Introduction

The number of children with diabetes mellitus (DM) is increasing worldwide in industrialized and developing countries. DM is characterized by an increase in serum blood glucose caused by defects in insulin production, mechanism of action, or both. Type 1 DM (T1DM) is the most common type of DM to affect children, in which B cell destruction usually caused by an autoimmune process leads to absolute insulin deficiency (1). Awareness on T1DM in Indonesia is still low; hence, diagnosis and treatment is often delayed and worsen the prognosis. This paper aims to review the current situation, diagnosis, and management of T1DM in children in Indonesia.

Epidemiology

Indonesia is a developing country with an expansive population pyramid. In 2010, the number of children was 83 million, which accounted for approximately 31% of the total population (2). Nevertheless, the Indonesian Pediatric Society (IPS) had only recorded 1,249 Indonesian children with T1DM from 2017–2019. The prevalence of T1DM in Indonesia raised sevenfold over the course of 10 yr, from 3.88 per 100 million population in 2000 to 28.19 per 100 million population in 2010 (3–5). The number of T1DM children in Indonesia with diabetic ketoacidosis (DKA) at diagnosis remained high, 71% in 2017, which increased when compared to the number recorded in 2015–2016 (63%). The real prevalence of T1DM in children is predicted to be higher due to high rates of underdiagnosis and misdiagnosis. From 2008–2010, the IPS in conjunction with the World Diabetes Federation conducted massive T1DM in children campaigns and workshops for general practitioners and pediatricians. The incidence of T1DM at that time soared because new cases were diagnosed; on the contrary, the rate of DKA decreased. Hence, the incidence of pediatric T1DM is also affected by public and healthcare workers' awareness. As one target of the sustainable development goals (SDGs) is to reduce by one third premature death caused by noncommunicable diseases by 2030; preventing death caused by T1DM in children is of importance.

Pediatric Diabetes Practice Indonesia

An online survey had been conducted by authors targeting pediatric endocrinologists within the working group of the IPS which aimed to describe the current diabetes practices among pediatric endocrinologists in Indonesia. Forty-three out of 47 pediatric endocrinologists (91.5% response rate) completed the survey. More than half (60% and 80%) respondents had been practicing as pediatric endocrinologists for more than 10 yr and...
are currently working in public (government) hospitals, respectively. Most pediatric endocrinologists (n = 26; 60.5%) had managed more than 20 patients with T1DM. Thirty pediatric endocrinologists (69.8%) had been familiar with and adapting T1DM recommendations from IPS. Other results from the survey will be further elaborated in the article.

**Pathogenesis of T1DM**

T1DM develop as a result of destruction of insulin-secreting beta-cells of the Langerhans islets in the pancreas. In contrast to T2DM, an absolute deficiency of insulin occurs in T1DM. Autoimmunity is believed to be the pathologic basis of T1DM, although evidence of autoimmunity was not found in a small proportion of patients. Generally, clinical manifestations appear if beta-cells destruction reach at least 90% (6, 7). A complex set of interaction between genetics, epigenetics, environmental factors, and immunologic factors contribute to the pathogenesis of T1DM. The specific role of each factors towards T1DM pathogenesis is not fully understood. Gene damage is known to be associated with an increased risk of T1DM and 40 gene locus related to T1DM had been identified. Family history is seldomly found in T1DM patients; only 10–15% had first- and second-degree family members with T1DM (6,8).

Environmental components related to T1DM include viral infection and diet. Congenital rubella syndrome and human enterovirus infection were reported to elicit T1DM. Cowmilk consumption, early cereal consumption, and low maternal vitamin D levels are also thought to be correlated with T1DM although further researches are needed (6, 9).

In some patients with new-onset T1DM, a small proportion of beta-cells remain. With insulin administration, the remaining beta-cells’ function improve and decreasing the need for exogen insulin. This phenomenon is known as the honeymoon period, where patients experience good glycemic control. This phase usually commences a few weeks after therapy initiation until 3–6 mo afterwards, and can extend up to 2 yr in a few patients.(7)

**Diagnosis**

The classical manifestations of diabetes in children are similar to adults: polyuria, nocturia, polyphagia, polydipsia, and weight loss (6, 10). Other common clinical presentations include tingling sensations, malaise, delayed wound healing, blurred vision, and behavioral changes. A combination of clinical history and laboratory studies confirms the diagnosis of diabetes. The IPS currently follows the American Diabetes Association recommendation for DM diagnosis, as seen in Table 1.

A critical step in diagnosing DM in children is to identify the type as it implies to different treatment and education. Most prepubertal children with diabetes are classified as T1DM, although some children with T2DM present before puberty notably those with overweight, obesity, or insulin resistance. Nevertheless, distinguishing type 1 and type 2 DM can be challenging in overweight or obese adolescents. Hence, in this group of patients, family pedigree, islet autoantibody, and plasma or urine C-peptide should be evaluated (11). A study by Cho et al. reported that fasting C-peptide can help diagnose different DM types in children and adolescents.(12)

Serologic markers for autoimmunity towards beta-cells of the pancreas include (1) glutamic acid decarboxylase 65 autoantibodies (GAD antibody), (2) insulin autoantibodies (IAA), (3) Tyrosine phosphatase-like insulinoma antigen 2 (IA2), and (4) beta-cell specific zinc transporter 8 autoantibodies (ZnT8). A positive result in any of these serologic markers ensures the diagnosis of T1DM (6). However, this examination is not routinely conducted in Indonesia due to high costs and low availability. T1DM screening in asymptomatic children and adolescents using an antibody panel is only recommended in research settings or in patients with family history of T1DM in first-degree relatives (10). Ideally, antibodies should be tested in obese patients with diabetic manifestations to distinguish between the types of diabetes, considering the heterogeneity of diabetes in Asian children and adolescents (13).

**Management**

The goal of diabetes management is to achieve optimal metabolic control, prevent acute complications, prevent long-term microvascular and macrovascular complications, as well as to improve the psychological aspects of patients and families (10). Five pillars of T1DM management in children and adolescents are (1) insulin injection, (2) blood glucose monitoring, (3) nutrition, (4) physical activity, and (5) education. An integrated healthcare team is important to treat T1DM optimally, which consists of a pediatric endocrinologist,

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**Table 1.** Diagnosis criteria of diabetes mellitus (DM) in children (Indonesian Pediatric Society 2017, adapted from the American Diabetes Association)

| Fulfilling at least one criteria: |
|----------------------------------|
| 1. Classical manifestations of diabetes or hyperglycemia and plasma glucose ≥200 mg/dL (11.1 mmol/L), or |
| 2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L), or |
| 3. Two-hours postprandial plasma glucose ≥200 mg/dL (11.1 mmol/L) with oral glucose tolerance test, or |
| 4. HbA1c > 6.5% according to National Glycohemoglobin Standardization Program (NGSP) in a certified laboratory. |
a nutritionist, a psychiatrist or psychologist, and a DM educator (7).

**Insulin injection**

Insulin regimens are tailored according to the child: age, weight, duration of disease, glycemic control target, lifestyle, and comorbidity. The recommended regimen is basal-bolus administered with a pump or subcutaneously minimum twice a day, using both basal and short or rapid acting insulin. This regimen resembles physiological insulin secretion (8). Basal insulin requirement ranges from 30% (if regular insulin is used) to 50% (if rapid-acting insulin is used) out of the total daily insulin requirement. In patients using regular insulin, a lower dose of basal insulin may be given because of the basal effect of regular insulin. The remaining preprandial insulin dose is adjusted according to the child’s need, using rapid-acting or regular insulin. (14)

Rapid-acting insulin dosage can be determined by the insulin-to-carbohydrate ratio, calculated with the “500 formula”: 500/total insulin daily dose. The result signifies the quantity of carbohydrate in gram covered by one unit of insulin (14). The use of intensive regimen and insulin-to-carbohydrate ratio should be followed by adequate information and education for diabetes management, which may be potential challenges in certain adolescents.

Other adjustments of insulin dosage are made based on daily random blood glucose levels. If rapid-acting insulin is given, blood glucose monitoring 1–2 h after meal is recommended to determine insulin efficacy. Insulin dosage modification is needed in the following conditions (1) increase in blood glucose before breakfast – adjustment of intermediate- or long-acting insulin dose before dinner or bedtime; (2) increase in post-prandial blood glucose – adjustment of rapid-acting or regular insulin; (3) increase in preprandial blood glucose before lunch or breakfast – adjustment of basal insulin or preprandial rapid or short-acting insulin (14).

Insulin dose needs to be corrected when an increase of blood glucose occurs. Corrected insulin dose is calculated using insulin sensitivity factor, which is the amount of blood glucose that can be decreased with 1 unit of insulin. To simplify, the corrected insulin dose can be calculated as follows: (1) for rapid-acting insulin: 1800/total daily insulin dose, (2) short-acting/regular insulin: 1500/total daily insulin dose. The result indicates the level of blood glucose that can be decreased with 1 IU of insulin (14).

Currently, continuous subcutaneous insulin infusion (CSII) is not widely available in Indonesia. Based on the data by The Endocrinology Working Group of IPS, the use of conventional, intensive, and CSII insulin regimen in 721 T1DM patients at registration were 48.7, 48.3, and 0.7%, respectively. While it is not yet commonly used in Indonesia, due to high prices and frequent changes of supplying companies, the CSII regimen is used by most T1DM patients in developed countries. The basal dose can be fixed or modified based on food consumption and data can be downloaded to monitor bolus dose (14). Previous studies showed that the benefits of CSII used include better glycemic control (15) and HbA1c level, less hypoglycemia events, and improved of insulin requirement. However, conventional therapy may still be applicable in developing countries such as in Indonesia (16, 17).

An online survey by the IPS reported that 39 pediatric endocrinologists in Indonesia (90.7%) responded that they initiated insulin regimen with intensive regimen (basal-bolus) to most of their T1D patients. Nineteen pediatric endocrinologists (44.2%) were aware of insulin price they had prescribed. It costed variably within 100,000–300,000 IDR. Barriers to insulin use in Indonesia can be seen in Table 2.

**Blood glucose monitoring**

Monitoring in T1DM patients include self-monitoring of blood glucose (SMBG), HbA1c, ketone, and blood glucose. The IPS recommends SMBG at least 4-6 times a day: (1) in the morning when waking up, (2) before meals, (3) 1.5–2 h after meals, and (4) at night (10). However, SMBG can be conducted more often as needed. The American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent

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| Table 2. Barriers to insulin use in Indonesia (Based on the Indonesian Pediatric Society Survey, 2020, n = 43) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Patient factor** | **Physician factor** | **Environment/System factor** |
| Refusal to insulin use due to many reasons, e.g. fear, shy, anxiety, discomfort (n = 9; 20.9%) | Lack of clinical experiences in managing diabetes in children and adolescents (n = 3; 7%) | Inability to prescribe insulin due to financial issues (n = 8; 18.6%) |
| Low motivation to start insulin therapy (n = 5; 11.6%) | Lack of access to adequate information about insulin (n = 1; 2.3%) | Insulin unavailability in healthcare facilities (n = 5; 11.6%) |
| | Low motivation in managing diabetes in children and adolescents (n = 3; 7%) | Supporting laboratory, team personnel limitation (n = 10; 23.3%) |
| | Insufficient time due to high workload (n = 3; 7%) | |
| | Fear of insulin side/adverse effects, e.g. hypoglycemia (n = 2; 4.7%) | |
| | Fear of complexity or difficulty in insulin dose titration (n = 5; 11.6%) | |
Diabetes (ISPAD) recommends SMBG more often, 6–10 times a day (11, 18). The IPS registered only 20% of patients who conducted SMBG minimum 3 times a day (3).

HbA1c should be measured at least every 3 mo. The HbA1c target by IPS and ADA for T1DM patients is below 7.5%, while the target by ISPAD is lower, below 7%. Based on the IPS Endocrinology Working Group Registry, more than half of the patients (62.6%) examined HbA1c every 3 mo and almost a third (32.3%) did not check their HbA1c levels routinely (3). Data from seven pediatric diabetes centers in Indonesia in 2002 showed that 90% of children with T1DM did not achieve the targeted glycemic control of HbA1c < 7.5% (19). Based the IPS online survey, most pediatric endocrinologists (n = 34; 79.1%) responded that most of their T1DM patients had HbA1c levels above 8.5%.

Blood glucose can be continuously monitored using a minimally invasive device which measures subcutaneous interstitial fluid every 1–5 min and alerts the patient if blood glucose is predicted to fall below target in 10–30 min (8). Cemeroglu et al. found that continuous blood glucose monitoring is beneficial to prevent hypoglycemia, decrease hypoglycemia-related anxiety, ease T1DM management, and improve diabetic control (20).

Urine and blood ketone should be measured in uncontrolled hyperglycemia, sick days, and when signs and symptoms of DKA are present. Blood ketone is superior compared to urine ketone to diagnose DKA. Pulungan et al. reported that b-hydroxybutyrate showed better correlation towards pH and bicarbonate levels compared to urine ketone (21).

Nutrition

Adequate nutrition is needed for optimal growth and development, as well as to prevent acute and chronic complications. Patients are advised to consume balanced nutrition consisting of vegetables, fruits, whole wheat, dairy products, and low-fat meat. Daily calorie intake can be counted based on ideal weight and the recommended calorie intake (10). Macronutrient distribution is carbohydrate 45–50% of total energy, fat < 35% of total energy, protein 15–20% of total energy. Patients and their families should be taught to adjust insulin dose based on carbohydrate consumption to increase glycemic control and quality of life (22). Based on a study by Hatun et al., carbohydrate counting and insulin correction significantly correlated with lower HbA1c levels (23).

Physical activity

Routine physical activity brings many benefits to children with T1DM. Beside increasing insulin sensitivity and decreasing insulin requirement, physical activity is beneficial for the child’s self-esteem, cardiac capacity, and prevention of acute or chronic complications.

As in healthy youths, children with T1DM are recommended to endure a minimum of 60 min/d of physical activity which combines aerobic, muscle-strengthening, and bone-strengthening activities. Aerobic activities should be prioritized, while muscle- and bone-strengthening activities are encouraged at least thrice weekly. Medical workers should ensure that T1DM pediatric patients get enough physical activity because they are usually less active compared to their non-diabetic peers. Adolescents with T1DM whom met physical activity requirement (60 min/d at least 5 d per week) was reported to have better quality of life compared to those who do not (24).

Education

Education is an integral part of T1DM management. A multidisciplinary team consisting of a pediatric endocrinologist or trained general practitioner, a nurse of DM educator, and nutritionist should take part in educating patients and families. The first phase of education is conducted when the patient is first diagnosed or during inpatient treatment, and consists of basic knowledge on T1DM, nutrition regulation, insulin use, and first aid during acute complication. The second phase is conducted in outpatient clinics.

Mass education on T1DM, including to healthcare workers, may play an important role to increase diabetes awareness and support prevention programs. Vanelli et al. reported that prevention programs using posters and flyers were effective to reduce the rate of DKA even after evaluated 8 yr afterwards (25, 26).

Fasting during Ramadan

Indonesia is a Muslim-majority country; hence, many adolescents with T1DM choose to fast in Ramadan. Despite risks of complications, studies show many children and adolescents insist on fasting, some due to peer pressure or due to the desire to feel “mature and capable” (27). A study on the attitude of children aged 10–18 yr old with T1DM towards the Ramadan fast described more than half of their subjects fasted more than half the month of Ramadan. Most of the younger age group (10–12 yr old) fasted less than 14 d (27).

In this case, pre-Ramadan counseling and education should be given to patients and parents by experts. The necessity of self blood glucose monitoring should be emphasized to prevent acute complications, such as hypoglycemia and DKA. The suhor, or pre-dawn meal, should be consumed as late as possible and the sunset (iftar) meals as early as possible. Youth should be taught carbohydrate counting to match insulin dose with carbohydrate intake and be reminded to hydrate with water often. If hypoglycemia occurs, the child should break the fast regardless of the time (28). Aside from changes in meal schedules, other changes in the patients’ daily routines such as sleep-wake cycles also need to be considered in disease management during Ramadan (29).

The IPS does not recommend children with DM to
fast, but fasting is permissible since the age of 8 yr old. Regardless that recommendation, to prepare children and adolescents with T1DM and to promote safety during Ramadan fasting, Ramadan Day Camp and Workshop are still held by IPS each year prior to the holy month. The IPS Guidelines for T1DM management describe several criteria of high risk patients who are advised against fasting in Ramadan, including history of severe hypoglycemia in the last 3 mo before Ramadan, HbA1c ≥ 8, and history of diabetic ketoacidosis or hyperosmolar hyperglycemic state in the last 3 mo before Ramadan (10). Studies found optimal glycemic control prior to Ramadan may reduce the risks of diabetic complications associated with fasting and may help minimize fluctuating glucose levels. Adolescents whose pre-Ramadan glycemic control was poor were observed to experience wider fluctuations of blood glucose with longer episodes of hypoglycemia and hyperglycemia (30). Large-scale studies investigating T1DM patients who fast during Ramadan are limited, but some groups have reported that it’s possible for T1DM to fast safely, if they work closely with their doctors and receive appropriate information (31, 32). A literature review found that Ramadan fasting is feasible for people with insulin-dependent diabetes, with inconsequential major complications (33). Some studies reported improvements in post-Ramadan glycemic profile, including HbA1c (27, 34).

### Psychological Issues in Youth with T1DM

Children with T1DM have a heightened risk of developing psychological issues. Rahmawati et al. in Jakarta reported that psychological problems detected using the Pediatric Symptom Check-List-18 occurred in 45.8% of children with T1DM with the highest proportion being internalization disorder (33.3%). The risk of having a mental emotional problem was 41.7%. Patients with duration of disease more than 5 yr and with a past history of complication had a higher proportion of emotional mental problems (35). In Taiwan, a nationwide retrospective cohort study found that the incidence rate of depression in school-aged T1DM female was 228.4 per 100,000 person year compared to 73.9 per 100 with the incidence rate ratio of 3.09 (36). Parental distress have also become an issue especially at diagnosis of the child’s diabetes (37).

The ISPAD recommends an interdisciplinary team which also consists of psychologists and/or psychiatrists to help in the treatment of T1DM children. A thorough assessment in all functional domains should be conducted routinely because these youths have an increased risk of having cognitive and academic problems especially when the disease course is more severe (e.g. earlier onset of diabetes, history of severe hyperglycemia or hypoglycemia). Healthcare workers should encourage family involvement and support to increase adherence to therapy (38).

### Screening for Acute and Chronic Complications

T1DM chronic complications in children seldom manifest under the supervision of pediatricians. On the contrary, children are prone to acute complications of DM — diabetic ketoacidosis and hypoglycemia. The SEARCH study found that approximately 30% of children with T1DM present with DKA at diagnosis. DKA is often misdiagnosed because symptoms may mimic other conditions, such as appendicitis or other gastrointestinal infections. Children who routinely visit pediatricians or general practitioners have a lower risk to manifest with DKA at T1DM presentation. On the contrary, DKA at presentation was significantly related to low family income, no health insurance, and low parental education (39). A case series of 16 cases of 12 children with DKA in Jakarta found that recurrence occurred in 75% of patients and most were adolescents. Poor compliance was the precipitating factor of the majority of subjects (62.5%) (40). Another study by Himawan et al. reported that out of 39 patients aged 5–31 yr studied, the most common complications of T1DM were DKA (76.9%) and microalbuminuria (7.9%) (41).

The online survey by the IPS reported that 17 pediatric endocrinologists (39.5%) had managed DKA more than 20 times throughout their career. When managing DKA, 31 pediatric endocrinologists (72.1%) responded that their DKA patients would resolve in more than 72 h. The majority of pediatric endocrinologists (n = 39, 90.7%) prescribed 0.9% saline and only 4 (9.3%) prescribed Ringer’s for initial fluid replacement for DKA patients. Most Indonesian pediatric endocrinologists (n = 33, 90.7%) prescribed short-acting/regular insulin for initial DKA management for their patients.

Based on the IPS guideline, hypoglycemia is defined as blood glucose below 70 mg/dL. In very young patients, the adrenergic activation or neuroglycopenic symptoms may not be seen but in the form of irritability, agitation, tantrum, or hypoactivity (42).

The IPS currently follows the ISPAD recommendation of microvascular and macrovascular screening in children with T1DM. Screening of nephropathy, retinopathy, neuropathy, and macrovascular diseases should start at the age of 11 yr and in patients with duration of disease of ≥ 2–5 yr. Risk factors which should be noted in screening for complications are hyperglycemia, high blood pressure, dyslipidemia, smoking, and high body mass index (43). A retrospective cohort study by Wang et al. in 2240 T1DM and 1768 youth < 21 years estimated that after 6 yr 27.6% and 8.6% of T1DM and T2DM, respectively, would develop diabetic retinopathy (DR). T1DM youth developed DR sooner compared to T2DM, and each increase of 1 HbA1c point increased the hazard by 20% (44).
Challenges in T1DM Management in Indonesia

As cases of children with T1DM in Indonesia increases, there is an urgent need for healthcare workers competent in caring for these patients. A few efforts by the IPS to increase society and health workers’ awareness are health campaigns, trainings for general practitioners and pediatricians, DM educator and family trainings, as well as diabetic camp. Stakeholders – including the Ministry of Health, health insurance, and pharmacy – hold important roles in increasing healthcare quality in T1DM patients. Another challenge is related to better survival of T1DM patients: healthcare workers must be prepared to give the best effort to prevent, screen for, and treat chronic complications. Based on daily clinical practice, T1DM awareness in Indonesia is predicted to be low but no data had been published concerning this issue. The general society, especially those with low socioeconomic status, do not realize that diabetes can occur in children. Indonesia consists of 34 provinces and more than 17 thousand islands. Thus, inequities in DM care exist on many aspects, which include healthcare workers’ competence and facilities. As an example, diabetes care in Jakarta differs from rural areas which do not have pediatric endocrinologists, diabetes educators, nor dieticians. There is a large variation in geographic access across the country, and there is a lack of expertise and diagnostic equipments at primary healthcare providers (45). Up to 2020, there are only 51 pediatric endocrinologists in 16 provinces in Indonesia. This shortage of specialized care and high volumes of patients are the major issues in diabetes care in Indonesia, with stark inequality in urban and rural areas. Moreover, underfunding and drug availability also pose as obstacles in delivering adequate care to all patients (46).

To increase community involvement, the Indonesian pediatric endocrinologists initiated the formation of family support group called Ikatan Keluarga Penyandang Diabetes Anak dan Remaja (IKADAR) or translated as Families with Diabetic Children Organization. IKADAR is primarily run by parents of children with T1DM accompanied by the IPS. The IPS-IKADAR collaboration scopes from individual treatments, DM camps, world diabetes day campaigns, and other activities to increase the quality of T1DM care and awareness in Indonesia.

To improve awareness on T1DM in Indonesian children, a project conducted under the World Diabetes Foundation was implemented in 2008–2011. During the project, 381 paediatricians from seven cities were trained in T1DM management, 61 nurses were trained as diabetes educators, 150 families with T1DM children were trained in diabetes management, 731 children with T1DM were listed in a registry and had received care, T1DM treatment guidelines were revised, and efforts in media awareness reached up to 11 million people (47).

Funding for T1DM in Indonesia

The Indonesian national health insurance (BPJS) currently covers monthly insulin; this system can disrupt compliance if children cannot visit healthcare every month during school hours. Although insulin is covered, payment for glucometer strips are made out-of-pocket. Serum blood glucose and HbA1c examinations are covered by the national insurance, but not C-peptide and GAD antibody/ICA. Hence, T1DM diagnosis in children in Indonesia is often delayed (48).

Conclusion

The rise of T1DM in children in Indonesia not balanced by an increase of awareness in the society and healthcare workers are the main challenges in T1DM management. The IPS’ effort in tackling these issues include the establishment of a disease registry, publication of T1DM in children guideline, trainings for doctors, families, and DM educators, management of diabetic camps, as well as public health campaigns. Further collaboration with stakeholders and advocacy to policymakers are needed to upgrade the quality of care for T1DM pediatric patients in Indonesia (49). As the Indonesian government currently focuses on adult T2DM prevention and management; public health campaigns as well as pediatric T1DM workshops for healthcare workers should also start to be routinely conducted and integrated in national health programs.

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