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ORIGINAL ARTICLE

Use of expert consensus to improve the diagnosis and management of type 1 diabetes mellitus

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Abstract

Background: Although type 1 diabetes mellitus (T1DM) is recognized as a catastrophic disease among the different types of diabetes, it is often confusedly diagnosed in clinical practice and difficult in care. The objective of this study is to reach a multidisciplinary consensus for the establishment of clinical recommendations on T1DM to optimize its undoubtedly diagnostic evaluation and transitional care.

Methods: Scientific evidence was reviewed by a committee of researchers, based on which recommendations related to T1DM diagnosis were formulated. A two-round method was conducted to compare the opinions of a panel of 32 specialists (adult endocrinologists [53.1%], pediatric endocrinologists [43.8%], a diabetes educator for child and adolescent [3.1%]) on these issues.

Results: The panel reached consensus on two of the six items discussed. The four items on which no consensus was reached were related to autoantibody detection and age of onset. Up to 80% of the panelists favored items related to the glucagon test and diabetic ketoacidosis history for T1DM diagnosis. Consensus regarding transitional care through diabetes educators was established.

Conclusion: The assessment conducted by experts on T1DM showed a high level of professional agreement regarding the proposed diagnostic and transitional care recommendations. A comprehensive analysis of the latest evidence is warranted for the items on which consensus was not established.

Keywords: Consensus; Diagnosis; Type 1 diabetes

1. INTRODUCTION

The number of new-onset type 1 diabetes mellitus (T1DM) cases in Taiwan is about 500 each year.[1,2] Current incidence data reveal a trend towards an increasingly younger population with T1DM. The diagnosis of T1DM affects whether a patient qualifies for a partial waiver of self-paid medical expenses with catastrophic illness certificate in Taiwan; therefore, the accuracy of this diagnosis is essential.

Diabetes classification was adjusted from four to six categories by World Health Organization in 2019.[3] The newly added categories include hybrid forms of diabetes and unclassified diabetes. Hybrid forms of diabetes include ketosis-prone diabetes and slow evolving immune-mediated diabetes of adults, formerly called latent autoimmune diabetes in adults (LADA). Three criteria are suggested for the diagnosis of LADA: positivity for glutamic acid decarboxylase 65 (GAD65) or islet antigen 2 (IA-2) or Zinc transporter 8 (ZnT8) autoantibodies, age older than 35 years at diagnosis, and no need for insulin therapy in the first 6–12 months after onset.[3] There are no other subdivisions under T1DM. Age is a crucial reference for the classification of diabetes, but it is not the only diagnostic criterion for diabetes. Other conditions merit consideration as well. Due to the involving in the diagnosis of T1DM, we need to make a consensus through the cooperation of adult and pediatric endocrinologists in Taiwan.

2. METHODS

2.1. Study design

The Delphi method, which involves the participation of an expert panel in multiple discussions on a topic to reach a

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A complete list of the members in Taiwan Type 1 DM Consortium is provided in the Appendix.

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consensus, was employed to obtain reliable agreement regarding T1DM diagnosis in the present study. This approach prevents opinion conformity due to positional authority or peer pressure.[4] Consequently, the Delphi method was applicable in the current study. To ensure the robustness of the findings, 15–17 experts were included in each group, and the targeted response rate was >80%.

2.2. Participants and questionnaire formation

On the basis of relevant literature on care during the transition period for the unique T1DM patients from child, adolescents to young adults,[5] the following criteria were applied to the selection of experts: (a) adult endocrinologists: experts with clinical experiences for patients with T1DM aged above 18 years. The qualified experts were selected from medical centers from northern to southern Taiwan; (b) pediatric endocrinologists: experts from similar healthcare professionals caring about patients aged below 18 years across Taiwan; and (c) diabetes educators: specialists in pediatric and adult T1DM care and health education except endocrinologists. We selected the most credible one as representer for the robust and efficient operation of the Taiwan Type 1 DM Consortium. The collection, analysis of results, and discussion of the conclusions were conducted in a face-to-face formula of the scientific committee. All participants were members of the scientific committee.

The committee developed the questionnaire through collaboration with an external methodology consultant. For survey development, the literature was searched for studies centered on T1DM diagnosis. Each survey item evaluated by the panel was drafted according to whether it was a statement-positive or statement-negative expression. Clinical doubt, controversial elements, and matters of interest regarding the clinical diagnosis and care of patients with T1DM were addressed based on either professional opinion or clinical recommendation. The final version of the questionnaire comprised six items (Table 1) grouped into the following subject areas: clinical history (four items) and laboratory autoantibody measurement (two items). The questionnaire was anonymously completed.

3. RESULTS

3.1. Medical history, age of onset, and diagnosis

1. In the examination report, should the C-peptide/glucagon test result determine eligibility for applying for a catastrophic illness certificate?

Most physicians agreed that the C-peptide/glucagon test was an important diagnostic indicator of T1DM (84.4% of panelists in favor, Table 1 and Fig. 1). Other factors such as height, body weight, and age were not considered necessary indicators but could be used as a reference. The establishment of separate diagnostic standards for pediatric and adult patients was recommended.

2. Will a diagnosis of T1DM be ruled out based on the condition of "no insulin injections and no diabetic ketoacidosis (DKA) for at least 6 months after the onset of disease?"

In the first round: there were eight physicians in favor; nine physicians opposed (47.1% in favor). Those in favor suggested that relevant eligibility criteria should be established according to precise figures. In addition, because the clinical presentation was dynamic, criteria for determining eligibility for a catastrophic illness certificate should be implemented leniently. Most of those in opposition believed, based on their own clinical experience that DKA might not occur or patients might not require insulin in 6 months.

In the second round, there were two physicians in favor; 13 physicians opposed (13.3% in favor). Those in favor thought that they could be ruled out according to the above conditions, and reevaluated as additional supporting evidence (such as autoantibodies) available. Those who opposed considered that the C-peptide/glucagon or antibody test results were actually required by the National Health Insurance (NHI) Committee in central Taiwan, whereas medical history and DKA served only as supplementary information. Physicians practicing in southern Taiwan reported similar experiences.

In summary, the average percentage of panelists in favor was 31.3% (Table 1), and no consensus was reached (Table 1 and Figure). The regions of specialists were across from northern to southern Taiwan and the distribution was 76% from northern, 18% from central, and 6% from southern Taiwan in the first round; 20% from northern, 20% from central, and 60% from southern Taiwan in the second round. The consensus could not be reached due to the influence by different regions.

3. Is the history of DKA a sufficient, but not necessary, condition to apply for a catastrophic illness certificate?

Almost all panelists agreed that DKA history was sufficient but not necessary to application for a catastrophic illness certificate. The average percentage was 87.5% in favor and a consensus was reached (Table 1 and Fig. 1).

Table 1

Results of the level of agreement achieved by the experts after the 2 rounds of discussion

No.	Questionnaire	Panelists in favor (%)		
		1st round	2nd round	Average
I	Medical history, age of onset, and diagnosis			
1.	In the examination report, should the C-peptide/glucagon test result determine eligibility for applying for a catastrophic illness certificate?	13/17 (81.3)	14/15 (93.3)	27/32 (84.4)
2.	Will a diagnosis of T1DM be ruled out based on the condition of "no insulin injections and no ketoacidosis for at least 6 months after the onset of disease"?	8/17 (47.1)	2/15 (13.3)	10/32 (31.3)
3.	Is the history of DKA a sufficient, but not necessary, condition for applying for a catastrophic illness certificate?	15/17 (88.2)	13/15 (86.7)	28/32 (87.5)
4.	Is age of onset a critical determinant?	8/17 (47.1)	9/15 (60.0)	17/32 (53.1)
II	The requirement of autoantibodies			
5.	Is a positive test for autoantibodies such as GAD65 or IA-2 or ZnT8 antibody necessary for the confirmation of T1DM?	9/17 (52.9)	5/15 (33.3)	14/32 (43.8)
6.	Can the following three types of autoantibody testing in sequential order (GAD65, IA-2, ZnT8 antibody) be used as supplementary data for diagnosis of T1DM and catastrophic illness identification?	8/17 (47.1)	11/15 (73.3)	19/32 (59.4)

DKA = diabetic ketoacidosis; GAD65 = glutamic acid decarboxylase 65; IA-2 = islet antigen 2; T1DM = type 1 diabetes mellitus; ZnT8 = Zinc transporter 8.

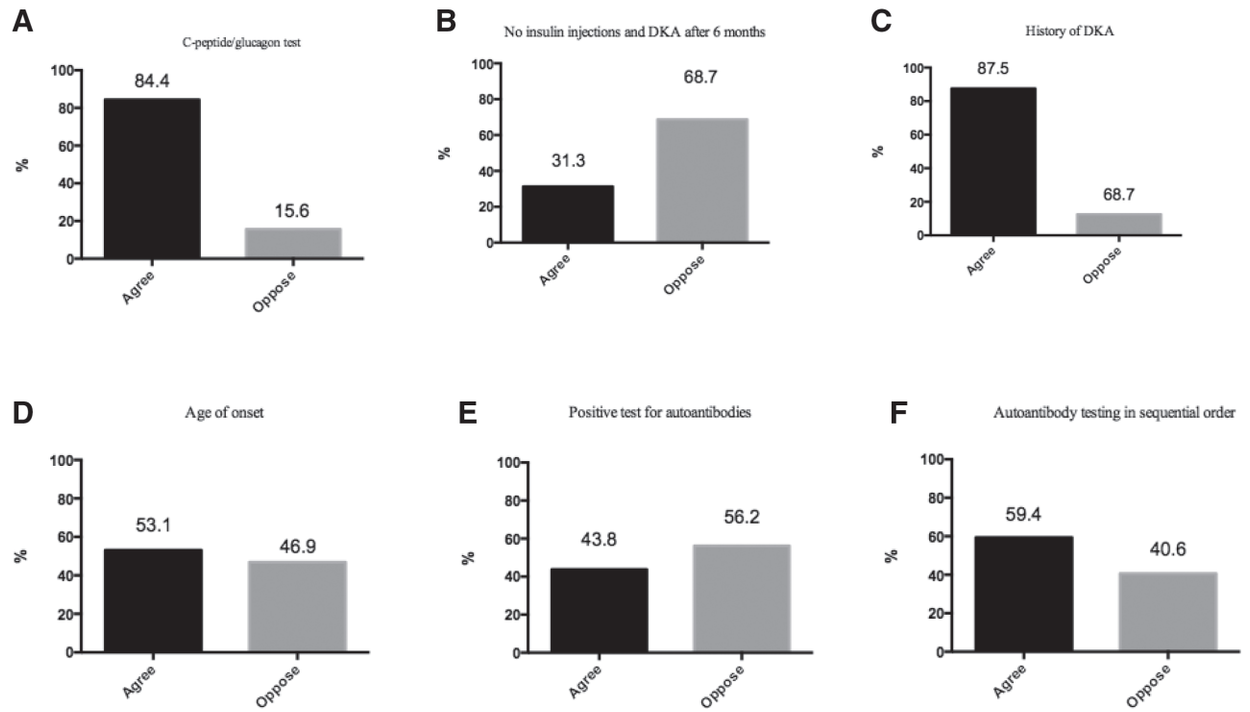

Fig. 1 Distribution of expert opinions on the items with or without agreement. A, In the examination report, should the C-peptide/glucagon test result determine eligibility for applying for a catastrophic illness certificate? B, Will a diagnosis of T1DM be ruled out based on the condition of "no insulin injections and no ketoacidosis for at least 6 months after the onset of disease"? C, Is the history of DKA a sufficient, but not necessary, condition for applying for a catastrophic illness certificate? D, Is age of onset a critical determinant? E, Is a positive test for autoantibodies such as GAD65 or IA-2 or ZnT8 antibody necessary for the confirmation of T1DM? F, Can the following three types of autoantibody testing in sequential order (GAD65, IA-2, ZnT8 antibody) be used as supplementary data for diagnosis of T1DM and catastrophic illness identification? DKA = diabetic ketoacidosis; GAD65 = glutamic acid decarboxylase 65; IA-2 = islet antigen 2; T1DM = type 1 diabetes mellitus; ZnT8 = Zinc transporter 8.

4. Is age of onset a critical determinant?

There was no consensus among panelists on whether T1DM could be identified by the age of onset (average percentage was 53.1% in favor) (Table 1 and Figure). Some panelists contended that the purpose of the catastrophic illness certificate was to help disadvantaged individuals; therefore, they believed that the eligibility criteria should be applied leniently to young patients. Others asserted that age was not an absolute criterion for determining financial status.

Most of the pediatric endocrinologists were in favor of using age of onset to identify T1DM, whereas most of the adult endocrinologists were in opposition.

3.2. The requirement of autoantibodies

5. Is a positive test for autoantibodies such as GAD65 or IA-2, or ZnT8 transporter antibody necessary for the confirmation of T1DM?

In the first round, 52.9% of the panelists were in favor. The proponents of this requirement reported that 92% of patients aged younger than 18 years test positive for at least one of these three autoantibodies and noted that this status does not change with treatment.

In the second round, 5 (33.3%) and 10 panelists were in favor and in opposition of this requirement. Overall, 43.8% of panelists were in favor; therefore, no consensus was established (Table 1 and Figure). Those in opposition averred that although testing positive for relevant autoantibodies indicate the presence of T1DM, testing negative result does not exclude the possibility that a patient does not have this condition. Because these autoantibody tests were performed out of pocket in Taiwan, those in opposition believed that it was unreasonable for this requirement to be under diagnostic review.

Many physicians were unaware that GAD65 antibody testing is covered by the NHI because most hospitals list it as not being covered. Given that the NHI reimbursement rate is low, these hospitals seek to recover their losses by insisting that patients pay for their own tests. Following these findings, the Diabetes Association of the Republic of China (DAROC) was requested to appeal to the NHI Administration for a rate adjustment.

6. Can the following three types of autoantibody testing[6–8] in sequential order be used as supplementary data for diagnosis of T1DM and catastrophic illness (Table 2)?

In the first round, only 47.1% in favor was reached. Most of the endocrinologists tested all three autoantibodies together without considering the order. The fact that these tests are paid out of pocket must be clearly communicated to patients.

Table 2

The three types of autoantibody testing available in Taiwan

Autoantibody	Natural of islet autoantibodies
GAD 65	Detective at 70%–80% regardless of age
IA-2A	Diagnostic sensitivity decreases with increasing age
ZnT8	Detective later in the development of the disease

GAD65 = glutamic acid decarboxylase 65; IA-2 = islet antigen 2; ZnT8 = Zinc transporter 8.

In the second round, 11 panelists were in favor (73.1%) of the positive autoantibody test requirement, whereas four panelists were in opposition. The opponents argued that the presence of certain autoantibodies does not necessarily indicate disease onset. Moreover, they believed that testing the autoantibodies in a specific order was not supported by the evidence. The average proportion of panelists in favor was only 59.4%, and no consensus was reached (Table 1 and Figure).

3.3. Documents necessary for applying for catastrophic illness certificates

The panelists representing DAROC, the Taiwanese Association of Diabetes Educators (TADE), and the Taiwan Pediatric Association have conducted research on evidence-based studies,[9–14] and reached a consensus (Table 3). In brief, the C-peptide/glucagon test is crucial for T1DM diagnosis and the diagnosis of LADA or slowly evolving immune-mediated diabetes of adults should be distinguished from that of T1DM. The application for catastrophic illness certificates in patients with LADA should not be considered if not in fully insulin-dependent status. Positive GAD65/IA-2/ZnT8 antibody test results can confirm that a patient has T1DM. However, testing negative for these antibodies cannot exclude the possibility that a patient has T1DM. The necessary documents are listed in Table 4. The cutoff point of C-peptide/glucagon test is set at C-peptide level <0.5 ng/mL at 0 minutes or <1.8 ng/mL at 6 minutes or increase < 0.7 ng/mL for age ≥18 years old in favor of T1DM.[10,13,14] At the age <18 years old, the cutoff point is set at C-peptide level <0.5 ng/mL at 0 minutes or <3.3 ng/mL at 6 minutes.[13,14]

3.4. Establishment of consensus for the transitional care in T1DM

Pediatric patients with T1DM and DKA episodes who are admitted to hospitals with no pediatric endocrinologists must be treated by an interdisciplinary care team. Pediatricians and adult endocrinologists initiate care of the patient. Once the patient's condition is stable, nutritionists and diabetes educators provide them with relevant information. Before discharge, the patient can decide whether to transfer their care to the adult endocrinology division or the pediatric endocrinology division of other hospitals. Some panelists suggested that all patients with T1DM can be included in the Diabetes Shared Care Network program for diabetes care. Diabetes educators can facilitate the transitional care from pediatric to adult endocrinologists. The consensus of transitional care in T1DM is list in Table 5.

T1DM care requires interdisciplinary teamwork and case management. Aside from physicians, such a team should include special nurses, nutritionists, social workers, and psychologists. Team members must exchange information and work in concert to provide comprehensive and integrated care. The core motivation for patients to continue participating in the Diabetes Shared Care Network is the interaction between patients and diabetes educators. This motivation is strengthened through the compassionate care of diabetes educators. It is recommended to identify interested and willing physicians to carry out long-term planning and training and establish an appropriate policies and procedures. It is also recommended for DAROC to either set up a competition or a ranking system for T1DM care in order to increase reimbursement for T1DM care providers.

4. DISCUSSION

Children or adolescents with type 1 diabetes typically present with the symptoms of polyuria or polydipsia or weight loss but only one-third present with DKA.[15] Since the diagnosis in adult is challenging, a reliable test of β-cell function must be developed. In the present study, consensus regarding the C-peptide/glucagon test requirement for T1DM diagnosis and catastrophic illness certificate eligibility was established. Furthermore, the panelists generally agreed that DKA history is relevant to application for such certificates. Because of the variable clinical presentation of T1DM, the panelists concurred that DKA history is not an absolute requirement for diagnostic confirmation; proof of other symptoms can be provided. No consensus was established on whether the possibility of T1DM should be excluded if a patient has no insulin injections and no ketoacidosis for at

Table 3

The recommendation for the diagnosis of T1DM

Consensus
1. The report of the C-peptide/glucagon test is an important observation to determine T1DM, and other clinical parameters (such as: height, weight, age, and DKA) can also be used as reference
2. GAD65/IA-2/ZnT8 antibody testing can confirm T1DM. But if there is no autoantibody, T1DM cannot be ruled out
3. T1DM can be diagnosed by age, but it is not easy to do in adults
4. The diagnosis of LADA or slowly evolving immune-mediated diabetes of adults should be separated from T1DM

DKA = diabetic ketoacidosis; GAD65 = glutamic acid decarboxylase 65; IA-2 = islet antigen 2; LADA = latent autoimmune diabetes in adults; T1DM = type 1 diabetes mellitus; ZnT8 = Zinc transporter 8.

Table 4

Necessary documents for applying for catastrophic illness certificates in Taiwan

Documents
1. Clinical features (height, weight, age, DKA, and insulin use after the onset) meet the manifestations of type 1 diabetes
2. The test report of C-peptide/glucagon test is in line with the course of type 1 diabetes
Adults (≥18 y old)
C-peptide level 0 min <0.5 ng/mL or 6 min <1.8 ng/mL or increase < 0.7 ng/mL
Children and adolescents (<18 y old)
C-peptide level 0 min <0.5 ng/mL or 6 min <3.3 ng/mL
3. One of the GAD65/IA-2/ZnT8 antibodies is tested positive
Those who are diagnosed with 1 + 2, or 1 + 3, or 1 + 2 + 3 of the above three documents are eligible to apply for catastrophic illness certificates

DKA = diabetic ketoacidosis; GAD65 = glutamic acid decarboxylase 65; IA-2 = islet antigen 2; ZnT8 = Zinc transporter 8.

Table 5

The consensus of transitional care for T1DM patients

Consensus
1. Enroll patients in the Diabetes Shared Care Network
2. Set up different health education goals for children with T1DM at different stage
3. Implement transitional care through the diabetes educators

T1DM = type 1 diabetes mellitus.

least 6 months after disease onset. More comprehensive research is needed to prove this observation.

T1DM is frequently diagnosed in childhood, but onset in adulthood is also possible.[3,16] So, consensus about the issue which age of onset is a critical determinant for the diagnosis of T1DM is not established here. But the diagnosis of LADA needs to be clarified and separated from the application of T1DM certificate in Taiwan. Therefore, the age is not an absolute but a possible indicator in the catastrophic illness confirmation for the T1DM, especially for the children and adolescents due to the need of economic support in this population.

About over half of patients with T1DM at diagnosis have evidence of an immune-mediated destruction with β-cell autoantibodies against GAD65, IA-2, and ZnT8[3,16,17] Herein, no consensus on whether positive autoantibody test results can be used to confirm T1DM diagnosis was established. Moreover, consensus was not reached on whether these autoantibodies should be sequentially tested, although the clinical aspects and cost-effectiveness of such testing were considered. The target population for autoimmune antibody testing, the probability of positive autoantibody test results in Taiwanese patients, and the status of their siblings' autoantibody testing all merit further exploration.

Because the fundamental differences in health care delivery exist between pediatric and adult care systems, the need of clinic facilities in transition for patients with T1DM in the young adult (over 18 years old) is urgent.[18] The multidisciplinary team work meets the goal of successfully transitioning patients from a pediatric to adult endocrinologist between the ages of 18 and 22 years. The Diabetes Shared Care Network is a matured care system for diabetes in Taiwan. With the care by the same diabetes educators or specialists, the network provides a paradigm and bridge between the pediatric and adult treatment periods. Future well-structured process for transition or ultimate transfer of care to an adult diabetes care team is needed through collaboration of adult and pediatric endocrinologists.

There were some limitations in this study. First, the accessibility and self-payment of different islet autoantibodies would be a factor to decide islets autoantibodies as criteria for the diagnosis of T1DM across different regions in Taiwan. Second, we could not sure how many specialists were also the current members in the NHI committee for the confidential policies of NIH, which certificated the catastrophic illness certificate in the study. This scenario would constitute a confounding factor in consensus establishment.

In conclusion, these recommendations serve as a valuable tool for improving the clinical diagnosis and care of patients with T1DM. The items on which consensus were not reached warrant further investigation. Moreover, further studies should be conducted to resolve doubt and standardize professional opinion regarding certain aspects of T1DM diagnosis in Taiwan.

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APPENDIX

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