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Adult-onset diabetes: novel subgroups and their association with differing outcomes

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Diabetes is currently classified into type 1 and type 2, but there is a significant heterogeneity in the type 2 group. A more accurate classification could facilitate the recognition at diagnosis of patients at higher risk of complications, and allow a more personalized treatment. A register-based cluster analysis (1) recently evaluated 8980 patients with a new diagnosis of type 2 diabetes in the Swedish province of Scania (ANDIS cohort: *All New Diabetics in Scania*). The clusters were developed on the basis of 6 variables (anti-GAD antibody status, age at diagnosis, BMI, HbA1c, evaluation of β-cell function and insulin-resistance by HOMA Index). These groups were subsequently assessed prospectively for development of complications and need for medicaments. The analysis was replicated in three independent cohorts: *Scania Diabetes Registry* (SDR, n = 1466), *All New Diabetics in Uppsala* (ANDIU, n = 844), and *Diabetes Registry Vaasa* (DIREVA, n = 3485). Cox and logistic regression analysis were used to compare time to treatment, time to therapeutic target, risk of complications and genetic associations.
The authors differentiated five subgroups:

1. **Severe Autoimmune Diabetes** (SAID): 577 patients (6.4%), with early-onset diabetes, relatively low BMI, poor metabolic control, insulin deficiency (low HOMA2-β index) and anti-GAD antibodies;
2. **Severe Insulin Deficiency Diabetes** (SIDD): 1575 patients (17.5%), similar to group 1, but without anti-GAD antibodies;
3. **Severe insulin resistance diabetes** (SIRD): 1373 patients (15.3%) with severe insulin resistance (high HOMA-IR index) and raised BMI;
4. **Mild obesity-related diabetes** (MOD): 1492 patients (21.6%), obese without insulin resistance;
5. **Mild age-related diabetes** (MARD): 3153 patients (39.1%), with more advanced age at onset of diabetes, and only mild metabolic abnormalities, similar to group 4.

Data at diagnosis: Patients in group 1 and 2 presented with significantly higher HbA1c than the other subgroups (difference which did not change during follow-up), more common occurrence of keto-acidosis (31% in group 1, and 25% in group 2 vs. less than 5% in the other subgroups) and increased prescription of insulin (42% in group 1 and 29% in group 2, vs. 4% in the other subgroups).
Treatment with metformin: this was more frequent in group 2 and less frequent in group 1. Surprisingly, treatment with metformin was also less prevalent in group 3, where benefit would be expected to be higher. This may point out that current classification does not allow individualization of therapy based on pathophysiologic mechanisms.
Prescription of a second oral hypoglycemic agent: an earlier event in group 2, which was also characterized by prolonged time to therapeutic target (HbA1c less than 6.9%), early onset of retinopathy (in the cohorts ANDIS, ANDIU and SDR), raised glycemic values and insulinopenia.
Non Alcoholic Steato-Hepatitis: more frequent in group 3.
Chronic Renal insufficiency: Higher risk in group 3 compared to groups 4 and 5. In ANDIS (follow-up 3.9 years) the risk was double for stage 3A and triple for stage 3B; in SDR (follow-up 11 years) the risk was quintupled. The authors emphasize the close link between insulin-resistance and nephropathy, mediated by increased sensitivity of the glomerulus to salt, with hypertension and hyperfiltration. The increased incidence of nephropathy in this group despite lower HbA1c seems to suggest that a treatment aiming at reducing glycemic values without tackling insulin-resistance may be limited in scope.
Risk of coronary events and stroke: similar in the different groups after adjustment for age and sex.
Finally, analysis of **genes** associated with type 2 diabetes mellitus suggests a different etiology for group 3 (SIRD).

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Discussion

This new classification might allow better identification at diagnosis of type 2 diabetics at increased risk of complications, and provide clues to underlying pathophysiology. While severe autoimmune diabetes (SAID) overlaps with type 1 diabetes, and with latent autoimmune diabetes of the adult (LADA), diabetes with severe deficit of insulin (SIDD) and diabetes with severe insulin-resistance (SIRD) represent two new subtypes, currently hidden in the larger group of patients with type 2 diabetes mellitus. Recognition of these patients may assist in providing **early and personalized therapy**, and prevent complications.

The study is limited by the almost exclusive focus on patients of Scandinavian origin, which requires validation in other ethnic groups. Another limit is that the immune phenotype was established on the basis of just two antibodies (anti-GAD and anti-ZnT8A), which does not allow extrapolations on the effect of other antibodies on the clinic manifestations of the different subgroups. Finally, there are no data on other risk factors known to predispose to complications of diabetes, like blood pressure and serum lipid levels.

References

1. Ahlqvist E, Storm P, Käräjämäki 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, 6: 361-9.