indication of insulin resistance, and found it to predict glycemic benefit of insulin sensitizer treatment with rosiglitazone and metformin in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial (<sup>7</sup>).

Will clinical markers of insulin secretion and insulin action, or of age, or of obesity, or of renal function, or of cardiac function, allow selection of diabetic persons who would show particular response to the glucagon - like peptide - 1 receptor agonists (GLP-1RA) and sodium - glucose cotransporter 2 inhibitors (SGLT2i)? Would markers of risk prior to development of renal or cardiovascular complications enable recognition of patients for whom cardiovascular and renal benefit will occur with use of the GLP-1RA and SGLT2i? Such tools would be of great importance in developing rational approaches to appropriate selection of these agents in clinical practice. Ultimately, prospective trials and/or extensive epidemiologic analysis of well-characterized patient datasets will be required to show benefit of an expanded view of type 2 diabetes subtypes into clinical practice.

Table (data from supplement to reference 1)

	HbA1c (%)	BMI, kg/m <sup>2</sup>	Age at diagnosis	HOMA2-B	HOMA2-IR
SIDD	11.4 (3.9)	28.86 (4.77)	56.74 (11.14)	47.64 (28.93)	3.18 (1.73)
SIRD	7.1 (3.6)	33.85 (5.24)	65.25 (9.34)	150.47 (47.20)	5.54 (2.74)
MOD	7.4 (3.6)	35.71 (5.43)	48.96 (9.54)	95.03 (32.45)	3.35 (1.21)
MARD	6.7 (3.1)	27.94 (3.44)	67.37 (8.55)	86.59 (26.37)	2.55 (0.84)

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<sup>1</sup>Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, Vikman P, Prasad RB, Aly DM, Almgren P, Wessman Y, Shaat N, Spégel P, Mulder H, Lindholm E, Melander O, Hansson O, Malmqvist U, Lernmark Å, Lahti K, Forsén T, Tuomi T, Rosengren AH, Groop L. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018 May;6(5):361-369.

<sup>2</sup>personal communication, Dr JCLevy, Oxford Centre for Diabetes, Endocrinology and Metabolism, downloaded 5-12-19 from <https://www.dtu.ox.ac.uk/homacalculator/HOMANoNormalRange.pdf>

<sup>3</sup>Zou X, Zhou X, Zhu Z, Ji L. Novel subgroups of patients with adult-onset diabetes in Chinese and US populations. *Lancet Diabetes Endocrinol*. 2019;7:9-11.

<sup>4</sup>Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol*. 2019 Apr 29. pii: S2213-8587(19)30087-7. doi:10.1016/S2213-8587(19)30087-7.

<sup>5</sup>Bloomgarden Z, Chilton R. Lipids as risk markers for type 2 diabetes. *J Diabetes*. 2019;11:176-178.

<sup>6</sup>Zheng D, Dou J, Liu G, Pan Y, Yan Y, Liu F, Gaisano HY, Lu J, He Y. Association Between Triglyceride Level and Glycemic Control Among Insulin-Treated Patients With Type 2 Diabetes. *J Clin Endocrinol Metab*. 2019;104:1211-1220.

<sup>7</sup>Zonszein J, Lombardero M, Ismail-Beigi F, Palumbo P, Foucher S, Groenewoud Y, Cushing G, Wajchenberg B, Genuth S; Bari 2D Study Group. Triglyceride High-Density Lipoprotein Ratios Predict Glycemia-Lowering in Response to Insulin Sensitizing Drugs in Type 2 Diabetes: A Post Hoc Analysis of the BARI 2D. *J Diabetes Res*. 2015;2015:129891. doi: 10.1155/2015/129891.