



Developing Research for Five Subtypes of Diabetes with Specific Characteristics

Hiroshi Bando^{1,2ID*}

¹Medical Research/Tokushima University, Tokushima, Japan

²Japan Low Carbohydrate Diet Promotion Association (JLCDPA), Kyoto, Japan

Corresponding Author: **Hiroshi Bando** [ORCID iD](#)

Address: Tokushima University /Medical Research, Nakashowa 1-61, Tokushima 770-0943, Japan;

Email: pianomed@bronze.ocn.ne.jp

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Abstract

Recently, sub-classifications for adult-onset diabetes have been presented based on cluster analysis. There are 5 exclusive subtypes, with clusters ranging from 1 to 5: 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), respectively. The related variables known include GAD antibody, age at diagnosis, BMI, HbA1c, and HOMA2-B and HOMA2-IR. From the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, the numerical numbers of the 5 subtypes are 241-1594-914-1595-2673, respectively. The prevalence percentages for the 5 subtypes in 3 countries are as follows: Japan: 5.4-19.0-7.2-28.9-39.5, Germany: 22.0-3.0-11.0-29.0-35.0, and Finland: 9.9-8.9-11.2-22.8-47.3, respectively.

Keywords

Diabetes Subtypes, Cluster Analysis, Adult-Onset Diabetes, Outcome Reduction with an Initial Glargine Intervention, Mild Age-Related Diabetes

Abbreviations

ORIGIN: Outcome Reduction with an Initial Glargine Intervention; MARD: Mild Age-Related Diabetes

Editorial

Diabetes mellitus results from the interrelationship of impaired insulin secretion and insulin resistance. Recent trials include sub-classifications for better prediction of pathology and therapeutic strategies. Several latest reports in 2024 concerning diabetes and its associations have emerged. They include the adipocentric approach to Type 2 diabetes (T2D) and chronic kidney disease (CKD)/diabetic kidney disease (DKD) [1]. Additionally, there are reports on perirenal fat (PRF) accumulation in CKD and eGFR with/without

diabetes [2], a certain link of small dense LDL [3], MAFLD/diabetes, some diabetic types of T2D, and slowly progressive insulin-dependent diabetes mellitus (SPIDDM) [4].

Regarding types of diabetes, the usual classification includes T1D, T2D, SPIDDM, and other types [5]. However, a novel sub-classification for adult-onset DM has been presented based on cluster analysis [6]. The results revealed five exclusive subtypes: cluster 1: severe autoimmune diabetes (SAID), cluster 2: severe

insulin-deficient diabetes (SIDD), cluster 3: severe insulin-resistant diabetes (SIRD), cluster 4: mild obesity-related diabetes (MOD), and cluster 5: mild age-related diabetes (MARD). These categorizations for DM are based on several biomarkers, including aging, obesity, autoimmunity, insulin resistance, and insulin secretion [7]. Furthermore, impressive results were reported regarding this categorization. When an individual is phenotyped before diabetic onset, they do not migrate among these cluster types, even if they show progression in diabetic duration [8].

According to these five subtypes of diabetes, strategies for improving glycemic control and preventing macro- and micro-angiopathic complications were proposed [9]. It introduced the novel concept of mapping 5 clusters in a 2-dimensional space with the x-axis representing insulin secretory capacity (high-normal-low) and the y-axis representing insulin demand (low-high). The five clusters were almost situated in a linear position from lower to higher order, making it easy to understand the general concept of the 5 subtypes. As to both axes from lower to higher positions, the five clusters were situated for SAID, SIDD, MARD, MOD, and SIRD as cluster 1-2-5-4-3. Each type has characteristic phenotypes of diabetic complications, such as neuropathy, retinopathy, CKD, DKD, ketoacidosis, as well as some comorbidities of ASCVD, heart failure, atrial fibrillation, NAFLD, NASH, fracture, frailty, dementia, and mild cognitive impairment (MCI).

Regarding treatment strategy in each cluster, a different perspective has been recommended [9]. Cluster 1 suggests multiple daily or continuous injections of insulin while preventing hypoglycemia, cluster 2 recommends early control using insulin administration with hypoglycemia prevention, cluster 5 emphasizes paying attention to activities of daily living (ADL), adherence, clinical inertia, and multifactorial treatment associated with preventing hypoglycemia and polypharmacy, cluster 4 involves continuing adequate weight control, diet, and exercise while maintaining a regular lifestyle, and cluster 3 involves conducting multifactorial therapy and weight control, associated with metabolic surgery if needed.

Applying the novel theory of 5 sub-types of diabetes, measuring six clinical variables were attempted to investigate clustering [10]. For a possible hypothesis, certain circulating proteins may be meaningful for distinguishing these diabetic subtypes. In the large program of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial, more than 7 thousand participants were categorized. They used five biomarkers out of six variables. The following prevalence data were obtained: SAID 241, SIDD 1594, SIRD 914, MOD 1595, and MARD 2673 as the numerical numbers. Among them, a certain subset of 233 cardiometabolic protein biomarkers was identified. A total of 25 biomarkers were shown as independent determinants of subtypes. They included SIDD 13, SIRD 2, MOD 7, and MARD 11, which showed significant differences. In the case of SAID, no other biomarkers were detected other than GAD antibodies. Consequently, further research development will be expected for detecting and investigating the combination of various determinants of T2D subtypes.

Related research was also developed in the ORIGIN trial for the same applicants [11]. Among subtypes, differences in cardiovascular and renal outcomes were compared for a follow-up of 6.2 years using Cox regression models. Compared with MARD, SIRD showed higher results, resulting in CKD stage 3A (HR) 1.49, stage 3B HR 2.25, and macroalbuminuria HR 1.56. There were no differences in the incidence of cardiovascular disease and retinopathy after adjusting for multiple factors. Diabetic subtypes showed a response of blood variability to the treatment of Glargine. Compared with MARD, SIDD showed a decreased incidence of hyperglycemia by 13%, with an odd ratio (OR) of 1.36 on glargine, and OR of 1.49 on standard care. It suggests the beneficial therapy of receiving glargine vs standard care in SIDD.

Several studies across the world have stratified diabetic patients into some phenotypical clusters. Recently, systematic examinations of cluster variations have been clarified in various ethnic groups. Related data were summarized in 12 Asian papers and 20 non-Asian papers [12]. Certain clusters seem to be more frequent for Asians, which show a probable lower body weight, poorer function of beta cells, and younger age

at T2D diagnosis. Three data of prevalence would be described for 5 subtypes as follows, where Japan: SAID 5.4, SIDD 19.0, SIRD 7.2, MOD 28.9, MARD 39.5, German: SAID 22.0, SIDD 3.0, SIRD 11.0, MOD 29.0, MARD 35.0, and Finnish SAID 9.9, SIDD 8.9, SIRD 11.2, MOD 22.8, MARD 47.3 [12,13].

As to the classification of 5 subtypes of diabetes, six diabetes-related variables have been identified: GAD antibody, age at diagnosis, BMI, HbA1c, and HOMA2-B and HOMA2-IR. Out of 1167 participants in the Iwaki Health Promotion Project in 2014, 868 nondiabetic cases were included for prospective investigation [14]. Current hierarchical cluster analysis was conducted using 4 variables of BMI, HbA1c, and HOMA2 indices. In 4 clusters identified, obese insulin-resistant type (n=136) and low insulin secretion type (n=136) were identified as having a higher risk of diabetes onset for a 5-year period. The adjusted HR was 14.7 for cluster 1 and 53.1 for cluster 2, respectively.

In conclusion, the risk of diabetes can be assessed from the cluster to which a case belongs. Such studies will be expected for the further development of diabetic research. For diabetic research, precision diabetes medicine (PDM) will contribute, associated with innovative proteomic technologies and genomics. This article will hopefully become a useful reference for clinical research in the future.

Conflict of Interest

The author has read and approved the final version of the manuscript. The author has no conflicts of interest to declare.

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