COMMENTARY

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Not All Patients with Type 2 Diabetes Are Equal

THE CURRENT TREATMENT ALGORITHM IS BASED ON THE TRADITIONAL DEFINITION OF TYPE 2 DIABETES

The treatment algorithm for the management of hyperglycemia in type 2 diabetes (T2DM) was recently updated based on large cardiovascular outcomes trials (CVOTs).[1] Obviously, these recommendations, endorsed by experts, are excellent and vital for guiding the worldwide management of diabetes. Nevertheless, they do not address the heterogeneity of T2DM.

A NEW CLASSIFICATION OF TYPE 2 DIABETES

Ahlqvist et al[2] proposed a revolutionary new classification of adult, recent-onset, T2DM into subtypes (clusters). It is founded on 6 rather simple variables: glutamate decarboxylase (GAD) antibodies, age at diagnosis, body mass index (BMI), HbA_1c levels, and homoeostatic model assessment estimates of β-cell function (HOMA2-B) and insulin resistance (HOMA2-IR). This landmark study included a large cohort ($n = 8980$) of an adult Swedish population with new-onset T2DM (All New Diabetics in Scania [ANDIS]).[2] The median follow-up period was 4 years. A cluster analysis based on these 6 variables identified 5 groups of patients: 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). These clusters included 6.4%, 17.5%, 15.3%, 21.6%, and 39.1% of the total cohort, respectively. Four independent cohorts in Sweden and Finland confirmed these findings.[2]

WHAT ARE THE CLINICAL IMPLICATIONS OF THIS NOVEL CLASSIFICATION?

Importantly, the clusters differed not only in their baseline characteristics, but the groups also varied in their risk to develop diabetes-related acute and chronic complications (Table 1). First, a quarter of the patients in the SIDD cluster of the ANDIS cohort presented with diabetic ketoacidosis (DKA), an acute, life-threatening condition.

Second, this cluster was also associated with an elevated risk of diabetic retinopathy. Hence, the SIDD subgroup of 2 large cohorts, the ANDIS and the All New Diabetics in Uppsala (ANDIU), had an elevated hazard ratio (HR) of this chronic complication, up to 1.6 (1.3-1.9) and 4.6 (3.0-7.0), respectively. Patients within the SIDD cluster had also an elevated rate of sensorimotor polyneuropathy.[2]

Third, the SIRD cluster had a remarkably high risk of another serious diabetes-related complication, chronic kidney disease (CKD). It was documented both at baseline and during follow-up, with an HR of 3.3 (2.6-4.3) compared with the MOD cluster.

Fourth, the SIRD subgroup had a high risk of developing coronary artery disease and nonalcoholic fatty liver disease (NAFLD).

Taken together, 2 important implications can be drawn. First, about a third of patients with T2DM, those within the SIDD and SIRD clusters, are especially prone to develop diabetes-related complications. Second, each of the 2 subgroups has a unique profile of complications.

THE NEW CLASSIFICATION IS CONSISTENT IN COMPLETELY DIFFERENT POPULATIONS

The data of the German Diabetes Study confirm and even strengthen the results of this cluster approach.[3] Partition of this cohort into clusters included additional assessment tools: evaluation of insulin sensitivity and secretion by hyperinsulinemic-euglycemic clamp and intravenous glucose tolerance test as well as liver lipid content determination by magnetic resonance spectroscopy and fibrosis by noninvasive scores. Their findings established the high-risk of the SIRD cluster to develop CKD, with a complication rate of up to 27% 5 years of follow-up. Moreover, the SIRD cluster was characterized by a high prevalence of advanced form of NAFLD and a quarter of them developed liver fibrosis (Table 1).

Surprisingly, the cluster distribution was also confirmed in a population of completely a different genetic background. As reported by Li et al,[4] application of the cluster-

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Table 1 Diabetes Complications in ANDIS, SDR and the German Diabetes Study Cohorts Stratified by the Cluster Approach[2,3]

Diabetes-Related Complications, %	SAID	SIDD	SIRD	MOD	MARD
ANDIS cohort (n = 8980)					
DKA at diagnosis	30	25	3	5	2
CKD 3A	6	8	22	3	3
CKD 3B	2	3	9	1	4
Macroalbuminuria	3	4	6	3	2
Coronary events	4	5	7	3	6
NAFLD	7	12	24	22	7
SDR cohort (n = 1466)					
Retinopathy	60	64	35	49	40
Coronary events	8	17	23	11	19
German Diabetes Study cohort* (n = 367)					
eGFR < 60 mL/min/1.73m^2 at baseline	1	0	12	1	2
At follow-up	0	0	27	4	5
Confirmed DSPN at baseline	5	36	17	11	15
At follow-up	12	50	12	17	9
Liver fibrosis at follow-up	7	0	26	15	12

*Patients who had 5 years of follow-up. ANDIS = all new diabetics in Scania; CKD = chronic kidney disease; DKA = diabetic ketoacidosis; DSPN = diabetic sensorimotor polyneuropathy; eGFR = estimated glomerular filtration rate; MARD = moderate age-related diabetes; MOD = moderate obesity-related diabetes; NAFLD = nonalcoholic fatty liver disease; SAID = severe autoimmune diabetes; SDR = Scania Diabetes Registry; SIDD = severe insulin deficient diabetes; SIRD = severe insulin resistant diabetes.

analysis approach was valid in a large cohort of 15,772 patients with newly diagnosed, adult-onset, diabetes in China. [5]

SHIFTING THE PARADIGM IN THE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

This novel classification may have a paramount importance on our treatment decisions, *mainly adopting a more aggressive approach for patients within the SIDD and SIRD clusters*.

The large CVOTs inclusion criteria were based on the traditional uniform diagnosis of T2DM. Therefore, the current consensus reports originating from those trials may provide a treatment algorithm that is too generalized. It stratifies each patient with T2DM according to existing clinical characteristics: established cardiovascular disease, cardiovascular risk factors, heart failure, nephropathy, obesity, high risk of hypoglycemia, and cost issues.[1] However, based on the intriguing and important recent data derived from the aforementioned trials,[2,3] we suggest also to stratify according to the appropriate cluster of T2DM. Hence, some important questions regarding the current therapy algorithm arise (Table 2):

1. *CKD and the SIRD cluster:* Currently, sodium-glucose linked transporter type-2 (SGLT2) inhibitors are recommended for patients with T2DM and CKD. *Shouldn't we consider this treatment in the SIRD cluster, long before the development of CKD?* Notably, progression of this complication was halted by SGLT2 inhibitors even in patients with relatively preserved kidney function.[6]

Table 2 Suggested Recommendations for Pharmacologic Treatment of Diabetes Mellitus Based on the Cluster Approach[2,3]

Cohort's Cluster	Risk of Complication	Potential Unsafe/Unrecommended Medications	Recommended Group of Medications
SIDD	Diabetic ketoacidosis	SGLT2 inhibitors	Insulin; insulin secretagogues
SAID	Diabetic ketoacidosis	SGLT2 inhibitors	Insulin
SIDD	Diabetic retinopathy	Semaglutide?*	Insulin; insulin secretagogues
SIRD	Chronic kidney disease		SGLT2 inhibitors
SIRD	ASCVD		GLP-1 RA; Pioglitazone
SIRD	NAFLD		Pioglitazone, GLP-1 RA; SGLT2 inhibitors

ASCVD = atherosclerotic cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; NAFLD = nonalcoholic fatty liver disease; SAID = severe autoimmune diabetes; SGLT2 = sodium glucose co-transporter 2; SIDD = severe insulin deficient diabetes; SIRD = severe insulin resistant diabetes.

*Under current study.

2. *Established atherosclerotic cardiovascular disease (ASCVD), and the SIRD cluster:* The algorithm proposes glucagon-like peptide-1 receptor agonists (GLP-1RA) as the first-choice therapy in patients with established ASCVD. *Shouldn't we consider early administration of GLP-1RA to patients with SIRD clusters' characteristics, even before they have evidence of ASCVD?* GLP-1RA has been shown in animal models, supported by human data, to have numerous advantageous effects on atherosclerosis through direct and indirect mechanisms.[7] Although not fully adopted mainly due to side effects, pioglitazone has also a favorable effect on ASCVD as shown in the PROactive trial.[8]
3. *DKA and the SIDD cluster:* The SGLT2 inhibitors have been shown to increase DKA risk.[4] They may be even more hazardous in the SIDD cluster, especially prone to develop DKA (Table 1).[2] *Therefore, how safe are SGLT2 inhibitors in this subgroup?*
4. *Retinopathy and the SIDD cluster:* Administration of insulin or insulin secretagogues treatment is capable of effectively controlling the marked hyperglycemia in patients within the SIDD cluster. Moreover, these therapies may also reduce retinopathy both within a short- and a long-term follow-up.[9] *Thus, shouldn't we initiate these treatment modalities earlier in the SIDD cluster?*
5. *NAFLD and the SIRD cluster:* As already mentioned, the SIRD cluster has a high risk of developing advanced form of NAFLD. *Therefore, shouldn't we consider including this serious complication in our treatment algorithm?* NAFLD and its more severe form nonalcoholic steatohepatitis (NASH) is currently a major worldwide health problem. Diabetes promotes not only the development of NASH but also cirrhosis and hepatocellular carcinoma. Although none of the current antihyperglycemic medications have been approved for the treatment of NAFLD, there are several trials showing a beneficial effect of pioglitazone, liraglutide, and SGLT2 inhibitors in reducing liver fat accumulation. Moreover, pioglitazone has been found to reduce liver fibrosis, while metformin and insulin have not been proven to have a beneficial effect.[10]

A PRACTICAL NOTE FOR FUTURE DIABETES TRIALS

Suggested recommendations that are based on the cluster-approach findings are provided in Table 2. The recommendations focus on the more aggressive clusters SIDD and SIRD with their high risk of developing diabetes-related complications, as discussed. We acknowledge that currently there is no evidence as to whether this approach enables a more precise choice of treatment. Therefore, the time has come to conduct further studies aimed to evaluate the effect of different treatment modalities on diabetes complications using these newly defined T2DM subclasses. This can be performed by reanalyzing previous CVOTs populations using the cluster approach. Furthermore, we call to apply this classification in planning future trials.

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