CEDA diabetes
Zentraleuropäische Diabetesgesellschaft
Central European Diabetes Association
Föderation der Internationalen Donau-Symposia über Diabetes mellitus
Federation of International Danube-Symposia on Diabetes mellitus

Novel Diabetes Subgroups and Risk of Diabetes-Associated Complications

C. Herder[1,2,3,4]

Diabetes mellitus is a heterogeneous disease with respect to clinical presentation and progression. Recent studies challenged the current classification of the disease, and this short review aims to provide a concise update on novel findings related to diabetes subgroups and potential differences in their risk to develop diabetes-associated complications.

Heterogeneity of diabetes based on pathophysiological processes

The issue of heterogeneity of diabetes has been investigated with different data-driven methods in cohorts with incident and prevalent diabetes. Two interesting studies used latent class trajectory analysis to characterise patterns of changes in diabetes risk factors in individuals who developed diabetes in order to classify these individuals based on pathophysiological processes contributing to the onset of diabetes [Hulman 2018, Vistisen 2014]. In the Whitehall II study three patterns of changes in body mass index (BMI) preceding the diagnosis could be identified. Individuals in these subgroups differed in their trajectories of insulin resistance, beta-cell function and other cardiometabolic risk factors including interleukin-1 receptor antagonist (IL-1Ra), a biomarker of subclinical inflammation [Vistisen 2014]. In the European Group for the Study of Insulin Resistance: Relationship between Insulin Sensitivity and Cardiovascular Disease (EGIR-RISC) study, data from a five-point oral glucose tolerance test were used to identify distinct glucose response patterns. Individuals in these four glucose response patterns also differed with respect to insulin resistance, beta-cell function and obesity. Several biomarkers showed different distributions between the four groups including C-peptide, lipids, and C-reactive protein and adiponectin, the latter both associated with subclinical inflammation [Hulman 2018]. Thus, data-driven analyses may be useful for cardiometabolic risk stratification based on pathophysiological processes.

CEDA Science

Unter CEDA Science veröffentlicht die Zentraleuropäische Diabetes-Gesellschaft (CEDA/FID) wissenschaftliche Artikel ihrer Mitglieder.

Five diabetes subgroups in a Swedish cohort

In 2018 a Swedish study aimed to refine diabetes classification in patients with newly diagnosed diabetes by conducting a cluster analysis based on glutamate decarboxylase (GAD) antibodies, age at diagnosis, BMI, HbA_{1c}, and homeostasis model assessment estimates of beta-cell function and insulin resistance (HOMA-B and HOMA-IR) [Ahlqvist 2018]. This analysis resulted in five subgroups which were labelled as

- severe autoimmune diabetes (SAID),
- severe insulin-deficient diabetes (SIDD),
- severe insulin-resistant diabetes (SIRD),
- mild obesity-related diabetes (MOD) and
- mild age-related diabetes (MARD).

The SAID subgroup was characterised by the presence of GAD antibodies, early age of diagnosis, low BMI, insulin deficiency and poor glycaemic control. The SIDD subgroup was similar to SAID, but without GAD antibodies. Individuals in the SIRD and MOD subgroups had the highest BMI with the strongest insulin resistance found in the SIRD patients. The MARD subgroup had the highest age at diagosis, a lower BMI comparable to SAID and SIDD and relatively good glycaemic control [Ahlqvist 2018]. With respect to diabetes complications, the SIRD subgroup showed the highest risk of diabetic kidney disease. In contrast, SIDD had the highest risk of retinopathy. Clusters also differed with respect

1) Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Düsseldorf, Germany
2) German Center for Diabetes Research, Partner Düsseldorf, Germany
3) Division of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany
4) General Secretary of CEDA

to coronary events and stroke, but this was abolished by adjusting for age and sex [Ahlqvist 2018].

Subgroup replication in the German Diabetes Study

The Swedish data were replicated in several other international cohorts [Dennis 2019, Zaharia 2019, Zou 2019]. In particular, the analysis in the German Diabetes Study (GDS) corroborated and extended the data pointing towards differences in the risk of diabetes-associated diseases between the aforementioned clusters [Zaharia 2019]. The GDS enrols adults within 12 months of their diagnosis of diabetes [Szendroedi 2016]. In this cohort, individuals in the SIRD subgroup not only had the highest prevalence of diabetic nephropathy, but also the highest hepatocellular lipid content at study baseline and the highest prevalence of hepatic fibrosis after five years of follow-up [Zaharia 2019]. Individuals in the SIDD subgroup were characterised by the highest prevalence of confirmed diabetic sensorimotor polyneuropathy (DSPN). Both SIRD and MOD had the highest levels of C-reactive protein, i.e. the biomarker of inflammation most frequently assessed in the context of diabetes-associated complications. Importantly, this study also evaluated the stability of subgroup allocation over a 5-year follow-up period. Changes of metabolic variables, especially glycaemia, lipid levels and fatty liver index, were related to switches between clusters which were observed for 23 % of all patients for whom data from both the baseline and the 5-year follow-up examinations were available [Zaharia 2019].

Diabetes subgroups and inflammation

Future studies need to investigate in more detail which other biochemical and clinical variables distinguish these novel diabetes subgroups and to what extent these differences may explain the differences in the risk of complications in patients with diabetes. Subclinical inflammation represents one candidate, because inflammatory processes and biomarkers are related not only to the development of cardiovascular disease [Herder 2015], diabetic neuropathies [Herder 2019b] and nephropathy [Niewczas 2019], but also to comorbidities such as depression [Herder 2019a]. In particular, the cascade of adipose tissue dysfunction, inflammation, insulin resistance and onset of complications merits more detailed studies [Roden 2019]. Further issues to be addressed comprise the stability of the cluster allocation over time, the reproducibility in different ethnic groups and most importantly the clinical relevance of the novel subgroups for prevention and therapy that requires testing in randomised controlled trials.

References

1. 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; 6: 361-369
2. 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; 7: 442-451
3. Herder C, Dalmas E, Böni-Schnetzler M, Donath MY: The IL-1 pathway in type 2 diabetes and cardiovascular complications. Trends Endocrinol Metab 2015; 26: 551-563
4. Herder C, Hermanns N: Subclinical inflammation and depressive symptoms in patients with type 1 and type 2 diabetes. Semin Immunopathol 2019a; 41: 477-489
5. Herder C, Roden M, Ziegler D: Novel insights into sensorimotor and cardiovascular autonomic neuropathy from recent-onset diabetes and population-based cohorts. Trends Endocrinol Metab 2019b; 30: 286-298
6. Hulman A, Witte DR, Vistisen D, Balkau B, Dekker JM, Herder C, Hatunic M, Konrad T, Færch K, Manco M: Pathophysiological characteristics underlying different glucose response curves: a latent class trajectory analysis from the prospective EGIR-RISC study. Diabetes Care 2018; 41: 1740-1748
7. Niewczas MA, Pavkov ME, Skupien J, Smiles A, Md Dom ZI, Wilson JM, Park J, Nair V, Schlafly A, Saulnier PJ, Satake E, Simeone CA, Shah H, Qiu C, Looker HC, Fiorina P, Ware CF, Sun JK, Doria A, Kretzler M, Susztak K, Duffin KL, Nelson RG, Krolewski AS: A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes. Nat Med 2019; 25: 805-813
8. Roden M, Shulman GI: The integrative biology of type 2 diabetes. Nature 2019; 576: 51-60
9. Szendroedi J, Saxena A, Weber KS, Strassburger K, Herder C, Burkart V, Nowotny B, Icks A, Kuss O, Ziegler D, Al-Hasani H, Müssig K, Roden M; GDS Group: Cohort profile: the German Diabetes Study (GDS). Cardiovasc Diabetol 2016; 15: 59
10. Vistisen D, Witte DR, Tabák AG, Herder C, Brunner EJ, Kivimäki M, Færch K: Patterns of obesity development before the diagnosis of type 2 diabetes: the Whitehall II cohort study. PLoS Med 2014; 11: e1001602
11. Zaharia OP, Strassburger K, Strom A, Bönhof GJ, Karusheva Y, Antoniou S, Bódis K, Markgraf DF, Burkart V, Müssig K, Hwang JH, Asplund O, Groop L, Ahlqvist E, Seissler J, Nawroth P, Kopf S, Schmid SM, Stumvoll M, Pfeiffer AFH, Kabisch S, Tselmin S, Häring HU, Ziegler D, Kuss O, Szendroedi J, Roden M; German Diabetes Study Group: Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. Lancet Diabetes Endocrinol 2019; 7: 684-694
12. 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

Prof. Dr. Christian Herder
Institute for Clinical Diabetology
German Diabetes Center
Auf'm Hennekamp 65
40225 Düsseldorf
Germany
E-Mail: Christian.Herder@ddz.de