



Type 2 Diabetes Mellitus (T2DM) may have Four Subtypes Beneficial for Adequate Treatment

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Abstract

Diabetes includes various heterogeneous factors. Similar to subtypes of type 1 diabetes, type 2 diabetes may show four subtype clusters. They are cluster A: severe insulin-deficient diabetes, B: severe insulin-resistant diabetes, C: mild obesity-related diabetes, and D: mild age-related diabetes. Comparing them, the prevalence of nephropathy and cardiovascular events was highest in the cluster A. Reference data are i) the ratio of cluster A-D is 18.7%, 23.7%, 21.1%, 36.4%, ii) HbA1c for A-D is 11.05%, 8.17%, 8.49%, 7.95%, iii) event ratio of MACE is 14.4%, 10.6%, 11.4%, 9.1%. Future diabetic treatment is hopefully provided suitable for each subtype.

Keywords

Type 2 diabetes mellitus (T2DM), Subtype, Cluster, All New Diabetes in Scania (ANDIS)

Abbreviations

Type 2 diabetes mellitus (T2DM); All New Diabetes in Scania (ANDIS)

Diabetes mellitus has been increasing worldwide, and become a crucial challenge to maintain and promote the health of people [1]. Since Type 2 diabetes mellitus (T2DM) shows marked heterogeneity in clinical symptoms, sign, various risk factors, multifactorial outcome, and course, the management cannot be conducted by an individualized approach [2]. If there are some subgroups in T2DM, adequate treatment suitable to each patient can be provided with more effectiveness and less cost [3].

Conventionally, type 1 diabetes mellitus (T1DM) may be classified according to the positive islet-related autoantibodies or presence of autoimmunity. However,

it is usually categorized into three types according to the mode of onset. The three types are as follows: i) Fulminant onset type: insulin secretion is dramatically depleted as diabetic ketoacidosis develops within a few days after the onset [4], ii) Acute onset type: diagnosed as diabetic, such as diabetic ketoacidosis within a few months after the development of the dry mouth, polydipsia, polyuria, and weight loss, iii) Slowly progressive type: insulin secretion is not depleted at the time of diagnosis, and after a period of one year or more, insulin is depleted and insulin injection will be indispensable [5]. It has been called slowly-progressive insulin-dependent diabetes mellitus (SPIDDM) or Latent autoimmune diabetes in adults (LADA) [6,7].

On the other hand, T2DM has been different, and the concept of classifying into subtypes has hardly existed so far. It is often observed that patients with T2DM in Western countries (white and black) have obesity [8]. In contrast, T2DM patients in Asia (yellow race) seem to be non-obese. Consequently, it is rather useful for considering the subtype of T2DM because the background factors of T2DM are heterogeneous with a variety of different factors [9].

There was an impressive study of T2DM in a large Swedish cohort study with adult-onset diabetes in 2018 [10]. It was the All New Diabetes in Scania (ANDIS) cohort with 8980 individuals, using clustering on 6 available diabetes-associated variables, which are age at diagnosis, insulin secretory ability, insulin resistance, body mass index (BMI), HbA1c and islet-cell autoantibody. Four clusters were found resembling type 2 diabetes phenotypes, that was characterized by age at diagnosis, insulin resistance (calculated by homeostatic model assessment [HOMA]) and beta-cell function, BMI and HbA1c. There was the fifth cluster, which was defined by autoantibodies and was similar to autoimmune type 1 diabetes [10].

Successively, a recent paper was reported in 2020 by Kahkoska et al., which shows the validation of distinct type 2 diabetes clusters [11]. The research is conducted by taking the most advantages of three cardiovascular outcomes trials (CVOT). These trials and number of subjects were DEVOTE (n=7637) [12], LEADER (n=9340) [13,14] and SUSTAIN-6 (n=3297) [15]. Clustering parameters were HbA1c, body mass index at baseline, and age at diabetes diagnosis. They analyzed the cumulative risk of a major adverse cardiovascular event (MACE), cardiovascular (CV) death and all-cause death by cluster in the DEVOTE, LEADER and SUSTAIN-6 trials. Using obtained data in three studies, subgrouping of T2DM were performed [11].

Combined these findings of the research together, there were four cluster labels corresponding to the ANDIS labels [11]. The characteristic of the Cluster A-D are as follows:

- i) Cluster A, severe insulin-deficient diabetes; symptoms are rather severe, and GAD antibody

is negative.

- ii) Cluster B, severe insulin resistant diabetes; usually high value of body mass index (BMI).
- iii) Cluster C, mild obesity-related diabetes; more related with obesity status compared with the presence of insulin resistance.
- iv) Cluster D, mild age-related diabetes; the patients tend to develop the onset at older age than that of Cluster C.

Among them, some important data are as follows:

- i) The ratio of cluster A-D in DEVOTE (n=7546) is 18.7%, 23.7%, 21.1%, 36.4%, respectively.
- ii) HbA1c for A-D in LEADER is 11.05%, 8.17%, 8.49%, 7.95%.
- iii) Event ratio for MACE for 2.5 years in DEVOTE seems to be 14.4%, 10.6%, 11.4%, 9.1%.
- iv) the ratio of new or worsening nephropathy in LEADER seems to be 12.6%, 4.9%, 8.8%, 6.7%, respectively [11].

In this study, the cases with positive islet-cell autoantibody were not included. Then, the number of subgroups was not five but four. When observing the results of HbA1c, BMI and age at diagnosis, data of median and 25%/75% quartiles were almost the same in three mega studies, and data of 4 clusters showed distribution apart [11]. This tendency suggests clinical significance for possible four clusters in T2DM. Comparing these four clusters, the prevalence of nephropathy and cardiovascular events (3-point MACE: non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) was highest in the cluster A.

Related to these clusters, Dennis and collaborators have replicated the clusters of ANDIS for the clinical trials of ADOPT trial (n=4351) and RECORD (n=4447) [16]. The obtained data was similar to that of Ahlqvist et al., and these models based on simple clinical features seemed to be beneficial to stratify diabetic patients. Furthermore, Clustering study was performed in German Diabetes Association for patients with recent-onset diabetes (n=1105) [17]. The results showed i) mild age-related diabetes (MARD) 35%, ii) mild obesity-related diabetes (MOD) 29%, iii) severe autoimmune diabetes (SAID) 22%, iv) severe insulin-

resistant diabetes (SIRD) 11%, and v) severe insulin-deficient diabetes (SIDD) 3%. Consequently, cluster analyses enable us to characterize cohort studies with different extent of insulin resistance for adipose tissue and whole body. These methods may lead to targeted prevention and treatment for diabetic precision medicine [17]).

Based on the above results, Kahkoska et al. suggested that the subtyping of the Swedish report would be appropriate and that each treatment method by subtype should be considered in the future [11]. It is certain that cluster A (12.6 years in average) showed higher prevalence of arteriosclerosis and nephropathy than that of cluster C (21.2 years in average), indicating the difference and probable benefit among 4 clusters categorization.

However, there are some limitations. Several situations may exist such as i) the same T2DM patients may have different characteristics in race, Europe, America, and Asia region, ii) the diabetic duration years may be influencing in addition to the age of onset, iii) judgment for clusters B or C may be difficult in the case of 50-year-old man with moderate obesity, and so on.

By accumulating various data, it is expected that the era will come in the future where treatment, management, and advice can be provided for each subtype cluster in T2DM.

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