CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/305.15(GU)

MANAGEMENT OF TYPE 1 DIABETES MELLITUS IN CHILDREN & ADOLESCENTS

Ministry of Health Malaysia

Malaysian Paediatric Association

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Academy of Medicine Malaysia

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Also available as a mobile app for Android and iOS platform: MyMaHTAS

STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2015 and will be reviewed in a minimum period of four years (2019) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

In line with the current development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N); Medline via Ovid, Cochrane Database of Systemic Reviews (CDSR) and CINAHL via EBSCOhost (refer to **Appendix 1** for **Example of Search Strategy**). The inclusion criteria are all literature on type 1 diabetes mellitus (T1DM) regardless of study design although emphasis was put for systematic review. The search was limited to literature published in the last 20 years, humans, "all child" (0 to 18 years) and English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify relevant studies. In certain situations, pivotal papers beyond the scope of search were used in the CPG. All searches were conducted from 23 January 2014 to 20 May 2015. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 August 2015 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to a CPG entitled Pediatric Diabetes developed by International Society for Pediatric and Adolescent Diabetes (ISPAD) in 2014. The CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 15 main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2** for **Clinical Questions**). The DG members met 24 times throughout the development of these guidelines. The literature retrieved was appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. The CPG was based largely on the findings of systematic reviews, meta-analyses and

clinical trials, with local practices taken into consideration.

The literature used in these guidelines was graded using the US/ Canadian Preventive Services Task Force Level of Evidence, while the grading of recommendation was done using the principles of GRADE (refer to the preceding page).

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/index.php/pages/view/117).

OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on T1DM in children and adolescents on the following aspects:

a. Diagnosis
b. Management

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Children and adolescents (<18 years old) with T1DM

TARGET GROUP/USER

This CPG is intended to guide healthcare providers and relevant stakeholders in primary and secondary/tertiary care who are in contact with and making decisions concerning the care of children and adolescents with T1DM including:

a. Doctors
b. Allied health professionals
c. Trainees and medical students
d. Professional societies
e. Patients, families and caregivers

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

GUIDELINES DEVELOPMENT GROUP

Chairperson

Dr. Janet Hong Yeow Hua
Consultant Paediatric Endocrinologist
Hospital Putrajaya, Putrajaya

Members (alphabetical order)

Dr. Cheah Yee Keat
Consultant Paediatrician
Hospital Tuanku Ja'afar,
Negeri Sembilan

Ms. Chow Yen Nee
Pharmacist
Klinik Kesihatan Batu, Kuala Lumpur

Dr. Fuziah Md. Zain
Head of Department & Consultant
Paediatric Endocrinologist
Hospital Putrajaya, Putrajaya

Ms. Loong Ah Moi
Nursing Matron
Health Technology Assessment Section,
MoH

Dr. Mohd. Aminuddin Mohd. Yusof
Head of CPG Unit
Health Technology Assessment Section,
MoH

Associate Professor
Dr. Muhammad Yazid Jalaludin
Senior Lecturer & Consultant Paediatric
Endocrinologist
Universiti Malaya, Kuala Lumpur

Dr. Norzaihan Hassan
Consultant Family Medicine Specialist
Klinik Kesihatan Bandar Kota Bharu,
Kelantan

Dr. Suhaimi Hussain
Senior Lecturer & Consultant Paediatric
Endocrinologist
Universiti Sains Malaysia, Kelantan

Dr. Rozaidah Jaafar
Psychiatrist
Hospital Tengku Ampuan Rahimah,
Selangor

Dr. Sharipah Fotimah Syed Abdullah
Consultant Family Medicine Specialist
Klinik Kesihatan Bandar Mentakab,
Pahang

Ms. Suriawati Abu Aziz
Dietitian
Klinik Kesihatan Jinjang, Kuala Lumpur

Dr. Zahidah Mohd. Kasim
Paediatrician
Hospital Kajang, Selangor

REVIEW COMMITTEE

The draft guidelines was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

Chairperson

Professor Dr. Wu Loo Ling
Senior Lecturer & Consultant Paediatric Endocrinologist
Universiti Kebangsaan Malaysia, Kuala Lumpur

Members (alphabetical order)

Dr. Hew Fen Lee
Consultant Endocrinologist
Sime Darby Medical Centre, Selangor

Dr. Noor Khatijah Nurani
Consultant Paediatrician
Hospital Raja Perempuan Bainun, Perak

Dr. Mastura Ismail
Consultant Family Medicine
Klinik Kesihatan Seremban 2
Negeri Sembilan

Dato' Hjh. Rahimah Dato' Hj. Ahmad
Patient Advocate
Diabetes Malaysia

Ms. Siti Hawa Mohd Taib
Dietitian
Pusat Perubatan Universiti Malaya
Kuala Lumpur

Mr. Subramaniam A/L Kalimuthu
Patient Advocate
Diabetes Malaysia

EXTERNAL REVIEWERS (in alphabetical order)

The following external reviewers provided feedback on the draft:

Mr. Albert Ting Siong Hung
Pharmacist
Hospital Umum Sarawak, Sarawak

Dato' Dr. Hussain Imam Haji Mohammad Ismail
Head of Department & Senior Consultant Paediatrician
Institut Pediatrik, Hospital Kuala Lumpur, Kuala Lumpur

Professor Dr. Kim Donaghue
Co-Head, Institute of Endocrinology & Diabetes
Head of Diabetes Services & Senior Staff Endocrinologist
The Children's Hospital at Westmead
Professor, University of Sydney, Australia

Dr. Kok Juan Loong
Consultant Paediatrician
Hospital Umum Sarawak, Sarawak

Associate Professor Dr. Ragnar Hanas
Consultant Pediatrician
Uddevalla Hospital, Uddevalla, Sweden &
President
International Society of Pediatric and Adolescent Diabetes

Associate Professor Dr. Rahmah Rasat
Senior lecturer & Consultant Paediatric Endocrinologist
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur

Dr. Sri Wahyu Taher
Consultant Family Medicine Specialist
Klinik Kesihatan Simpang Kuala, Kedah

Professor Dr. Winnie Chee Siew Swee
Senior Lecturer & Consultant Dietitian
Faculty of Medicine & Health
International Medical University, Kuala Lumpur

Dr. Zainah Shaikh Hedra
Consultant Paediatician
Hospital Sultanah Nora Ismail, Johor

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the most common type of diabetes mellitus in children and adolescents. The incidence of T1DM is very low in Asia, which is approximately 2 to 5 per 100,000 person-years.[1 - 3, level II-2] In Malaysia, the incidence of T1DM was not reported by the Malaysian Diabetes in Children and Adolescents Registry (DiCARE) 2006 - 2008 report due to several limitations. There were 34 sites that reported 408 patients to DiCARE from 2006 - 2008. Among children and adolescents under the age of 20 years with diabetes mellitus, 71.8% were diagnosed with T1DM. The median age of diagnosis was 7.6 (IQR 4.6, 10.8) years and majority (58.3%) presented with diabetic ketoacidosis (DKA).[4, level III] However, the sample size of DiCARE was small and could not represent the population.

T1DM is a chronic disease which is associated with various complications including retinopathy, nephropathy, neuropathy and cardiovascular morbidity. Studies have shown that good glycaemic control early in the disease results in lower frequency of chronic diabetes complications. In order to reduce health care cost due to the complications, appropriate treatment should be started early. Accurate classification of diabetes and proper management of these children to achieve glycaemic target is of utmost importance. DiCARE reported a mean HbA1c of 10.8% reflecting poor metabolic control.[4, level III]

Therefore, these clinical practice guidelines aim to provide evidence-based guidance to those who are involved in the management of children and adolescents with T1DM.

2. DIAGNOSIS

TIDM is primarily due to pancreatic islet β-cell destruction leading to severe insulin deficiency and manifested by low or undetectable plasma concentration of C-peptide. Markers of the immune-mediated β-cell destruction process include glutamic acid decarboxylase (GAD) antibody, insulin autoantibodies (IAA), anti-islet antibody (ICA), protein thyrosine phosphatase antibody (ICA512 or IA2A) and zinc transporter 8 (ZnT8).[5, level III] More than 90% of patients with newly diagnosed T1DM have more than one of these autoantibodies. T1DM patients with absence of islet β-cell antibody or so called type 1B diabetes have no evidence of β-cell autoimmunity. However, patients with false negative antibodies can be due to diminished titre over the course of the disease.[6, level III]

The diagnosis of diabetes mellitus should be made based on the presence or absence of symptoms and biochemical criteria according

to World Health Organization Diagnostic Criteria (1999). Diagnosis of diabetes can be made when:[7, level III]

1. classic symptoms and signs are present and
2. fasting venous plasma glucose concentration is ≥7.0 mmol/L, and/or the random venous plasma glucose concentration ≥11.1 mmol/L

The diagnosis must be confirmed by repeat blood glucose testing in the absence of unequivocal hyperglycaemia.

Patients with T1DM can present acutely with severe symptoms, and frequently with ketoacidosis. The diagnosis can be confirmed quickly with blood glucose (BG) value without waiting for another day as urgent treatment is needed.

In the presence of mild symptoms, the diagnosis of diabetes should never be made on a single abnormal BG value. Oral glucose tolerance test (OGTT) is rarely required, except in very early disease, in which most BG values are normal and the diagnosis of diabetes is uncertain. The role of HbA1c alone in the diagnosis of diabetes mellitus remains unclear and diabetes cannot be excluded when the value is <6.5%.[8]

Blood investigations that reflect β-cell function and immune-mediated β-cell destruction can be used to identify the aetiology and type of diabetes.[7, level III] Additional support for the diagnosis of T1DM include:[9, level III]

i. low or undetectable C-peptide levels
ii. presence of diabetes-associated autoantibodies (GAD/IAA/ICA512/IA2/ZnT8)

- Diagnostic criteria of diabetes mellitus:[7, level III]
  i. classic symptoms[a] of diabetes or hyperglycaemic crisis, with plasma glucose concentration ≥11.1 mmol/L
     OR
  ii. fasting plasma glucose[b] ≥7.0 mmol/L
     OR
  iii. two hour post-load glucose ≥11.1 mmol/L in OGTT[c]
     OR
  iv. HbA1c >6.5%[d]

[a]classic symptoms consist of thirst, polyuria, polydipsia, recurrent infection and weight loss

[b]fasting is defined as no caloric intake for at least eight hours

[c]the test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g

[d]the test should be performed in a laboratory using a method that is National Glycohaemoglobin Standardisation Programme certified and standardised to the Diabetes Control and Complications Trial (DCCT) assay

- The diagnosis must be confirmed by repeat blood glucose testing in the absence of unequivocal hyperglycaemia.
- The role of HbA1c alone in the diagnosis of diabetes mellitus remains unclear and diabetes cannot be excluded when the value is <6.5%.

Classification of diabetes mellitus:

i. type 1 diabetes mellitus
ii. type 2 diabetes mellitus
iii. gestational diabetes mellitus
iv. other specific types

Clinical presentation of T1DM

Clinical features of T1DM in children and adolescents are shown in **Table 1**.

Table 1. Clinical features of T1DM in children and adolescents

Age of onset	Six months to young adulthood
Clinical presentation	Most often acute, rapid onset of symptoms
Autoimmunity	Present
Ketosis	Common
Body habitus	Usually lean but can be overweight following population frequency
Acanthosis nigricans	Typically absent

Classically, T1DM children and adolescents present with history of polyuria, polydipsia and weight loss over 2 - 6 weeks. Some of them

can have rapid onset of symptoms within days and present in diabetic ketoacidosis (DKA), while others can have a slower onset of symptoms over several months. The clinical presentation of T1DM varies from non-emergency to emergency situations such as acute shock in DKA.[8]

- Non-emergency presentation
  - Recent onset of enuresis in previously toilet-trained children
  - Vaginal candidiasis especially in pre-pubertal girls
  - Chronic weight loss or failure to gain weight in growing children
  - Recurrent skin infections

- Emergency presentation
  - Moderate to severe dehydration
  - Frequent vomiting
  - Abdominal pain
  - Continuing polyuria despite the presence of dehydration
  - Weight loss due to fluid loss, and loss of muscle and fat
  - Acetone-smelling breath
  - Hyperventilation
  - Decreased level of consciousness
  - Hypotension
  - Shock

Diagnostic difficulties may lead to late diagnoses resulting in higher mortality and morbidity. Symptoms of T1DM may be misinterpreted:

- hyperventilation during DKA may be misdiagnosed as pneumonia or asthma
- abdominal pain associated with DKA can be mistaken as acute abdomen leading to unnecessary surgical referral
- polyuria and enuresis may be misdiagnosed as a urinary tract infection
- polydipsia may be thought to be psychogenic in origin
- vomiting may be misdiagnosed as gastroenteritis or sepsis
- impaired level of consciousness can be misdiagnosed as meningitis/encephalitis

Therefore, healthcare providers should have a high index suspicion of diabetes mellitus/DKA when managing such sick children.

Recommendation 1

- The diagnosis of diabetes mellitus in children and adolescents should be made based on clinical features and biochemical criteria (World Health Organization criteria*).
- Autoantibodies testing (glutamic acid decarboxylase antibody, anti-islet antibody, insulin autoantibodies and protein tyrosine phosphatase antibody) should be done to confirm the diagnosis of type 1 diabetes mellitus (T1DM).

*Refer to preceding yellow box

3. RISK FACTORS

It is important to identify the risk factors of T1DM to assist in early disease detection and possibly disease prevention.

Important risk factors associated with the development of T1DM are:

- genetics: the most susceptible haplotypes are the DRB1*0301-DQA1*0501-DQB1*0201 and the DRB1*0405-DQA1*0301-DQB1 *0302, DRB1*0401-DQA1*0301-DQB*0302, and DRB1*0402-DQA1*0301-DQB1*0302 with OR ranging from 3.63 to 11.37 [10 - 11, level III]
- presence of GAD antibody and/or IA-2A[12, level II-2]

Other risk factors that have been studied include:

- high birth weight (>4 kg) with OR=1.17 (95% CI 1.09 to 1.26)[13, level II-2]
- early introduction of cow's milk before three months of age (OR=1.53, 95% CI 1.1 to 2.2)[14, level II-2]
- rapid growth within first two years of life [OR in height=1.36 (95% CI 1.17 to1.58) and body mass index (BMI)=1.35 (95% CI 1.15 to 1.57)[15, level II-2]
- enterovirus infection (OR=9.8, 95% CI 5.5 to 17.4)[16, level II-2]
- high energy food intake especially disaccharides and sucrose (OR=5.23, 95% 1.67 to 16.38)[17, level II-2]

Breastfeeding of any duration[15, level II-2] and vitamin D supplementation in early childhood[18 - 19, level II-2] are possible protective factors against T1DM.

Maternal pre-eclampsia[20, level II-2] and childhood vaccination[21, level II-2] are not associated with T1DM.

4. CO-MORBIDITIES

Co-morbidites are medical conditions that co-exist with T1DM.

Patients with T1DM have higher prevalence of autoimmune diseases compared with patients without diabetes.[22, level III] The prevalence of high anti-thyroid peroxidase antibody (aTPO) and/or anti-thyroglobulin antibody ranges between 4.5% and 29.4%. Females are more affected than males ($p<0.001$).[23 - 24, level III] Children above 12 years old with T1DM have a higher mean thyroid stimulating hormone (TSH) compared with the younger patients and half of them are seropositive at diagnosis ($p<0.001$).[23, level III] The longer the duration of T1DM, the higher the tendencies of developing thyroid autoimmunity ($p<0.001$).[24, level III]

In ISPAD guidelines, screening of thyroid function by measurement of TSH and aTPO antibody is recommended at the diagnosis of diabetes and biennially thereafter in asymptomatic individuals without goitre or in the absence of thyroid autoantibodies.[8]

Coeliac disease is mostly asymptomatic in patients with T1DM. The disease can only be detected in these patients by serologic screening using anti-endomysium antibody and/or tissue transglutaminase antibody, and confirmatory diagnosis using intestinal biopsy. Most of the coeliac disease (60%) is detected at the onset of T1DM while the rest a few years after diagnosis.[25, level III] The prevalence of coeliac disease ranges from 1 to 10% in children with diabetes.[8] However, coeliac disease prevalence is unknown in Malaysia and therefore screening for the disease should be done in suspected cases. Primary adrenal insufficiency has also been found in T1DM with a prevalence of 0.7%.[22, level III] Although the prevalence is low, clinicians should be aware of the symptoms and signs of adrenal insufficiency in patients with T1DM.

Recommendation 2

- Screening of thyroid function and measurement of antithyroid peroxidase antibody should be done at diagnosis of type 1 diabetes mellitus.
  - If thyroid function is normal and antibody is absent, repeat screening every two years.
  - In patients with goitre or positive for thyroid antibody, repeat screening more frequently.

5. TREATMENT TARGETS

Long-term macrovascular, microvascular and neurologic complications cause major morbidity and mortality in patients with T1DM. Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in patients with T1DM by a range of 39% to 76%.[26, level I]

DCCT and similar studies, provide clear evidence in adults and adolescents that better metabolic control, as measured by a lower HbA1c level along with intensive management, is associated with fewer and delayed microvascular complications.[8]

Treatment targets should include:[8]

- achievement of the ideal BG level (near physiological glucose control)
- no significant hypoglycaemia or recurrent DKA through self-monitoring of blood glucose (SMBG) and optimal HbA1c level
- absence of hypoglycaemia unawareness
- normal growth and development
- normal psychosocial development and adjustment in dealing with a chronic disease
- prevention of long-term diabetic complications

5.1 Optimal HbA1c Levels

Glycated haemoglobin (HbA1/HbA1c) reflects the levels of glycaemia over the preceding 4 - 12 weeks.[8]

HbA1c monitoring has been shown to be the most useful measure in evaluating metabolic control and predicts long-term microvascular and macrovascular outcomes. Every patient should have a minimum of one measurement of HbA1c per year, ideally 3 to 6 measurements per year depending on age and degree of glycaemic control.[8] HbA1c may be affected by a variety of genetic, haematologic and illness-related factors such as haemoglobinopathy, certain anaemia and disorder associated with accelerated red cell turnover such as malaria.[27, level III]

- The recommended HbA1c target for all patients younger than 18 years is <7.5% (58 mmol/mol).
- Each patient should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycaemia and minimising frequent mild to moderate hypoglycaemia.[8]

Glycated haemoglobin is currently expressed as a percentage (%) with reference to the DCCT study. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) have produced a reference material which will be used for the calibration of all laboratory machines measuring HbA1c worldwide. The IFCC HbA1c is expressed in mmol/mol.[8]

HbA1c expressed in IFCC values (mmol/mol) can be converted to DCCT values (%) by using the following equation:

HbA1c (%) = 0.0915 x IFCC HbA1c (mmol/mol) + 2.15

The conversion of HbA1c from DCCT to IFCC is presented in **Table 2**.

Table 2. DCCT and IFCC conversion tables of glycated haemoglobin values

DCCT HbA1c (%)	IFCC HbA1c (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
8.5	69
9.0	75
9.5	80
10.0	86
11.0	97
12.0	108
13.0	119
14.0	129

Source: International Society for Pediatric and Adolescent Diabetes (ISPAD). Pediatic Diabetes. Oxford: Wiley Blackwell; 2014

5.2 Range of Ideal Blood Glucose Levels

Diabetes care includes performing SMBG. Frequent (4 - 6 times/day) and accurate SMBG with concomitant optimal adjustment of insulin to carbohydrate intake and exercise are required to attain and maintain optimal metabolic control.[8]

There is little scientific evidence for age-related glucose targets. Glycaemic targets of a child should be individually determined to achieve normoglycaemia while avoiding all degrees of hypoglycaemia. In patients beyond partial remission phase, the general rule is to achieve >50% of the total SMBG readings within target range and <10% of the readings below the range. Refer to **Table 3** for target range.[8]

Continuous glucose monitoring (CGM) through minimally invasive devices that measure subcutaneous (SC) interstitial fluid glucose every 1 - 5 minutes, may particularly benefit those with hypoglycaemic unawareness. It can also identify times of consistent hyperglycaemia and times of increased risk for hypoglycaemia. This enables immediate corrections to keep BG in range. However, these devices are expensive. CGM is beneficial in both patients using basal-bolus regimen and insulin pump. Refer to **Table 3** for target indicators of glycaemic control.

Table 3. Targets indicators of glycaemic control

Assessment	Level of control			
	Ideal (non-diabetic)	Optimal	Sub-optimal (action suggested)	High risk (action required)
Clinical assessment				
Symptoms of hyperglycaemia	No symptom	No symptom	Polyuria, polydipsia, enuresis	Blurred vision, poor weight gain, poor growth, delayed puberty, poor school attendance, skin or genital infections, and signs of vascular complications
Symptoms of hypoglycaemia	No symptom	No severe hypoglycaemia	Episodes of severe hypoglycaemia	Episodes of severe hypoglycaemia
Biochemical assessment*				
SMBG values in mmol/L				
AM fasting or pre-prandial	3.6 - 5.6	4 - 8	>8	>9 >14
Post-prandial	4.5 - 7.0	5 - 10	10 - 14	<4.4 or >11
Bedtime	4.0 - 5.6	6.7 - 10	<4.2 or >9	<4.0 or >11
Nocturnal	3.6 - 5.6	4.5 - 9	<4.2 or >9	>9.0***
HbA1c DCCT (%)	<6.5	<7.5**	7.5 - 9.0**	>75
HbA1c IFCC (mmol/mol)	<48	<58	58 - 75	

*These population-based target indicators must be adjusted according to individual circumstances. Different targets will be appropriate for various individuals such as those who have experienced severe hypoglycaemia or those with hypoglycaemia unawareness.

**These figures are based on clinical studies and expert opinion, but no strict evidence-based recommendations are available. PG levels are given because BG meters are internally calibrated to reflect the plasma glucose level.

***DCCT conventional adult cohort have a mean HbA1c value of 8.9%, and both DCCT and Epidemiology of Diabetes Intervention and Complications (EDIC) have shown poor outcomes with this level; therefore it seems prudent to recommend levels below this value.

Adapted from: International Society for Pediatric and Adolescent Diabetes (ISPAD). Pediatic Diabetes. Oxford: Wiley Blackwell; 2014

5.3 Growth and Puberty

T1DM is a chronic disease of childhood and it potentially affects the growth, onset of puberty and pubertal development of the patients.[28 - 29, level III] Thus, T1DM patients require monitoring of their growth and physical development. This can be achieved by plotting anthropometric measurements using appropriate percentile charts and mid-parental height.

There is a significant impairment in growth during puberty in young patients with T1DM and microalbuminuria which could be due to suboptimal glycaemic control.[30, level III] Pubertal onset is delayed in children and adolescents with less well-regulated T1DM and it increases with higher HbA1c level and lower BMI standard deviation score.[28, level III]

Conventional therapy (insulin injections twice daily) of diabetic children is significantly associated with impairment of physical growth and delayed sexual maturation.[29, level III] To promote optimal growth, adequate insulin secretion and concentrations are needed. The use of basal-bolus regimen, insulin analog and insulin pump have led to more physiological circulating insulin concentrations, thus improving growth. The effect of poor glycaemic control on growth appears to be exacerbated during puberty when physiological insulin resistance occurs.[8]

Mauriac syndrome, characterised by growth failure, delayed puberty, cushingoid appearance and hepatomegaly, is an uncommon complication in patients with poorly controlled T1DM.[31, level III]

Recommendation 3

- All patients with type 1 diabetes mellitus (T1DM) should aim to achieve glycaemic targets to maintain normal growth and pubertal development, while avoiding severe hypoglycaemia.
- Patients with T1DM and hypoglycaemia unawareness should perform more frequent self-monitoring of blood glucose.

6. DIABETIC KETOACIDOSIS

The rate of DKA occurrence at onset of T1DM ranges from 15 - 70% in Europe and North America.[8] In Malaysia, it is at 57.5%.[4, level III]

The goals of therapy in DKA are: [8; 32, level III]

- to correct dehydration, correct acidosis and reverse ketosis, and slowly correct hyperosmolality
- to restore BG to near normal
- to monitor for complications of DKA and its treatment
- to dentify and treat any precipitating event

Risk factors for DKA in newly diagnosed diabetes include:[33, level II-2; 34 - 35, level III; 36, level II-2]

- young patient (<2 years old)
- delayed diagnosis
- low socioeconomic status
- children in countries with low prevalence of T1DM

6.1 Diagnosis

- The clinical symptoms and signs of DKA include:[8]
  - nausea and vomiting
  - abdominal pain
  - confusion, drowsiness, progressive reduction in level of consciousness and eventually, loss of consciousness
  - dehydration
  - tachycardia
  - tachypnoea
  - deep, sighing (Kussmaul) respiration; acetone-smell breath
- Prior to the above presentations, patient usually has classical symptoms of diabetes mellitus.

The biochemical criteria for the diagnosis of DKA are:[8; 32, level III]

- hyperglycaemia [BG >11 mmol/L (≈200 mg/dL)]
- venous pH <7.3 or bicarbonate <15 mmol/L
- ketonaemia (>3 mmol/L) and/or ketonuria (>2+)

Blood ketone (β-hydroxybuterate/β-OHB) should be measured whenever possible. A β-OHB level of 3 mmol/L corresponds to a bicarbonate level of 18 mmol/L.[37, level III]

DKA is categorised by the severity of acidosis:[8; 32, level III]

- mild (venous pH <7.3, bicarbonate <15 mmol/L)
- moderate (venous pH <7.2, bicarbonate <10 mmol/L)
- severe (venous pH <7.1, bicarbonate <5 mmol/L)

- Estimation of the degree of dehydration in DKA generally shows fair to moderate agreement among physicians.[38, level II-2; 39, level III]
- The three most useful signs for predicting ≥5% dehydration in young children aged one month to five years are:[8; 40, level III]
  - prolonged capillary refill time (normal capillary refill time is ≤1.5 - 2 seconds)
  - abnormal skin turgor ('tenting' or inelastic skin)
  - abnormal respiratory pattern (hyperpnoea)

  Other useful signs include dry mucous membranes, sunken eyes, absent tears, weak pulses and cool extremities. More signs of dehydration tend to be associated with more severe dehydration.
- Presence of shock (weak or impalpable peripheral pulses, hypotension and oliguria) suggest ≥10% dehydration.
- **Shock is rare in paediatric DKA.**[8]

- Emergency assessment in DKA should comply to the standard paediatric resuscitation guidelines which include:[8]
  - secure the airway and give oxygen to patients with circulatory impairment or shock
  - insert nasogastric tube to prevent aspiration in an unconscious patient
  - assess severity of dehydration and level of consciousness
  - obtain venous access, at least two intravenous (IV) catheters should be secured
  - measure immediately BG, blood or urine ketones, serum electrolytes, blood gases (venous) and full blood count
  - monitor electrocardiography continuously for evidence of hyper- or hypokalaemia
  - catheterise for continuous bladder drainage in an unconscious or a very ill young patient
  - start antibiotics for febrile patients after obtaining samples for culture
  - weigh the patient (this weight should be used in fluid calculation)

Patients should ideally be managed in centres experienced in the treatment of DKA in children and adolescents. If management has to be initiated in a centre with less experience and fewer resources, the clinician in an experienced centre should be consulted on appropriate management.

High risk patients should be managed in an intensive care unit (paediatric if available). They are those with:[8; 32, level III]

- severe DKA (long duration of symptoms, compromised circulation or depressed level of consciousness)
- increased risk of cerebral oedema (e.g. <5 years of age, severe acidosis, low pCO2 or high blood urea nitrogen)

Clinical judgement must be used to optimise treatment of the individual patient. Adjustments of treatment (insulin dose, electrolyte composition and rate of infusion of rehydration fluids) should be based on careful clinical and biochemical monitoring of the patient's response.[8]

Recommendation 4
- Children and adolescents with diabetic ketoacidosis (DKA) should be managed in hospitals with specialists experienced in the management of the condition.
- Patients with severe DKA and at risk of cerebral oedema should be managed in an intensive care unit (if the facility is available in local setting).

The following recommendations are intended only as a general guide to DKA management. As there is considerable individual variability in presentation of DKA, some patients may require specific treatment outside the range of options presented below.

6.2 Treatment

6.2.1 Fluid therapy

- Fluid replacement should begin 1 - 2 hours before starting insulin therapy.
- Patients with DKA have a deficit in extracellular fluid volume that is usually in the range of 5 - 10%.[8]
- Clinical estimates of the volume deficit are subjective and inaccurate. Therefore in moderate DKA, use 5 - <7% and in severe DKA, 7 - 10% dehydration.[8]
- Initial fluid therapy will depend on whether the patient is in:
  - shock
  - severe volume depletion but not in shock (7 -10% dehydration)
  - mild to moderate volume depletion (5 - 7% dehydration)

a. DKA with shock

In patients with DKA in shock, infuse isotonic saline (0.9% saline) 10 - 20 ml/kg as quickly as possible to restore circulatory volume with reassessment after each bolus.[8] Each fluid bolus should be given in 10 ml/kg.

b. DKA with severe volume depletion but not in shock

In DKA patients with poor peripheral circulation but not in shock, infuse 10 - 20 ml/kg of isotonic saline over 1 - 2 hours. It may be repeated until tissue perfusion is adequate (maximum 30 ml/kg).[8; 32, level III] Each fluid bolus should be given in 10 ml/kg.

For both (a) and (b) above, subsequent rehydration and maintenance fluid should be calculated and infused over 48 hours.[32, level III; 41 - 43, level II-2] Resuscitation boluses should not be included as part of the total fluid requirement.[8] The rate of fluid administration usually do not exceed 1.5 - 2 times the daily maintenance requirement.[8; 32, level III]

Use isotonic solution (rehydration and maintenance fluid) for at least 4 - 6 hours before switching to a solution that has a tonicity ≥0.45% saline.[41, level II-2; 43, level II-2; 44 - 47, level III] The decision to switch solution depends on the patient's hydration status, serum sodium and osmolality. Oral intake can be resumed within 24 hours except in severely ill patients.[8]

The measured serum sodium concentration is inaccurate in patients with DKA due to:[8]

- dilutional hyponatremia as a result of high glucose in the extracellular space
- elevated lipid fraction

Therefore it is important to monitor the trend of corrected serum sodium.

- **Important calculations**

Corrected sodium (mmol/L)[8] = Measured sodium + $\frac{2\ (\text{plasma glucose} - 5.6)}{5.6}$ (mmol/L)

Effective plasma osmolality (mosmol/kg) = 2 (plasma sodium) + Plasma glucose (mmol/L)

c. DKA with mild to moderate volume depletion

Isotonic saline bolus infusion is not required in mild to moderate volume depletion of DKA. In moderately dehydrated patients, rehydration and maintenance fluid using isotonic saline should be infused over 48 hours. The decision to switch solution or reduce the rate of infusion depends on the patient's hydration status, serum sodium and osmolality.[8]

In patients with mild dehydration, oral fluid can be continued as tolerated. IV fluid may be needed to maintain total daily fluid requirement.[8]

- Clinical assessment of hydration status and calculated effective osmolality are valuable guides to fluid and electrolyte therapy. The aim is to gradually reduce serum effective osmolality to normal.[42, level II-2; 48, level III]
- Serum sodium level should increase simultaneously as the serum glucose level decreases (sodium should rise by 0.5 mmol/L for each 1 mmol/L decrease in glucose concentration).[8]

Refer to **Algorithm 1** and **2** in **Appendix 3** and **4**.

6.2.2 Potassium replacement

Children with DKA may have total body potassium deficits between 3 and 6 mmol/kg. The major loss of potassium is from the intracellular compartment and this is further aggravated by vomiting and osmotic diuresis.[8]

Potassium replacement is needed irrespective of the serum potassium level unless renal failure is present (refer to **Table 4**). Electrocardiogramme (ECG) may help to determine whether the child has hypo- or hyperkalaemia*.[8]

*ECG changes:
Hypokalaemia: prolongation of PR interval, T-wave flattening and inversion, ST depression, prominent U waves and apparent long QT interval
Hyperkalaemia: tall, peaked and symmetrical T waves, and shortening of the QT interval

Table 4. Potassium replacement

Situation (at presentation)	Treatment
Normokalaemia	• Start potassium replacement after initial volume expansion and before starting insulin infusion. • Commence with 40 mmol of potassium per litre in the infusate (1.5 g potassium chloride/500 ml). • Subsequent potassium replacement should be based on serum potassium measurements.
Hypokalaemia	• Potassium replacement should be started at the time of initial volume expansion at not more than 20 mmol/L of potassium in the infusate and thereafter at 40 mmol/L during rehydration.
Hyperkalaemia	• Start potassium replacement only after urine output is documented.

- IV potassium replacement must not exceed 0.5 mmol/kg/hour.

Potassium replacement should continue throughout IV fluid therapy. If hypokalaemia persists despite a maximum rate of potassium replacement, the rate of insulin infusion may be reduced. Potassium phosphate may be used together with potassium chloride or acetate to avoid hyperchloraemic metabolic acidosis or hypophosphataemia.[8]

6.2.3 Insulin therapy

Insulin therapy in DKA should begin with a rate of 0.05 - 0.1 unit/kg/h about 1 - 2 hours **after** starting fluid replacement therapy.[8; 49 - 50, level III; 51, level II-2; 52, level III]

Do not administer IV bolus of insulin at the start of therapy.[8] It may increase the risk of cerebral oedema[48, level III; 51, level II-2] and exacerbate hypokalaemia.[8]

The dose of insulin should remain at 0.05 - 0.1 unit/kg/h until DKA resolves (pH >7.3, bicarbonate >15 mmol/L, β-OHB <1 mmol/L or closure of the anion gap), which usually takes longer than normalisation of BG levels. If no improvement is seen in pH, anion gap or β-OHB concentration, reassess the patient, review insulin therapy and consider other possible causes of impaired response to insulin such as infection or errors in insulin preparation. For patients with marked sensitivity to insulin (e.g. young children with DKA), the dose may be decreased provided that metabolic acidosis continues to resolve.[8]

Duration and dose of insulin infusion should be kept in the lower range to avoid severe hypokalaemia as insulin has an aldosterone-like effect leading to increased urinary potassium excretion.[8]

- Adjustment of glucose administration:[8]
  - BG level typically decreases at a rate of 2 - 5 mmol/L/hour, depending on the timing and amount of glucose administration.
  - When BG falls to approximately 14 - 17 mmol/L, 5% glucose should be added to the IV fluid.
  - If BG falls very rapidly (>5 mmol/L/hour) after initial fluid expansion, consider adding glucose even before BG has decreased to 17 mmol/L.
  - While correcting metabolic acidosis with insulin infusion, 10% or even 12.5% dextrose may be needed to prevent hypoglycaemia.

If there is no improvement in biochemical parameters of DKA (pH, anion gap and β-OHB level), reassess the patient, review insulin therapy and consider other possible causes of poor response to insulin (e.g. infection or errors in insulin preparation).

6.2.4 Introduction of oral fluids and transition to SC insulin injections

Allow oral fluids only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present). Reduce IV fluid accordingly when oral fluid is tolerated.[8]

The most convenient time to change to SC insulin is just before a mealtime. The first SC injection should be given 15 - 30 minutes (with rapid-acting insulin) or 1 - 2 hours (with short-acting insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be

absorbed. Frequent BG monitoring should be continued to avoid hyper- and/or hypoglycaemia after transitioning to SC insulin.[8]

6.2.5 Bicarbonate therapy

Bicarbonate therapy may lead to paradoxical central nervous system acidosis and rapid correction of acidosis with bicarbonate causes hypokalaemia. Administration is not recommended except for treatment of life-threatening hyperkalaemia.[8]

Recommendation 5

- In diabetic ketoacidosis (DKA) patients with poor peripheral circulation, only isotonic saline (0.9% saline) infusion should be used in initial resuscitation but not exceeding 30 ml/kg in total.
  - Fluid replacement (maintenance and deficit) should be given over 48 hours.
- **Do not administer insulin as bolus at the start of therapy in DKA**.
  - Insulin infusion should begin about 1 - 2 hours **after** starting fluid replacement therapy.
- The dose of insulin should remain at 0.05 - 0.1 unit/kg/h until DKA resolves.
  - Dextrose 5% should be added when blood glucose falls to 14 - 17 mmol/L.
  - If blood glucose level falls too rapidly before DKA resolves, dextrose concentration should be increased.
- Potassium replacement is needed in DKA irrespective of the serum potassium level unless renal failure is present. Electrocardiography helps to determine whether the patient has hypo- or hyperkalaemia.
- Bicarbonate should not be given in DKA except for treatment of life-threatening hyperkalaemia.

- Monitoring of DKA:[8]
  a. hourly (or more frequently as indicated) bedside monitoring
    - vital signs (pulse rate, respiratory rate and blood pressure)
    - neurological observations for warning signs and symptoms of cerebral oedema
    - capillary BG
    - insulin dose
    - accurate fluid input (including oral fluid) and output
  b. two to four hourly (or more frequently) laboratory tests
    - BG
    - blood gases
    - serum electrolytes
    - blood urea nitrogen
    - serum calcium, magnesium and phosphorus
    - haematocrit
  c. two hourly blood β-OHB (capillary blood)

6.3 Morbidity and Mortality

The mortality rate from DKA in children is 0.15 - 0.30%. Cerebral oedema accounts for 60 - 90% of all DKA mortality. Among the survivors, 10 - 25% have significant residual morbidity.[53, level II-2; 54, level III] Those without overt neurological symptoms during DKA may have subtle brain injury, especially memory deficits, after recovery from DKA.[55, level II-2]

Cerebral oedema

The occurrence of clinically overt cerebral oedema is <1.0%.[53, level II-2; 54, level III] However, newer studies show that approximately 15% of children treated for DKA have a GCS score <14 and is associated with cerebral oedema detected by neuroimaging.[56, level III; 57, level II-3]

- Risks of cerebral oedema include:
  - younger age, new onset diabetes[58, level III]
  - longer duration of symptoms, greater hypocapnia at presentation after adjusting for degree of acidosis[53, level II-2; 56, level III; 59, level III]
  - increased serum urea nitrogen at presentation[53, level II-2; 56, level III; 60, level III]
  - severe acidosis at presentation[61, level II-2; 62, level III]
  - bicarbonate treatment for correction of acidosis[53, level II-2]
  - marked early decrease in serum effective osmolality[48, level III; 61, level II-2]
  - attenuated rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy[53, level II-2; 61, level II-2; 63, level II-2]
  - administration of insulin in the first hour of fluid treatment[62, level III]
  - greater (large) volumes of fluid given in the first four hours[59, level III; 61, level II-2; 62, level III]

- Warning signs and symptoms of cerebral oedema:[8]
  - headache (variable severity)
  - change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
  - specific neurological signs (e.g. cranial nerve palsies, papilloedema)
  - slowing of heart rate
  - rising blood pressure
  - decreased oxygen saturation

Clinically significant cerebral oedema usually develops within the first 12 hours after treatment has started but can occur before treatment has begun[53, level II-2; 64, level II-2] or rarely may develop as late as 24 - 48 h after the start of treatment.[65, level III]

Clinical diagnosis based on bedside evaluation:[66, level III]

- one diagnostic criterion or
- two major criteria or
- one major and two minor criteria

These criteria have a sensitivity of 92% and a false positive rate of only 4%. Refer to **Table 5** below.

Table 5. Diagnostic criteria for cerebral oedema

Diagnostic criteria	
• Abnormal motor or verbal response to pain • Decorticate or decerebrate posture • Cranial nerve palsy (especially III, IV and VI) • Abnormal neurogenic respiratory pattern (e.g. grunting, tachypnoea, Cheyne-Stokes respiration, apneusis)	
Major criteria	**Minor criteria**
• Altered mentation/fluctuating level of consciousness • Sustained heart rate deceleration (decrease more than 20 beats/min) not attributable to improved intravascular volume or sleep state • Age-inappropriate incontinence	• Vomiting • Headache • Lethargy or not easily arousable • Diastolic blood pressure >90 mmHg • Age <5 years

In patients with T1DM with multiple risk factors for cerebral oedema, mannitol or hypertonic saline should be readily available and the dose to be given calculated beforehand. If neurologic status deteriorates acutely, treatment should be given immediately.[8]

Treatment of suspected cerebral oedema:[8]

- Prop the patient up at 30°.
- Reduce the rate of fluid administration by one-third.
- Give IV mannitol, 0.5 - 1 g/kg over 10 - 15 minutes, and repeat if there is no initial response in 30 minutes to two hours.
- If there is no initial response to mannitol, hypertonic saline (3%) 2.5 - 5 mL/kg over 10 - 15 minutes may be used as an alternative.
- Consider intubating the patient if there is impending respiratory failure.
- Cranial imaging may be considered after treatment for cerebral oedema has been started.

Recommendation 6

- To reduce the risk of cerebral oedema in diabetic ketoacidosis:
  - large volumes of fluid should not be given after initial volume expansion
  - insulin should not be administered in the first hour of fluid treatment
  - bicarbonate should not be used for the correction of acidosis
  - intravenous fluids should be decreased when the patient begins drinking

6.4 Prevention of Recurrent DKA

Recurrent DKA without a preceding febrile or vomiting illness is almost always due to psychosocial problems and poor compliance to insulin therapy.[67, level I] Thus, attempts to identify and treat the cause of DKA are essential.[8]

7. INSULIN THERAPY

The aim of insulin therapy is to mimic physiological insulin replacement as close as possible in all age groups.

The DCCT defines conventional therapy as administration of one or two daily insulin injections while intensive therapy refers to three or more injections/day.[26, level I] However, for this CPG, classification of insulin therapy is based on the latest ISPAD guidelines which define intensive regimens as four or more injections in a day.[8]

Most insulin regimens include a proportion of rapid-acting or short-acting insulin as prandial insulin and intermediate-acting insulin or long-acting as basal insulin. Some children may only require basal insulin during the partial remission phase.[8]

- The choice of insulin regimen will depend on many factors that include:[8]
  - age of patient
  - duration of diabetes
  - lifestyle (dietary patterns, exercise schedules, schooling, work commitments, etc.)
  - target of metabolic control
  - preference of the patient/caregiver

7.1 Principles of Insulin Therapy

Common insulin regimen includes:

- intensive insulin therapy
  - basal-bolus regimen
  - pump therapy [Continuous Subcutaneous Insulin Infusion (CSII)]
  - sensor-augmented therapy with basal-bolus regimen or pump therapy
- less intensive insulin therapy
  - three injections daily using a mixture of rapid-acting/short-acting and intermediate-acting insulin pre-breakfast, rapid-acting/short-acting pre-dinner and intermediate-acting insulin pre-bed
  - two injections daily that consists of a mixture of rapid-acting/short-acting and intermediate-acting insulin pre-breakfast and pre-dinner

Refer **Appendix 5** for **Types of Insulin Preparations and their Action Profiles**

7.1.1 Intensive insulin therapy

Intensive insulin therapy refers to four or more insulin injections per day or CSII.

In DCCT, intensive insulin therapy compared with conventional insulin therapy efficaciously delayed the onset and slowed the progression of long-term (average follow-up of 6.5 years) diabetic complications in patients with T1DM:[26, level I]

- Retinopathy
  - Primary-prevention cohort: reduction in mean risk of retinopathy by 76% (95% CI 62 to 85)
  - Secondary-intervention cohort: delay the progression of retinopathy by 54% (95% CI 39 to 66) and reduction in risk of proliferative or severe non-proliferative retinopathy by 47% (95% CI 14 to 67)
- Nephropathy
  - Combined cohort: reduction in microalbuminuria by 39% (95% CI 21 to 52) and albuminuria by 54% (95% CI 19 to 74)
- Neuropathy
  - Reduction in clinical neuropathy by 60% (95% 38 to 74)

The Epidemiology of Diabetes Interventions and Complications (EDIC) study, an observational follow-up of the DCCT cohort, demonstrated that further 3-step progression of retinopathy in adolescents at EDIC year four follow-up was lower in the intensive group compared with the conventional group (odds reduction of 72%, 95% CI 17 to 90) despite similar HbA1c levels at entry of EDIC. However, this beneficial effect was not seen at year ten follow-up (odds reduction of 0%, 95% CI -88 to 49).[68, level II-2]

Patients with T1DM on intensified insulin regimens have lower HbA1c levels compared with less intensive regimen at two years follow-up and this difference remains significant when adjusted for baseline HbA1c ($p<0.05$).[69, level II-2]

Basal-bolus regimen

The basal-bolus regimen (intermediate-acting insulin/long-acting basal once or twice daily and rapid-acting/short-acting boluses with meals and snacks) mimics the physiological insulin secretion. Basal insulin constitutes about 40 - 60% of the total daily insulin dose (TDD) requirements; the remainder is pre-prandial rapid-acting/short-acting insulin.[8]

Pump therapy

Insulin pump therapy is gaining popularity with a variable basal rate and bolus doses with meals.

CSII results in better metabolic control and lower TDD requirement compared with multiple daily injection (MDI) in short-term:[70, level I]

- metabolic control, pooled WMD in HbA1c value of -0.29 (95% CI -0.47 to -0.11) at three months and -0.24 (95% CI -0.41 to -0.07) at one year
- insulin requirement, pooled WMD of -0.22 (95% CI -0.31 to -0.14)

There is no difference in hypoglycaemia and risk of DKA between CSII and MDI.

Insulin pump use in children provides a sustained improvement in glycaemic control ($p<0.001$) and reductions of severe hypoglycaemia ($p<0.001$) and hospitalisation for DKA ($p=0.003$) compared with a matched cohort using injections at seven years follow-up.[71, level II-2]

In young children 1 - 6 years old with T1DM, insulin pump therapy is a safe and efficacious alternative compared with insulin injection. The advantages include potential decrease in hypoglycaemic episodes and improvement in quality of life.[72, level I]

7.1.2 Less intensive insulin therapy

Less intensive regimen consists of three or less injections a day.

Three injections daily consist of:[8]

- rapid-acting/short-acting and intermediate-acting insulin pre-breakfast
- rapid-acting/short-acting alone pre-lunch or pre-dinner
- intermediate-acting insulin pre-bed

Premixed insulin is not recommended for paediatric use because of its fixed ratio of insulin components and does not allow flexibility of dosing. However, if patients and their caregivers prefer less injections, self-mixed insulin (rapid-acting/short-acting and intermediate-acting insulin) given twice a day may be acceptable.[8]

7.2 Insulin Formulation

7.2.1 Short-acting insulin

Short-acting insulin is still used as an essential component of most daily replacement regimens either:

- in combination with intermediate-acting insulin in twice daily regimen
- as pre-meal bolus injections in basal-bolus regimen together with intermediate-acting insulin/basal analog once or twice daily
- as rescue insulin during crisis

In a RCT on patients of 7 - 11 years of age with T1DM, the efficacy of rapid-acting insulin and short-acting insulin was found to be similar.[73, level I] However, in a later RCT on patients with a mean age of eight years (pre-pubertal), short-acting insulin showed better fasting BG ($p=0.012$)

and HbA1c (p=0.018) compared with the rapid-acting insulin. This study suggested that short-acting insulin can assure better plasma insulin levels between meals as compared with rapid-acting insulin in children who did not administer pre-snack insulin injection.[74, level I]

7.2.2 Rapid-acting insulin

Rapid-acting insulin has a faster onset and shorter duration of action than short-acting insulin.

Insulin aspart given post-prandially is non-inferior and safe compared with pre-prandial administration in children and adolescents who require flexibility in timing of injections and dose adjustment according to meal.[75, level I]

Rapid-acting insulin given before the evening meal (as part of a thrice daily insulin regimen) reduce the risk of early nocturnal hypoglycaemia (p=0.01).[73, level I]

In patients on a twice daily insulin regimen (combination of intermediate-acting insulin and rapid-acting/short-acting insulin), an additional injection of insulin lispro before the afternoon meal (two hours before dinner) reduces the pre-dinner BG (p=0.001).[76, level I]

7.2.3 Basal insulin

- **Glargine**

In children aged 2 - 6 years, a daily injection of insulin glargine is as efficacious as twice daily injection of intermediate-acting insulin. Although the rate of composite hypoglycaemia [symptomatic hypoglycaemia, confirmed low CGM excursions (<3.9 mmol/L) and low fingerstick BG (<3.9 mmol/L)] is significantly higher with insulin glargine, there is no significant difference in severe and nocturnal hypoglycaemia between the two types of insulin.[77, level I]

In children and adolescents with T1DM, insulin glargine is safe and non-inferior compared with intermediate-acting insulin/Lente as basal insulin options in MDI regimens. However in those with high baseline HbA1c, insulin glargine is more efficacious than intermediate-acting insulin/Lente in reducing HbA1c.[78, level I] In a similar age group, a daily insulin glargine injection is equally efficacious either given pre-breakfast or at bedtime.[79, level I]

- **Detemir**

Insulin detemir is equally efficacious in reducing HbA1c compared with intermediate-acting insulin of a basal-bolus regimen in children with T1DM at 26 weeks. However, it has a significantly lower and more predictable fasting BG, lower weight gain and lower risk of nocturnal hypoglycaemia.[80, level I]

In a study on children and adolescents aged 2 - 16 years, insulin detemir given once or twice daily was non-inferior to intermediate-acting insulin in glycaemic control at 52 weeks and was associated with a significantly lower risk of hypoglycaemia and lower weight SD score.[81, level I] Similar findings were observed in children aged 2 - 5 years.[82, level I]

7.3 Insulin Dosage

Insulin dosage depends on many factors:[8]

- age
- weight
- stage of puberty
- duration and phase of diabetes
- state of injection sites
- nutritional intake and distribution
- exercise duration and intensity
- daily routine
- SMBG and HbA1c level
- intercurrent illness

- The guidelines on TDD are as follows:[8]
  - during partial remission phase, the TDD is often <0.5 IU/kg/day
  - pre-pubertal children usually require 0.7 - 1.0 IU/kg/day
  - during puberty, higher requirements may be needed, 1.2 - 2 IU/kg/day

Children on twice daily regimens often require about two thirds of their TDD in the morning and about one third in the evening. About one third of each insulin dose is rapid-acting or short-acting insulin and about two thirds is intermediate-acting insulin.[8]

Children on basal-bolus regimen require night-time intermediate-acting insulin between 30% (if on short-acting insulin) and 50% (if on rapid-acting insulin) of TDD; the remainder is pre-prandial rapid-acting/short-acting insulin.[8]

Refer to **Appendix 5** on **Types of Insulin Preparations and their Action Profiles**.
Refer to **Appendix 5** on I**nsulin Approval by U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMEA)**

Recommendation 7

- Intensive insulin therapy is the preferred regimen in patients with type 1 diabetes mellitus (T1DM).
- Rapid-acting or short-acting insulin should be made available to patients with T1DM for crisis management*.
- Comprehensive education appropriate for the age, maturity and individual needs of the child should be offered to all patients with T1DM and their caregivers.

*Refer to **Chapter 14** on **Special Situations (Sick Day)**.

8. INSULIN DOSE ADJUSTMENT

For patients with T1DM on basal bolus therapy, pre-meal insulin dose may be adjusted based on insulin to carbohydrate ratio (ICR) or insulin sensitivity factor (ISF). Detailed record of SMBG, carbohydrate intake and insulin doses are crucial when making insulin dose adjustments.[83, level III]

8.1 Insulin to Carbohydrate Ratio

- ICR is defined as the amount of carbohydrate in gramme covered by one unit (IU) of rapid-acting or short-acting insulin.
- It can be calculated by using the 500 (for rapid-acting insulin) [8; 83, level III] and 450 (for short-acting insulin)[84, level III] rules.
- ICR for most children are 1:20 or 1:25.[83, level III] However in practice, adolescents may require more insulin and thus giving a higher ICR (e.g. 1:15). ICR is often higher for breakfast due to higher insulin resistance.
- For very young children requiring <10 IU of insulin per day, the 300 - 450 rule may be used.[83, level III]
- The 500 rule for rapid-acting insulin:

$$\text{ICR} = \frac{500}{\text{Total daily insulin*}}$$

*basal and bolus insulin

For example, a child requires 6 IU of rapid-acting insulin for breakfast, lunch and dinner, and 12 IU of basal insulin. The total daily insulin dose is 30 IU (6 IU + 6 IU + 6 IU +12 IU) and the ICR is 16.7 g/IU (500 divided by 30 IU). Therefore, every 16.7 g of carbohydrate consumed will require 1 IU of rapid-acting insulin.

- The 450 rule for short-acting insulin:

$$\text{ICR} = \frac{450}{\text{Total daily insulin*}}$$

*basal and bolus insulin

- Alternatively, ICR for individual meal can be calculated by dividing the carbohydrate content in gramme by the insulin dose in IU. This formula can only be used if the difference in BG level between the pre- and post-meal is not more than 3 mmol/L.[8]

For example, a child consumes a meal with carbohydrate content of 45 g and requires 3 IU of insulin. The ICR is 15 g/IU (45 g divided by 3 IU). Therefore, every 15 g of carbohydrate consumed will require 1 IU of rapid-acting insulin.

8.2 Insulin Sensitivity Factor

- ISF is defined as the amount of BG in mmol/L reduced by one unit (IU) of rapid-acting or short-acting insulin and used to correct hyperglycaemia.
- The 100 rule for rapid-acting insulin:[8; 83, level III]

$$ISF = \frac{100}{\text{Total daily insulin*}}$$

*basal and bolus insulin

- The 83 rule is for short-acting insulin:[8; 83, level III]

$$ISF = \frac{83}{\text{Total daily insulin*}}$$

*basal and bolus insulin

For example, a child requires 6 IU of short-acting insulin for breakfast, lunch and dinner, and 12 IU of basal insulin. The total daily insulin dose is 30 IU (6 IU + 6 IU + 6 IU + 12 IU) and the ISF is 2.76 mmol/L/IU (83 divided by 30 IU). Therefore, every 1 IU of short-acting insulin will reduce the BG by 2.76 mmol/L.

If the BG level is persistently above the target during:[8]

- pre-breakfast - increase pre-dinner or basal insulin
- pre-lunch - increase pre-breakfast rapid-acting or short-acting insulin, or pre-breakfast basal insulin
- pre-dinner - increase pre-lunch rapid-acting or short-acting insulin, or pre-breakfast basal insulin
- post-meal - increase pre-meal rapid-acting or short-acting insulin

Although evidence on insulin dose adjustments is based on guidelines and a narrative review, ICR and ISF are the only objective methods that are widely practiced at the moment. Thus, the DG CPG strongly recommends its use for the purpose.

Recommendation 8

- Insulin dose adjustment may be done based on insulin to carbohydrate ratio and insulin sensitivity factor in patients with type 1 diabetes mellitus on basal bolus regimen.

9. HYPOGLYCAEMIA

Hypoglycaemia is common among patients with T1DM and is defined as low BG level that predisposes patients to potential harm. Counter-regulation begins at <4 mmol/L in a non-diabetic person. There is no single numerical definition of hypoglycaemia for all patients and situations. However, it is often defined as a BG level of <3.6 mmol/L but the threshold for initiation of treatment is 3.9 mmol/L because of the risk of it falling further.[8]

Hypoglycaemia can be symptomatic or asymptomatic. Signs and symptoms of hypoglycaemia are due to adrenergic activation and neuroglycopaenia as shown below.[8]

Autonomic signs and symptoms	Neuroglycopaenic signs and symptoms	Behavioural signs and symptoms	Non-specific symptoms
• Shakiness • Sweatiness • Tremors • Palpitations • Pallor	• Poor concentration • Blurred or double vision • Disturbed colour vision • Difficulty in hearing • Slurred speech • Poor judgment and confusion • Problems with short-term memory • Dizziness and unsteady gait • Loss of consciousness • Seizure • Death	• Irritability • Erratic behaviour • Agitation • Nightmares • Inconsolable crying	• Hunger • Headache • Nausea • Tiredness

Precipitating and risk factors of hypoglycaemia are listed in the following box.[8]

Precipitating factors	Risk factors
• Excess insulin • Less food consumption • Exercise • Alcohol ingestion	• Young age • Low HbA1c level • Hypoglycaemia unawareness • Previous severe hypoglycaemia • Longer duration of diabetes

Treatment

The goal of hypoglycaemia treatment is to restore the BG to normal level (5.6 mmol/L).[8]

- **Mild/moderate hypoglycaemia**[8]

If the BG level is low (3.3 - 3.9 mmol/L) and although patient is asymptomatic, oral glucose of 0.3 g/kg (1 tablespoon≈10 g and 1 teaspoon≈5 g) will increase the BG level sufficiently. Check BG after 10 - 15 minutes and repeat oral glucose administration if there is no improvement. Thereafter, complex carbohydrates in the form of fruit, bread, cereal or milk can be consumed to prevent recurrent hypoglycaemia.

Patients should carry with them a hypokit consisting of glucose sachet or glucose tablet and a serving of complex carbohydrates such as biscuits.

If sucrose is used, a greater amount of it will be needed to provide the same increase in BG level compared with glucose. Foods containing fat will slow down the glucose absorption and should be avoided as the initial treatment of hypoglycaemia.

- **Severe hypoglycaemia**[8]

Severe hypoglycaemia is defined as an event of low BG requiring assistance of another person to reverse the condition. However in young children, even mild to moderate hypoglycaemia often require assistance of caregivers. Therefore, the above definition is not applicable to them. Generally, severe hypoglycaemia in paediatric population is defined as an event associated with severe neuroglycopaenia which usually results in coma or seizure and requires parenteral therapy [SC/intamuscular (IM) glucagon or IV glucose].

- Severe hypoglycaemia warrants urgent treatment.
  - In the hospital environment, this can be safely and rapidly treated by IV dextrose 10% (2 - 3 ml/kg) administration.
  - If IV access is not available, SC/IM glucagon can be given (0.5 mg for patients <12 years old and 1.0 mg for those >12 years old).

Ideally, glucagon (SC/IM) should be accessible to all patients and caregivers, particularly if there is high risk of severe hypoglycaemia. Education on its administration is important.[8] Although glucagon pen is not available locally, hopefully it will be more readily available in future.

When parenteral dextrose and glucagon are not available, a practical management is to administer a rapid-acting source of glucose such as honey onto the buccal mucosa; however this is not based on scientific evidence. In the recovery phase after treatment, close observation and glucose monitoring is essential. Hypoglycaemia may recur and patients may require oral glucose and/or IV infusion of dextrose.

- **Nocturnal hypoglycaemia**[8]

Nocturnal hypoglycaemia is common in patients with T1DM and often undetected by the patients or their caregivers. During sleep, the counter regulatory responses to hypoglycaemia are decreased in patients with T1DM who are less likely to be awakened by this condition.

- Nocturnal hypoglycaemia should be suspected in the following conditions:
  - low pre-breakfast BG
  - confusional states
  - nightmares
  - seizures at night
  - impaired thinking, lethargy, altered mood or headaches upon waking

Regular overnight BG monitoring should be done to detect nocturnal hypoglycaemia especially in the presence of precipitating/risk factors.

Recommendation 9

- Patients with type 1 diabetes mellitus (T1DM) and their caregivers:
  - should be able to recognise precipitating factors of hypoglycaemia and take appropriate precautions
  - must be able to recognise symptoms of hypoglycaemia and give prompt treatment
  - should always have hypokit consisting of glucose sachet or glucose tablet and a serving of complex carbohydrates easily accessible at all times
- Patients with T1DM and their caregivers should monitor overnight blood glucose level on a regular basis to prevent nocturnal hypoglycaemia.

10. MEDICAL NUTRITION THERAPY

Medical nutrition therapy (MNT) is an essential component of T1DM management. It involves nutritional assessment, diagnosis, intervention, monitoring and evaluation.[85] It is recommended for all children and adolescents with T1DM. Glycaemic control can be improved by implementing an individualised meal plan with appropriate insulin adjustments.[8]

MNT consists of:[8]
- energy balance, energy intake and food components
- nutritional care, education and meal planning
- dietary recommendations for specific insulin regimes
- nutritional management of physical activities

The aims of MNT are:[8]
- to provide adequate energy intake and nutrients for optimal growth and development while maintaining quality of life
- to achieve optimum glycaemic control by maintaining a balance between food intake, energy expenditure and insulin action profiles
- to prevent and treat acute complications (hypoglycaemia, hyperglycaemia, illness and exercise-related problems) and reduce the risk of long-term complications
- to provide an individualised meal plan consisting of three meals a day with appropriate healthy snacks (when necessary) in order to have a framework for regular BG monitoring

10.1 Energy Balance, Energy Intake and Food Components

- Daily energy intake varies among children and adolescents, depending on age, stages of growth, physical activities and type of food.
- Total calorie intake should be distributed as follows:[8]
  - carbohydrate (carb) 50 - 55%
  - fat 25 - 35%
  - protein 15 - 20% [high protein diet (>25% total daily calorie intake) are not recommended]
- Food components:[8]
  - healthy sources of carbohydrate - e.g. whole grain breads and cereals, legumes, fruits, vegetables and low-fat dairy products (full-fat in children under two years)
  - fat - reduce the intake of saturated fat and trans-fatty acids. Substitute saturated fat with monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) to improve the lipid profile. Examples of MUFA are olive, canola, sesame and rapeseed oil. Examples of PUFA are sunflower, safflower, corn, soybean, cottonseed, rice bran, peanut oil and oily marine fish [e.g. salmon, toli shad (terubok), mackerel and anchovy]

- protein - intake should be similar to normal healthy children
- fibre - consume fruits and vegetables daily according to age requirement. One serving of vegetable is equivalent to ½ cup of cooked vegetable or 1 cup for raw vegetable. The recommended amount of fibre per day follows the formula of:

Age in years + 5 = Amount of fiber per day (g) for patients more than two years old

Refer to **Appendix 6**.

10.2 Nutritional Care, Education and Meal Planning

Carb counting is widely used in MNT for T1DM. It is a meal planning approach for T1DM focusing on carbohydrate which is the primary nutrient affecting post-prandial glycaemic response.[8; 83, level III]

Carb counting significantly improves metabolic control in children and adolescents with T1DM compared to those without the intervention at two years follow-up. It does not cause significant weight gain or increase in insulin requirement.[86, level I]

Carb counting combined with nutritional education reduce HbA1c without changing insulin requirement ($p<0.001$) and do not negatively affect dietary habits and waist-to-height ratio (a relatively constant anthropometric index in detecting central intra-abdominal obesity and related cardio metabolic risk among children) at 18 months.[87, level II-3]

In calculating mealtime insulin to maintain post-prandial control, carbohydrate estimations should be within 10 g of the actual meal carbohydrate content.[88, level I] A deviation of more than 20 g in the estimations will cause significant hyper- or hypoglycaemia.[89, level II-3] Carb counting in gramme increments (e.g. 30 g) does not significantly increase accuracy compared with portions or exchange estimations (e.g. 2 exchanges). Large meals tend to be underestimated and snacks overestimated.[90, level III]

The usual method of quantifying carbohydrate is to use a 15 g carbohydrate exchange. Refer to **Appendix 7** and **Appendix 8**.

Photographic materials is better than list materials in training adolescents with T1DM to perform carb counting ($p=0.03$). It is easier to be used for teenagers who have no experience in portioning of food and parents with low educational level.[91, level I]

Recommendation 10

- Carbohydrate counting should be incorporated as part of the management of type 1 diabetes mellitus patients.

It is helpful to consider the glycaemic index (GI) and glycaemic load of the food consumed in the management of T1DM. Low GI diet has additional benefit to glycaemic control when practised together with carb counting.[8]

Children on low GI diet together with carb counting achieve significantly better HbA1c and less hyperglycaemia episodes compared with those on carb counting alone at 12 months.[92, level I] A low GI day results in significantly better glycaemic control but more episodes of mild hypoglycaemia compared to a high GI day.[93, level II-1] Refer to **Appendix 8**.

10.3 Dietary Recommendations for Specific Insulin Regimes

10.3.1 Conventional therapy

Consistency in carbohydrate intake is required for patients on twice daily insulin regimens to prevent hypoglycaemia during periods of peak insulin action. However, this meal plan requires regular review in a growing child. Patients/caregivers who can adjust the rapid-acting/short-acting insulin (self-mixed insulin) have more flexibility with carbohydrate consumption. Pre-bed carbohydrate intake is required to prevent nocturnal hypoglycaemia.[8]

Patients on conventional therapies will require:

- fixed meal times
- consistent carbohydrate intake/meal/day

Patients may require snacks in between main meals to prevent hypoglycaemia during the peak action of self-mixed insulin.

10.3.2 Intensive Insulin Therapy

Intensive insulin therapy mimics endogenous insulin production. Individualised ICR using more flexible approach enables insulin dose to be matched to carbohydrate intake. The need for snacking between meals will be reduced due to the greater variety of food intake, which is allowed at different meal times. Refer to **Section 8.1**.

10.4 Nutritional Management of Physical Activities

10.4.1 Unplanned and Spontaneous Activity

Hypoglycaemia commonly occurs during unplanned physical activities. Nutritional strategies to avoid this are:[8]

- Quick acting carbohydrate (beverages) for a short duration activity if necessary but this should not exceed the energy expenditure. Example is isotonic sport drink containing 6 - 8% carbohydrate per serving.
- Carbohydrate requirement depends on the:
  - pre-exercise BG level

  - the intensity and duration of the exercise
  - the insulin regimen, and the time and dose of the last insulin injection
  - the age and weight of the patient
- BG testing need to be done after an activity to allow appropriate management. Delayed hypoglycaemia can be prevented by reducing the evening insulin doses and increasing carbohydrate intake.
- Nocturnal hypoglycaemia can be prevented by monitoring the pre-bed and overnight BG and adding carbohydrate consumption at dinner and pre-bed if necessary.

10.4.2 Planned or competitive sports

The planning for nutritional strategy prior to exercise includes appropriate insulin adjustment, adequate nutrition and fluid intake:[8]

- Low-fat meal (carbohydrate-based) should be eaten 1 - 3 hours prior to a sport to reduce the risk of gastrointestinal discomfort and make digestion easier. Examples are fruit, milk, yoghurt, milkshake, sport or cereal bars (check labels for carbohydrate and protein content) and breakfast cereal with milk.
- Prior to and during strenuous exercise, additional 'quick acting carbohydrate' as beverages may be needed.
- If aerobic exercise is performed during peak insulin action without insulin adjustment, an intake of 1.0 - 1.5 g carbohydrate/kg/hour of exercise may be required.
- Pre-exercise carbohydrate consumption should be tailored according to pre-exercise BG. Consume 10 - 15 g of carbohydrate if BG is low or alternatively adjust insulin dose.
- Adequate fluid intake is important to maintain optimal hydration.
- To prevent post-exercise hypoglycaemia, carbohydrate intake needs to be adequate. Carbohydrate mixed with protein may be beneficial.

Recommendation 11

- Appropriate nutritional strategies should be tailored to the age, insulin regimen and physical activities of the patient with type 1 diabetes mellitus.

11. PSYCHOSOCIAL SUPPORT

Young patients with T1DM have higher prevalence of affective disorders (anxiety and depression) compared to non-diabetics ($p<0.001$).[94, level III] The prevalence of mild depression in T1DM youth is 14% while moderate to severe depression at 8.6%. Depressed mood is associated with poor glycaemic control and more frequent visit to emergency department ($p<0.005$).[95, level III] Psychiatric co-morbidites (depressive disorders, anxiety disorders and phobic disorders) in T1DM adolescents increase the odds for repeat hospital admission for diabetes (OR=1.79, 95% CI 1.27 to 2.52).[96, level III]

There is also increased incidence of eating disorders among patients with T1DM compared to non-diabetics.[8; 96, level III] The standardised mortality rate in patients with concurrent T1DM and anorexia nervosa patients is 2.18 (95% CI 1.15 to 4.42).[97, level III]

T1DM is an important risk factor for cognitive deficits. TIDM patients with longer duration of diabetes, earlier age of diabetes onset and DKA have lower test score in comprehension, abstract reasoning and intelligent quotient compared to non-diabetics.[98, level II-2]

The relationship between psychological factors and metabolic control is bidirectional. Therefore, psychosocial supports are important in managing children and adolescents with T1DM.

- Psychosocial factors that predict poor metabolic control in T1DM are:[99 -100, level II-2]
  - low family support/cohesion
  - single parent
  - family stress/conflict
  - presence of psychiatric disorder/eating disorder
  - extreme peer pressure
  - others:
    - low conscientiousness
    - low self-efficacy
    - avoidant emotion-focused coping style
    - low executive functioning

Psychosocial interventions improve HbA1c in children and adolescents with T1DM (SMD= -0.35, 95% CI -0.66 to -0.04).[101, level I] These interventions also significantly improve the psychological distress in the patients.[101 - 102, level I]

The psychosocial interventions involving parents/caregivers have been shown to be efficacious in improving metabolic control. These interventions include:[101 - 103, level I; 104, level II-2]

- psychoeducation
- problem solving skills
- coping skills
- supportive or counselling therapy
- family therapy
- cognitive behaviour therapy

The above psychosocial interventions are commonly carried out in hospital outpatient and community settings such as diabetes summer camps. Diabetes camps are shown to improve both diabetes knowledge and metabolic control in patients with T1DM.[102, level I] Participation of the patients in diabetes camp is a component of total diabetes care and it should be encouraged.

Recommendation 12

- Periodic assessment should be performed in all patients with type 1 diabetes mellitus for early recognition of psychosocial problems and referral to appropriate expertise.
- Diabetes team should consist of paediatrician, diabetes educator, dietitian, pharmacist, psychiatrist/clinical psychologist/counsellor and medical social officer.

12. PHYSICAL ACTIVITY (EXERCISE)

Physical activity is an essential component in the management of T1DM. Diabetic patients have higher risk of developing cardiovascular disease.[105] It is important for the patients to engage in regular physical activity, together with insulin therapy and dietary adjustment.

Physical activity (exercise) can be divided into types:[8]

i. Aerobic (cardiovascular) exercise is a low intensity physical activity that depends primarily on the aerobic energy-generating process and the use of oxygen adequately to meet energy demands. Examples of aerobic/cardiovascular exercise are medium to long distance running/jogging, swimming, cycling, and walking.

   Aerobic exercise tends to lower BG level both during (usually within 20 - 60 minutes from the start of exercise) and after the exercise.

ii. Anaerobic exercise is a high intensity physical activity. It is intense enough to trigger lactate formation and performed in excess of 90% maximum heart rate. Examples include weight training, sprinting and burst training.

Although anaerobic exercise last only a short time (sometimes only seconds), it may increase the BG level dramatically due to the release of the hormones epinephrine and glucagon. This rise in BG is usually transient, lasting typically 30 - 60 minutes, and may be followed by hypoglycaemia a few hours after the exercise ends.

12.1 Benefits of Physical Activity

There are benefits of physical activity on HbA1c (SMD= -0.52, 95% CI -0.97 to -0.07), triglyceride (SMD= -0.70, 95% CI -1.25 to -0.14), total cholesterol (SMD= -0.91, 95% CI -1.66 to -0.17) and BMI (SMD= -0.41, 95% CI -0.7 to -0.12).[106, level II-1]

Physical activity that significantly improve glycaemic control are:[107, level I]

- duration of >60minutes per session
- higher frequency of >3 times in a week
- longer duration programme of >3 months
- combined aerobic and resistance training

12.2 Risk of Hypoglycaemia Associated with Physical Activity

Although hypoglycaemia is a common problem in children and adolescent with T1DM, there is no significant severe hypoglycaemia reported in post-physical activity.[106, level II-1] It can occur during, immediately after or several hours after (mainly 12 - 14 hours or longer) physical activity.[8]

Possible reasons for hypoglycaemia are:[8]

- high intensity and long duration exercise (>30 - 60 minutes)
- >3 hours interval between the last meal and exercise
- not having a snack before and during exercise
- hyperinsulinemia during exercise (exercise during peak action of insulin)

- If hypoglycaemia occurs during exercise:[8]
  - stop physical activity immediately
  - consume a rapid-acting 15 g carbohydrate
  - take additional carbohydrate if hypoglycaemia persists
  - monitor BG level until it is normal

Post-exercise hypoglycaemia and late onset hypoglycaemia can present between four and 24 hours after exercise especially in prolonged and moderate or high intensity physical activity. This is due to the late effect of increased insulin sensitivity and, delay in replenishing liver and muscle glycogen stores.[8]

12.3 Prevention of Hypoglycaemia during Physical Activity

Hypoglycaemia during physical activity can be prevented by adjustment of insulin injections and carbohydrate supplement.

- **Adjustment of insulin injections**[8]

The use of insulin should be tailored to type and duration of exercise.

  - Reduction in bolus insulin is required to prevent hypoglycaemia during prolonged exercise. The usual recommendation is to reduce rapid-acting insulin prior to exercise lasting longer than 30 minutes.
  - Substitution of basal analog (long-acting insulin) given in the evening with an intermediate-acting insulin if the patient is taking part in all-day tournaments. Alternatively, split the TDD in half to be given as basal analog. Take half of the basal analog in the evening and then lower the second dose in the morning by 20 - 50% to compensate for the increased activity.

- **Carbohydrate supplement**
  - Refer to **Chapter 10** on **Medical Nutritional Therapies (Nutritional Management of Physical Activities)**

- The following steps should be observed regarding physical activity:[8]
  - Avoid strenuous physical activity if pre-exercise BG is high (>14mmol/L) with ketonuria or ketonaemia.
  - Increase the intensity and duration of physical activity in a progressive manner.
  - Do not inject insulin in the site that will be heavily involved in muscular activity e.g. not to inject in the thigh before cycling.
  - Avoid physical activity exercise at peak action of insulin.
  - Consider reducing evening basal insulin.
  - Monitor BG in evening and night after physical activity to avoid nocturnal hypoglycaemia.
  - Carry some sugar and drink more water.

Children with T1DM should be able to adjust insulin therapy before and after physical activities to avoid major metabolic complications.[108, level III] During unplanned physical activity, carbohydrate supplement before moderate-intensity exercise can prevent dramatic drop in BG in adolescents.[109, level III]

Recommendation 13

- Physical activities should be performed regularly and in a safe manner* in patients with type 1 diabetes mellitus.

*Refer to the preceding text.

13. SELF-MONITORING BLOOD GLUCOSE

SMBG is an important aspect of diabetes self-care practice and should be practiced by all children and adolescents with T1DM. Maintaining BG at or very near the normal range is known to decrease the progression of microvascular disease in the affected young patients. SMBG is conducted by measuring capillary BG via glucometer.

The aims of SMBG are:[8]

i. to accurately assess the level of glycaemic control of each individual so that they can achieve their glycaemic targets
ii. to reduce the risk of hypoglycaemia, DKA, and chronic complications of microvascular and macrovascular diseases
iii. to minimise the fluctuation of blood glucose and its effect on cognitive function and mood
iv. to understand determinants of glycaemic control in each individual and specific patient groups

Frequency of SMBG correlates with glycaemic control. It should be prescribed at a frequency that can optimise patient's diabetes control, usually four to six times a day. The number and regularity of SMBG should be individualised based on:[8]

- availability and cost of equipment
- type of insulin regimen
- ability of the patient to identify hypoglycaemia

- SMBG provides immediate documentation of glucose levels. It allows prompt actions to be taken for optimal treatment and prevention of hypo- or hyperglycaemia when it is performed at the correct timing as suggested below:[8]
  - To optimise basal insulin, blood testing should be done at bedtime, during the night (e.g. 3 am to detect nocturnal hypoglycaemia and hyperglycaemia) and after the overnight fast (pre-breakfast).
  - For immediate adjustment of meal insulin dose, pre-meal blood testing should be done. For subsequent adjustment of meal insulin dose, blood testing should be done pre-meal and two hours post-meal to show levels of BG in response to the meal insulin.
  - For glycaemic control during vigorous/prolonged exercise, blood testing should be done before, during and several hours after the exercise.
  - Blood testing should be done when hypoglycaemia is suspected. It should also be done during intercurrent illness to prevent hyperglycaemia.

- It is a good practice to keep a diary to record glucose levels, insulin dosages and dietary details for treatment adjustments. This diary should be reviewed regularly by patients, families and healthcare providers.

Recommendation 14
- Self-monitoring of blood glucose (SMBG) should be practised by all children and adolescents with type 1 diabetes mellitus.
- SMBG should be performed four to six times a day and more frequent in certain conditions such as sick day or during exercise.

Continuous Glucose Monitoring System

Continuous Glucose Monitoring System (CGMS) uses minimally invasive device to measure SC interstitial fluid glucose every 1 - 5 minutes (continuously). This device is expensive and not affordable to most families.

In a multicentre RCT, there was no significant difference in HbA1c reduction between continuous glucose monitoring and SMBG (>5 times per day) in patients with T1DM aged 8 - 24 years old at 26 weeks follow-up. However, in patients aged 8 to 14 years, secondary indexes of glycaemic control (measured as relative reduction of ≥10% in HbA1c level from baseline and HbA1c levels of <7.0%) significantly improved in the continuous monitoring group compared with the control group.[110, level I]

In a small RCT on patients with T1DM and mean age of 11.4±3.7 years, the HbA1c was significantly lower in the intervention group (adjustments in therapy based on both CGMS and SMBG data) compared with control group (adjustments based on SMBG data only) at six months (p=0.02) without increasing the risk for hypoglycaemia.[111, level I]

Indications for CGMS are:[112, level III]
- failure to achieve individual's glycaemic target (HbA1c) despite optimal use of intensive insulin regimens
- suspected nocturnal hypoglycaemia and/or early morning hyperglycaemia
- suspected unrecognised hypoglycaemia e.g. exceptionally low HbA1c without reported hypoglycaemia
- recurrent severe hypoglycaemia and hypoglycaemia unawareness

Self-monitoring of urinary or blood ketones

Urine or blood ketones measurement should be monitored during episodes of uncontrolled hyperglycaemia, intercurrent illness (sick days) and impending ketoacidosis:[8]

- especially with presence of abdominal pains, vomiting, drowsiness or rapid breathing
- when there is persistent BG levels >14 mmol/L (250 mg/dL)

However in local setting, the blood ketone strips are expensive and urinary ketone strips for self-monitoring are not widely available or affordable.

14. SPECIAL SITUATIONS

In children and adolescents with T1DM, there are special circumstances when glucose metabolism is significantly altered, requiring additional monitoring of BG and/or adjustment of the patients' daily insulin dose. The school or daycare setting also presents challenges in the management of the patients with T1DM. The healthcare team needs to provide clear guidance to patients and their caregivers on how to manage these special situations.

14.1 Sick Day

Some illnesses, especially those associated with fever, raise BG levels because of higher levels of stress hormones promoting gluconeogenesis and insulin resistance. Illness often increases ketone body production due to inadequate insulin levels leading increased insulin requirement. The increased need for insulin may persist for a few days after recovery from an illness due to insulin resistance.

In contrast, illness associated with vomiting and diarrhoea (e.g. viral gastroenteritis) may lower BG with the increased possibility of hypoglycaemia. Decreased food intake, poorer absorption and a slower emptying of the stomach or overt diarrhoea with more rapid transit during gastroenteritis may contribute to such hypoglycaemia.

Healthcare providers should provide clear guidance to patients and their caregivers on the management of diabetes during intercurrent illnesses. The patients and their caregivers should know the contacts of emergency medical service during this period. Education on sick day management should be given to patients and their caregivers periodically to avoid complications such as DKA, dehydration, uncontrolled hyperglycaemia and hypoglycaemia.[8]

The insulin dose usually needs to be increased when there is fever or intercurrent illness, based on frequent BG and urine/blood ketone measurements.[8] Guidelines for insulin adjustment during sick days are shown in **Table 6**.

- General Principles of Diabetes Sick Day Management:[8]
  1. DO NOT STOP INSULIN.
  2. Monitor BG and ketone (urine or blood) more frequently.
  3. Monitor and maintain electrolytes and water balance.
  4. Patients and their caregivers should be taught on sick day management guidelines soon after diagnosis and periodically thereafter.
  5. Treat the underlying precipitating illness.

Table 6. Guidelines for insulin adjustment during sick days

Ketones		Blood Glucose				
Blood ketones mmol/L	Urine ketones	<5.5 mmol/L	5.5 to 10 mmol/L	>10 to 14 mmol/L	>14 to 22 mmol/L	>22 mmol/L
<0.6	Negative or trace	• Do not give extra insulin • Recheck BG & ketones in 2 hours	No insulin adjustment needed	Add correction dose of insulin according to ISF	Give extra 5% of TDD or 0.05 IU/kg	• Give extra 10% of TDD or 0.1 IU/kg • Repeat if needed
0.6 - 1.4	Trace, small to moderate	• Starvation ketones • Extra carb & fluid are needed	• Starvation ketones • Extra carb & fluid are needed • No insulin adjustment needed	• Extra carb & fluid may be needed • Give 5 - 10% of TDD or 0.05 - 0.1 IU/kg	Give extra 5 - 10% of TDD or 0.05 - 0.1 IU/kg	• Give extra 10% of TDD or 0.1 IU/kg • Repeat if needed
1.5 - 2.9	Moderate to large	• High levels of starvation ketones • Check BG meter • Recheck BG & ketones • Extra carb & fluid are needed	• High levels of starvation ketones • Extra carb & fluid are needed • Give 5% of TDD or 0.05 IU/kg; repeat insulin dose when BG has risen	• Extra carb & fluid are needed • Give 10% of TDD or 0.1 IU/kg	Give extra 10 - 20% of TDD or 0.1 IU/kg; repeat insulin dose after 2 hours if ketones do not decrease	
>3.0	Large	• Very high levels of starvation ketones • Check BG meter • Recheck BG & ketones • Extra carb & fluid are needed	• Very high levels of starvation ketones • Extra carb & fluid are needed. • Give 5% of TDD or 0.05 IU/kg; repeat insulin dose when BG has risen	• Extra carb & fluid are needed • Give 10% of TDD or 0.1 IU/kg	Give extra 10 - 20% of TDD or 0.1 IU/kg; repeat insulin dose after 2 hours if ketones do not decrease	
There is an immediate risk of ketoacidosis if the blood ketone level is ≥3.0 mmol/L.						

Refer to **Chapter 8** for the **Insulin Dose Adjustment**.

Modified: International Society for Pediatric and Adolescent Diabetes (ISPAD). Pediatric Diabetes. Oxford: Wiley Blackwell; 2014

Vomiting in a sick child or adolescent with diabetes should be considered as a sign of insulin deficiency until proven otherwise. (Blood ketones are preferred over urine ketones if available. Aim for a BG between 4 and 10 mmol/L and blood ketones below 0.6 mmol/L.[8]

Refer to **Chapter 6** on **Diabetes Ketoacidosis (Diagnosis)**.

- URGENT medical consultation must be obtained when a child or adolescent with T1DM has the following features:[8]
  - persistent fever or the underlying illness is unclear
  - caregivers are uncomfortable in providing home care
  - weight loss suggesting dehydration and potential circulatory compromise
  - persistent vomiting beyond two hours (particularly in young children)
  - altered neurological status (e.g. mental confusion and loss of consciousness) and seizures which may indicate impending cerebral oedema

Emergency medical consultation should be facilitated including transfer of patients to the hospital.

Recommendation 15

- For management of patients with type 1 diabetes mellitus during sick days:
  - insulin should not be omitted
  - blood glucose and blood/urine ketone should be monitored more frequently
  - insulin dose should be adjusted accordingly

14.2 Eating Out

Children and adolescents with T1DM should be allowed to eat out at restaurant, festival, parties or “kenduri” to the same extent as their friends. To ensure that target BG range is maintained when eating out, patients and their caregivers should practise carb counting and insulin adjustment based on the food consumed and level of physical activities.[113 - 114, level III]

The following advice on eating out should be given to patients with T1DM and their caregivers:[113 - 114, level III]

- occasional sugary food treats may not provoke hyperglycaemia if
  - physical activity levels are high
  - insulin dose adjustments are made based on carbohydrate counting, ICR and ISF

- additional (rapid-acting or short-acting) insulin may be useful to prevent or treat hyperglycemia
- BG level should be checked before and after eating out, and the results documented. This infomation will guide patients and their caregivers in planning for similar future occasions
- when eating out, the meal may be served later than usual; to avoid hypoglycaemia, adjust the administration of meal insulin in accordance to the timing of carbohydrate consumption

Recommendation 16
- Patients with type 1 diabetes mellitus having meals outside home should adjust the dose and timing of meal insulin accordingly.
  - Pre- and post-meal blood glucose should be checked when eating out.

14.3 Fasting during Ramadan

Fasting from dawn till sunset, during the month of Ramadan is obligatory for Muslims. During this period, one has to abstain from eating and drinking. Islam has allowed various categories of people to be exempted from fasting, for example young children, sick people and travellers. Major risks associated with fasting in diabetic patients include hypoglycaemia, hyperglycaemia, DKA, dehydration and thrombosis. Nevertheless, many patients with T1DM insist on fasting during Ramadan. Those who intend to fast should have good glycaemic control, perform regular self-monitoring and be under professional supervision.

Patients with T1DM and the following features are at very high risk for complications during fasting:[115, level III]
- severe hypoglycaemia within three months prior to Ramadan
- history of recurrent hypoglycaemia
- hypoglycaemia unawareness
- poor glycaemic control
- DKA within three months prior to Ramadan
- acute illness
- pregnancy
- chronic dialysis

These patients are discouraged from fasting.

Management plan for patients with T1DM who intend to fast should be individualised:[115, level III]

a. **Ramadan-focused patient education**
   Ramadan-focused diabetes education includes the following:
   - Meal planning and dietary advice
   - SMBG

- Adjustment and compliance to insulin therapy
- Focus on the causation, early recognition and emergency management of hypoglycaemia, hyperglycaemia, dehydration and impending DKA
- Timing and intensity of physical activity

b. Pre-Ramadan medical assessment

- Preferably undertaken 1 - 2 months before the fasting month starts
- Include physical status, glycaemic status and appropriate blood tests
- Evaluation for any acute and chronic complications, and individual risk stratification to identify those not fit to fast

c. Diet and nutrition

- Avoidance of large amount of foods rich in carbohydrate and fat during 'iftar'
- Consumption of complex carbohydrate (slow-digesting foods) during 'sahur' (taken as late as possible) will result in delayed digestion and absorption
- Balanced diet with inclusion of fruits, vegetables, lentils, yogurt and cereal
- Liberal fluid intake during non-fasting hours

d. Exercise and physical activity

- Maintain normal level of physical activity
- Avoid rigorous exercise during fasting hours

e. Monitoring glycaemic status

- Blood testing or insulin injection is allowed during fasting (under Fatwa law)
- Encourage patients to do frequent SMBG
- Check urine/blood for ketone if BG is high (>14 mmol/L)

f. Indications to break the fast

- BG levels are low (<4 mmol/L) or experiences signs/symptoms of hypoglycaemia
- BG level is >16.7 mmol/L
- Patient is unwell

g. Insulin regimens

Fasting during Ramadan in T1DM is safe with adjustment of insulin dose and regular BG monitoring.[116, level II-2; 117, level III]

- **Insulin adjustment in patients on basal-bolus regimen**[115, level III]
  - Reduction of basal insulin by 10 - 20% and further if needed.
  - Use rapid-acting insulin with meal and perform carbohydrate counting.

- If glucose rises above 15 mmol/L, a correction dose of rapid-acting insulin should be given.
- If long-acting and rapid-acting insulin are unavailable, it may be sufficient to use intermediate-acting and short-acting insulin.

- **Insulin adjustment in patients on two-dose insulin regimen**
  Premixed insulins are not recommended for paediatric use.[8]

  In a small study, 60% of patients with T1DM on conventional twice-a-day regimen were able to fast safely with proper education and intensive follow-up.[118, level III] Patients are advised to change their insulin dosages such that they take combined intermediate- and short-acting insulin before iftar (break fast), which is their usual morning dose, and only short-acting insulin before sahur (pre-dawn meal) at a dose of 0.1 - 0.2 IU/kg.[115, level III]

- **Insulin adjustment in patients on three-dose insulin regimen** [115, level III]
  - Use short-acting insulin during sahur and iftar.
  - Use intermediate-acting insulin in the late evening.
  - Perform frequent SMBG especially
    - before iftar and three hours afterwards
    - before sahur and two hours afterwards
  - Adjust insulin dose accordingly.

- **Insulin adjustment in patients on insulin pump**[115, level III]
  Fasting during Ramadan can be successfully accomplished by patients with T1DM if they are fully educated and metabolically stable. Most will need to reduce their basal infusion rate while adjusting the bolus doses to cover the sahur and iftar.

Recommendation 17
- Patients with type 1 diabetes mellitus who intend to fast should receive Ramadan-focused patient education and follow individualised management plan.

14.4 Schooling

Schools and daycare centres have an important role in providing appropriate diabetes care to ensure that patients with T1DM can participate fully and safely in their activities and achieve optimal academic performance.

Individualised diabetes medical management plan in school/daycare centre include:[119, level III]
- blood glucose monitoring: frequency and circumstances
- insulin administration: doses/injection times

- meals and snacks: food content, amounts and timing
- recognition and appropriate treatment of hypoglycaemia/ hyperglycaemia
- participation in physical activity

Schools/daycare centres need to provide the following:[119, level III]

- availability of knowledgeable person in the immediate treatment of hypoglycaemia
- a suitable place for blood glucose monitoring and insulin administration
- permission to carry equipment (including medic alert bracelet) and medication
- permission to snack and drink anywhere if necessary

Hypoglycaemia can occur in patients with T1DM during and after physical activities. It can be prevented by monitoring BG levels before and after exercises, adjusting insulin doses and having supplemental snacks.[120, level III] During long school examinations, blood glucose should be checked immediately prior to and midway to detect hypo/ hyperglycaemia.[8]

Recommendation 18

- Patients with type 1 diabetes mellitus should have individualised diabetes medical management plan in school/daycare centre.

14.5 Travelling

During long distance travel, patients with T1DM need to plan in advance and seek advice wherever necessary. They and their caregivers should be offered education on the practical issues related to such travel.[121] The differing conditions during travel such as sitting still for long hours when in a plane or car, eating food with different carbohydrate contents and the excitement of being in a new place may increase the BG level.[113, level III]

High altitude, heat and humidity can sometimes affect meters and test strips. Be aware of possible false readings.[122, level III] The pressure differences in the cabin can lead to air bubbles accumulation in the insulin cartridges. Leaving the needle on the pen during the flight will allow for pressure equalisation. After landing, prime the insulin injection device to remove any air bubbles before injection.[113, level III]

Management of insulin pump therapy during air travel:[123, level III]

- Before takeoff, disconnect the pump.
- At cruising altitude, take the cartridge out of the pump and remove any air bubbles before re-connecting.
- After landing, disconnect the pump and prime the line with 2 IU of insulin before re-connecting.

Practical advice for patients with T1DM who intend to travel long distance:[113, level III; 122, level III]

- Bring a letter from the attending doctor certifying the condition and treatment.
- Bring a diabetes identity card or medic alert bracelet if available.
- Take extra supply of insulin, needles, pens and SMBG equipment.
- If travelling with others, split the amount of insulin supply between each passenger's hand luggage just in case one of the luggage is lost.
- Do not keep insulin in check-in luggage, as there may be extreme temperature excursions at high altitudes.
- Bring a cool bag to store extra insulin.
- Bring carbohydrate (glucose tablets, sweets, snacks and juices) in the hand luggage to cover any travelling delays in case of hypoglycaemia.
- Find out the types, formulations and strengths of insulin which are available in the area of destination.

Adjustment of insulin doses during long distance air travel[113, level III; 122, level III]
During travelling, insulin adjustment for patients with T1DM is advised as the following:

- Frequent BG monitoring
- Extra doses of mealtime insulin needs to be considered if extra meals are taken
- Timing of insulin administration needs to be adjusted according to the new time zone.
  - Travelling north or south does not require any changes in 24-hour schedule.
  - Travelling east will shorten the day and therefore require less insulin.
  - Travelling west will lengthen the day and therefore require more insulin.

Recommendation 19

- Patients with type 1 diabetes mellitus who wish to travel should have appropriate education and planning with their health care team*.

*Refer to yellow box above

14.6 Surgery

Surgery in children and adolescents with diabetes should be performed at centres with appropriate personnel and facilities. Careful liaison between surgical, anaesthetic and children's diabetes care teams is crucial before admission to the hospital for elective surgery and as soon as possible after admission for emergency surgery.[8]

Management of T1DM children and adolescents undergoing surgery depends on whether the surgery is major or minor.[8]

a. Features of minor surgery/procedure:
   - requires brief general anaesthesia (GA) or no GA
   - duration of surgery usually <2 hours
   - should not have a major impact on glycaemic control
   - patients can usually be discharged from the hospital on the day of surgery
   - include common daycare surgical procedures

b. Features of major surgery:
   - requires prolonged GA
   - duration of surgery usually ≥2 hours
   - greater risks of metabolic decompensation
   - patients are unlikely to be discharged from the hospital on the day of surgery

Pre-surgical assessment[8]

- Assessment of glycaemic control, electrolyte status and ketones should be done several days before surgery.
- If necessary, delay the surgery until glycaemic control has improved.
- If surgery cannot be delayed, admit the patient to the hospital for stabilisation of glycaemic control prior to surgery.

Pre-surgical care[8]

- Patients receiving GA must be admitted to the hospital.
- Schedule the surgery as the first case of the day.
- All patients will require insulin despite fasting to avoid DKA.
- In minor surgery, patients treated with basal/bolus insulin regimen or CSII may initially receive an IV infusion without dextrose except those treated with intermediate-acting insulin.
- In major surgery, IV infusion of dextrose (dextrose 5 - 10%) and frequent BG monitoring are essential. Bedside monitoring of ketone is useful to detect ketonaemia.
- In emergency surgery:
  - check BG, blood/urine ketone concentration and serum electrolytes
  - if ketone is positive or BG levels are high, check blood gases
  - if DKA is present, treat the DKA and delay the surgery

Intraoperative care[8]

- Hourly BG monitoring
- Dextrose infusion and insulin need to be adjusted to maintain BG in the range 5 - 10 mmol/L
- Constant IV insulin infusion is significantly better than SC insulin regime in achieving glycaemic control in the perioperative period. [124, level II-1]

For adjustment of insulin regimen during minor surgery, refer to **Table 7**.

Table 7. Adjustment of insulin regimen during minor surgery

Insulin regimen	Management (morning surgeries)
Twice daily basal (intermediate-acting insulin, insulin detemir or insulin glargine) and rapid-acting or short-acting insulin	• On the morning of the procedure, give 50% of the usual morning dose of intermediate-acting insulin or the full usual morning dose of long-acting insulin (detemir or glargine). • Omit the rapid-acting or short-acting insulin unless it is needed to correct hyperglycaemia.*
Twice daily with premixed insulin	• Give only 50% of the equivalent dose of the basal (intermediate-acting insulin) component.*
Basal-bolus regimen	• If the usual basal insulin is in the morning, give the usual dose of long-acting insulin (glargine or detemir) in the morning of the surgery. • Consider reducing the dose of the long-acting insulin by 20 - 30% if pre-surgical assessment shows persistent low BG levels in the morning. • Omit the rapid-acting or short-acting insulin unless needed to correct hyperglycaemia.*
CSII	• CSII may be continued during procedure. • Secure the placement of SC infusion cannula away from surgical site. • Continue to infuse at the usual basal rate of insulin if the GA is short (<2 hours). • Avoid unnecessary bolus dose of rapid-acting insulin.*

*Commence IV fluids containing dextrose 5 - 10%, as necessary, to prevent hypoglycaemia. Alternatively, IV insulin infusion may be started.

Modified: International Society for Pediatric and Adolescent Diabetes (ISPAD). Pediatric Diabetes. Oxford: Wiley Blackwell; 2014

Adjustment of insulin regimen during major surgery:[8]
- on the evening before surgery, give the usual evening and/or bedtime insulin(s) and bedtime snack
- omit the usual morning insulin dose
- start IV insulin infusion at least two hours before surgery and provide IV maintenance fluids consisting of 5% dextrose and half-normal saline [0.45% natrium chloride (NaCL)] (refer to **Table 8**)

Table 8. Fluid and insulin infusion guides for surgical procedures

(i) Maintenance fluid	
Dextrose (for major surgery and any surgery when intermediate-acting insulin has been given)	• Use 5% dextrose; 10% if there is concern about hypoglycaemia. • If BG >14 mmol/L, use half-normal saline (0.45% NaCl) without dextrose and increase insulin infusion. • Once BG <14 mmol/L, add 5% dextrose.
Sodium	• Use saline 0.45 - 0.9% (77 - 154 mmol/L). • Change to 0.9% saline if plasma sodium concentration is decreasing. • Monitor electrolytes. *There may be a risk of acute hyponatraemia when hypotonic maintenance solutions (i.e. <0.9% NaCl) are used.
Potassium	• Add potassium chloride 20 mmol to each litre of IV fluid after surgery. • Add potassium only if infusion is required for >12 hours.

Example of fluid maintenance calculation:

	Body weight (kg)	**Fluid requirement per 24 hours**
For each kg between	3 - 9	100 mL/kg
For each kg between	10 - 20	Add an additional 50 mL/kg
For each kg over	20	Add an additional 20 mL/kg
(Maximum 2000 mL female, 2500 mL male)		

(ii) Insulin infusion

Preparation of insulin dilution:

- Add soluble (short-acting) insulin 50 IU to 50 mL normal saline (0.9% NaCl), making a solution of 1 IU insulin/mL; attach to syringe pump and label clearly.

BG (mmol/L)	**Infusion rate**
<6 - 7	start infusion at 0.025 IU/kg/hour
8 - 12	0.05 IU/kg/hour
12 - 15	0.075 IU/kg/hour
>15	0.1 IU/kg/hour

- Adjust insulin infusion hourly to maintain blood glucose between 5 and 10 mmol/L.
- Monitor BG hourly.
- If BG <5 - 6 mmol/L, reduce the rate of insulin infusion but **do not stop the insulin** infusion (to avoid rebound hyperglycaemia).
- If BG <4 mmol/L, the insulin infusion may be stopped temporarily **(not >15 min).**

Post-surgical care

- Resume patient's usual diabetes regimen once tolerating orally.

Recommendation 20

- Patients with type 1 diabetes mellitus who require surgery should be referred to hospitals with appropriate personnel and facilities.
  - Pre-operative assessment of glycaemic control, electrolyte status and ketones should be done in advance.
  - Surgery should be scheduled as the first case of the day.
  - To avoid diabetic ketoacidosis, all patients will require insulin despite fasting.
  - Blood glucose monitoring during surgery should be performed hourly and insulin infusion rate adjusted to maintain blood glucose in the range of 5 - 10 mmol/L.

14.7 Partial Remission Phase

In many young patients with T1DM, insulin requirements decrease transiently following initiation of insulin treatment. This partial remission phase (honeymoon period) is defined as insulin requirements of <0.5 IU/kg/day with an HbA1c <7%. The onset starts within days or weeks of insulin therapy initiation and may persist for weeks to months. BG levels are frequently stable within the target range, despite fluctuations in diet and exercise. The probability of partial remission phase is reduced in those with DKA at presentation and young age.[8]

Recommendation 21

- Patients with type 1 diabetes mellitus and caregivers should receive education on the transient nature of the partial remission phase.

15. SUPPLEMENTS/COMPLEMENTARY MEDICATIONS

Complementary and alternative medicine may include medicinal (such as herbal remedies, dietary supplements, vitamins and minerals, naturopathic and homeopathic remedies) or nonmedicinal remedies (such as chiropractic, osteopathy and naturopathy).

Patients with T1DM and their caregivers should be informed about the danger of omitting insulin when seeking alternative treatments. DKA and death due to insulin omission have been reported and therefore patients should never reduce or omit insulin unnecessarily while on alternative treatment.[125, level III]

There is insufficient evidence to support the use of supplements or complementary medications in patients with T1DM. Unsupervised use may cause adverse effects to the patients.

Recommendation 22

- Patients with type 1 diabetes mellitus and their caregivers should be informed that unsupervised use of supplements or complementary medications may cause adverse events.

16. LONG-TERM COMPLICATIONS

In Malaysia, the common T1DM complications detected in children older than 10 years are microalbuminuria (7.3%), nephropathy (3.2%), retinopathy (2.4%) and neuropathy (0.8%). Good metabolic control (HbA1c <7.5%) is only seen in 25.0% of the patients while more than half of them (54.2%) have poor metabolic control with HbA1c >10.0%.[4, level III]

Apart from that, only 11.3% carried the medic alert and almost all did not keep glucagon at home. A substantial proportion of patients with T1DM reported that they had consultation with the dietitian (41.1%), diabetes nurse educator (30.7%), ophthalmologist (55.7%) and psychologist (4.0%) in the past 12 months. Approximately 11.0% reported having participated in diabetes camp in the past 12 months.[4, level III]

It is important to maintain good glycaemic control in patients with T1DM to prevent long-term complications. The suggested screening schedule is shown in the table below.

Table 9. Screening, risk factors and interventions for vascular complications in T1DM

Complications	Screening schedule	Screening methods	Risk factors	Potential interventions
Retinopathy	• Start at age 10 or at onset of puberty if this is earlier, after 2 - 5 years' diabetes duration • Annually thereafter	• Fundal photography or • Mydriatic ophthalmo-scopy (less sensitive)	• Hyperglycaemia • High BP • Lipid abnormalities • Higher BMI	• Improved glycaemic control • Laser therapy
Nephropathy	• Start at age 10 or at onset of puberty if this is earlier, after 2 - 5 years' diabetes duration • Annually thereafter	• Urinary albumin: creatinine ratio (ACR) or • First morning urinary albumin concentration or • Timed urine collections for albumin excretion rates (AER)	• Hyperglycaemia • High BP • Lipid abnormalities • Smoking	• Improved glycaemic control • ACEi or ARB • BP control
Neuropathy	Unclear	History and physical examination	• Hyperglycaemia • Higher BMI	Improved glycaemic control
Macrovascular disease	After age 10 years	• Lipid profile every 5 years • BP annually	• Hyperglycaemia • High BP • Lipid abnormalities • Higher BMI • Smoking	• Improved glycaemic control • BP control • Statins

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BMI=body mass index; blood pressure (BP)

Modified: International Society for Pediatric and Adolescent Diabetes (ISPAD). Pediatric Diabetes. Oxford: Wiley Blackwell; 2014

16.1 Nephropathy

The incidence of persistent microalbuminuria was 4.6/1,000 patient-years (95% CI 3.3 to 6.1) in Australian youth with a mean HbA1c of 8.4%. The group that developed microalbuminuria had a higher HbA1c (9.1%); median diabetes duration at the onset of persistent microalbuminuria was 9.3 years and the earliest case was 1.6 years after diagnosis of diabetes.[126, level II-3]

Risk factors for microalbuminuria are:[127, level III]

- hypertension (p=0.001)
- higher HbA1c levels (p=0.001)
- longer diabetes duration (p=0.036)
- dyslipidaemia (p=0.034)

The first clinical sign of nephropathy is elevation of albumin excretion. This is generally defined as any of those below:[8]

i. AER of 20 - 200 µg/min
ii. AER of 30 - 300 mg/24 hours
iii. albumin concentration of 30 - 300 mg/L (early morning urine sample)
iv. ACR 2.5 - 25 mg/mmol in males and 3.5 - 25 mg/mmol in females (early morning urine sample)

Spot urine ACR is closely correlated with 24-hours urine albumin excretion in patients with T1DM (R^2=0.828, $p<0.001$).[128, level III]

Because of biological variability, two of three consecutive urine collections over a period of 3 - 6 months should be used as evidence of microalbuminuria. Abnormal screening tests should be repeated as microalbuminuria may not be persistent.[8]

When interpreting urine microalbuminuria, false positive results should be considered which may occur in the following conditions:[8]

- exercise
- menstrual bleeding
- infections
- fever
- kidney diseases
- marked hyperglycaemia

ACEi or ARB should be used in adolescent patients with persistent microalbuminuria to prevent progression to proteinuria. An important safety issue related to the use of both medications is the potential risk of congenital malformation when used during pregnancy. Therefore, adolescent girls need to be informed about this risk and advised on contraception before starting medication.[8] Patients with transient microalbuminuria generally do not need to be treated with ACEi or ARB.

16.2 Retinopathy

Assessment for retinopathy in patients with T1DM should be performed by an ophthalmologist or any trained healthcare provider through dilated pupils. Initial eye examination should also be considered to detect major refractive errors or cataracts. The frequency of retinopathy screening in general should be done annually and more frequently if there are high risk features for visual loss. Biennial assessment by fundal photography should be performed for those with:[8]

- diabetes duration <10 years
- minimal background retinopathy on fundus photography
- reasonable glycaemic control

The prevalence of diabetic retinopathy is higher in pubertal than in pre-pubertal patients, for any grade of diabetic retinopathy (p=0.002).[129, level III] At 10 years follow-up in EDIC study, adults in the former intensive group continued to show slower progression of diabetic retinopathy than those in the conventional group (hazard reduction of 56%, p<0.0001). However, this beneficial effect was not seen in adolescents (hazard reduction of 32%, p=0.13).[68, level II-2]

16.3 Neuropathy

Based on nerve conduction study, 57% of children with a mean diabetes duration of 8.1+2.6 years and a mean HbA1c of 9.0+1.0% had diabetic neuropathy. Using nerve conduction study as a gold standard, the sensitivity and specificity of vibration perception thresholds were 62% and 65% respectively, while the sensitivity and specificity of tactile perception thresholds were 19% and 64% respectively.[130, level III]

16.4 Macrovascular Complications

Aortic intima media thickness is greater in T1DM children compared with control subjects (p<0.001). It is correlated with HbA1c (r=0.31, p=0.01) and is independently associated with age (p=0.001) and low-density lipoprotein (LDL) cholesterol level (p=0.001). Vascular function is worse in children with T1DM who have an aortic intima media thickness >95th percentile compared with control subjects.[131, level II-2]

Factors independently correlated with carotid intima media thickness in children are:[132, level II-2]

- type 1 diabetes (p<0.001)
- systolic blood pressure (p<0.001)
- LDL cholesterol level (p<0.001)

Age-adjusted pulse wave velocity-trunk (aorto-femoral) indicating vascular stiffness is higher in subjects with T1DM than non-diabetic subjects (p<0.05).[133, level II-2]

Recommendation 23
- Screening for vascular complications of type 1 diabetes mellitus should be done to detect early changes and reduce the risk of long-term complications.
  - Screening for retinopathy and microalbuminuria should start from 10 years of age or at pubertal onset, with 2 - 5 year diabetes duration*.

*Refer to **Table 9.**

16.5 Other Complications

i. Dyslipidaemia

Young patients with T1DM demonstrate significantly higher levels of total cholesterol, LDL, triglyceride, lipoprotein(a) and apolipoprotein B compared to non-diabetics.[134, level III]

Screening for dyslipidaemia should be done soon after diagnosis in all children with T1DM aged >10 years old. If the result is normal, it should be repeated every five years. In those with strong family history of hypercholesterolaemia, premature cardiovascular disease or if the family history is unknown, screening should be performed as early as two years old.[8] Refer to **Table 9**.

If the LDL is high (>2.6 mmol/L), intervention to improve metabolic control, dietary changes and exercise should be emphasised. Although long-term safety is not established, statin should be considered in children >10 years old if LDL is >4.1 mmol/L (or >3.4 mmol/L if one or more cardiovascular risk factors is present) despite the above interventions.[8]

Recommendation 24
- Lipid profile should be screened every five years in patients with type 1 diabetes mellitus aged >10 years old or at an earlier age if there is family history of premature cardiovascular disease or hypercholestrolaemia.

ii. Hypertension

Hypertension is defined as average systolic blood pressure and/or diastolic pressure (measurements on ≥3 occasions) >95th percentile for gender, age and height on three occasions. Confirmation of hypertension may be assisted by 24-hour ambulatory blood pressure measurements. Pre-hypertension is defined as BP that is between 90thand 95th percentile.[8]

The prevalence of hypertension in young patients with T1DM based on ambulatory blood pressure monitoring is 28.4%.[135, level III] In a study on patients with average HbA1c between 6.5 to 10.7%, the cumulative mortality rate was 35% in adulthood from coronary artery disease compared with 4 - 8% in the general population. Female adolescents and young adults with T1DM have more centrally distributed fat than male which increases their cardiovascular risk.[136, level III] ACEi are recommended for use in children with diabetes and hypertension. They have been shown to be effective and safe in children in short-term studies but are not safe during pregnancy.[8]

BP should be measured with an appropriate cuff at least annually in patients with T1DM. Refer to **Table 9**.

Recommendation 25
- Blood pressure should be measured at least annually in patients with type 1 diabetes mellitus.

iii. Limited joint mobility

Limited joint mobility (LJM) is a bilateral painless contracture of the finger joints and large joints, and associated with tight skin. It can be demonstrated by asking the patient to approximate palmar surfaces of the interphalangeal joints. Passive examination is essential to confirm that inability to do so is due to LJM. This deformity usually appears after the age of 10 years. The progression from mild to moderate or severe changes ranges from a few months to four years, following which stabilisation occurs. For every unit increase in average HbA1c, there is an approximately 46% increase risk of developing LJM. LJM is associated with a two- to four-fold risk for retinopathy, nephropathy and neuropathy.[8]

iv. Lipodystrophy (lipoatrophy and lipohypertrophy)

Lipohypertrophy is a frequent complication of insulin therapy. It has been found up to 48% in those with T1DM and is associated with higher HbA1c, greater number of injections and longer duration of diabetes. The lesion can be detected by both visualisation and palpation of the injecting sites. The affected site cannot be pinched tightly together in contrast to normal skin. The independent risk factors for lipohypertrophy are:[8]
- lack of rotation in injection sites
- use of small injection zones
- reuse of needles

Insulin may be absorbed unpredictably from these areas, affecting BG control. Treatment of lipohypertrophy involves avoidance of the affected sites for at least 2 - 3 months, while prevention strategies include avoidance of its risk factors as mentioned above.[8]

With the use of human insulin, lipoatrophy is now rarely seen and is reported in <1% of patients with T1DM. It has also been associated with Hashimoto's thyroiditis and coeliac disease resulting in speculation that an immune complex-mediated inflammation may contribute to its development.[8]

17. REFERRAL

The ongoing care of children and adolescents with T1DM requires the care of a specialised diabetes team consists of paediatric endocrinologists, paediatricians, paediatric diabetes nurses, dietitians, psychologists/psychiatrists and often consultations with the ophthalmologists. In hospitals without these services, paediatric endocrine specialists can provide consultation at intervals to guide the management of complicated cases. The recommendations for referral to paediatric endocrine service below are formulated based on the expert opinion of the DG CPG.

Recommendation 26

- Referral of children and adolescents with type 1 diabetes mellitus to paediatric endocrinologists should be made in the following conditions:
  - uncertainty with classification of diabetes
  - difficult metabolic control
  - concomitant co-morbidities and other management issues
  - inadequate resources and expertise in management

18. IMPLEMENTING THE GUIDELINES

It is important to standardise the management of T1DM at all healthcare levels in Malaysia by using an evidence-based CPG. This aims to prevent long-term morbidity and mortality.

a. Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

i. wide dissemination of the CPG to healthcare providers (hard- and soft-copies)
ii. regular T1DM update for healthcare providers
iii. national T1DM registry (DiCARE)
iv. diabetes camp

Existing barriers for application of the recommendations of the CPG are:

i. poor understanding/limited knowledge on diagnosis and management of the T1DM
ii. insufficient resources in the management of T1DM:
    - expertise: paediatric endocrinologist, pediatrician with a special interest in diabetes, child psychiatrist, psychologist, clinical paediatric nurse educator, paediatric-trained dietitian
    - diagnostic tools: antibody testing and blood ketone monitoring

- medications: insulin analog
- medical equipments: glucometer, glucose testing strips, lancets, insulin pump, CGMS

iii. variation in clinical management and preferences

b. Potential Resource Implications

To implement the CPG, there must be strong commitment to:-

i. ensure widespread distribution of the CPG to healthcare providers via printed and electronic copies
ii. train (with adequate funding) healthcare providers by regular seminars or workshops to provide up-to-date information
iii. provide sufficient resources in the management of T1DM including expertise, diagnostic tools, medications and medical equipment
iv. develop and disseminate patient education materials through various activities such as diabetes camp
v. ensure sustainability of DiCARE

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:

$$\text{Percentage of patients with T1DM who have at least one HbA1c per year*} = \frac{\text{Number of patients with T1DM who have at least one HbA1c per year in a period}}{\text{Total number of patients with T1DM in the same period}} \times 100\%$$

*Target: 90%

$$\text{Percentage of patients with T1DM having reduction in HbA1c by at least 0.5% from the previous reading} = \frac{\text{Number of patients with T1DM having reduction in HbA1c by at least 0.5% from the previous reading in a period}}{\text{Total number of patients with T1DM in the same period}} \times 100\%$$

$$\text{Percentage of patients with T1DM admitted due to DKA*} = \frac{\text{Number of patients with T1DM admitted due to DKA in a period}}{\text{Total number of patients with T1DM on follow-up in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH. They are such as a Quick Reference and a Training Module.

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Appendix 1

Example of Search Strategy

The following MeSH terms or free text terms were used either singly or in combination, search was limit to English, humans, all child (0 to 18 years) and 1994 to current:-

1. DIABETES MELLITUS, TYPE 1/
2. diabetes adj1 (autoimmune or juvenile onset or juvenile-onset).tw.
3. iddm.tw.
4. diabetes mellitus adj1 (insulin dependent or insulin-dependent or juvenile onset or juvenile-onset or type 1 or type i or ketosis prone or ketosis-prone).tw.
5. 1 or 2 or 3 or 4
6. INSULIN/
7. INSULIN ASPART/
8. INSULIN, ISOPHANE/
9. INSULIN LISPRO/
10. INSULIN, LONG-ACTING/
11. INSULIN, REGULAR, HUMAN/
12. INSULIN, SHORT-ACTING/
13. insulin.tw.
14. insulin therapy.tw.
15. (insulin adj1 (soluble or regular or aspart or isophane or nph or neutral protamine hagedorn or protamine zinc or lispro or long acting or long-acting or regular human or rapid acting or rapid-acting or short-acting or short acting)).tw.
16. novorapid.tw.
17. novolog.tw.
18. lispro.tw.
19. humalog.tw.
20. humulin s.tw.
21. humulin.tw.
22. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 5 and 22
24. limit 23 to (english language and humans and “all child (0 to 18 years)” and (meta analysis or randomized controlled trial or systematic reviews) and last 20 years)

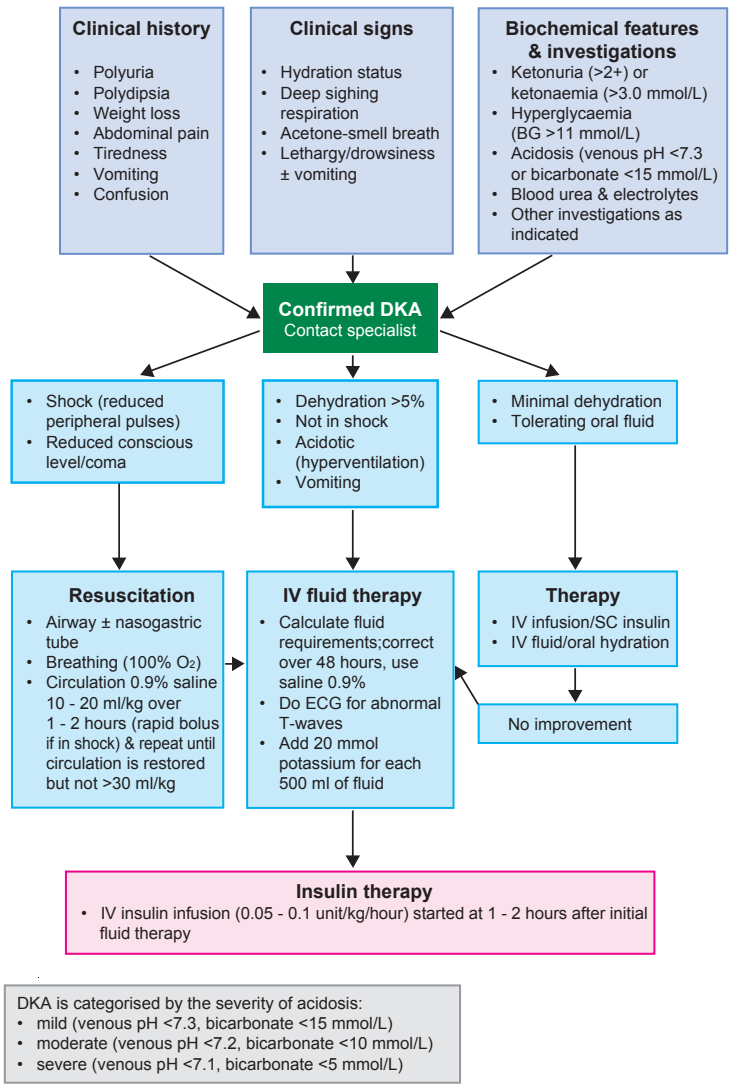
Appendix 2

Clinical Questions

1. How to diagnose T1DM?
2. What are the risk factors of T1DM?
3. What are the common co-morbidities in T1DM?
4. What are the treatment goals in T1DM?
   - optimal HbA1c levels
   - range of ideal blood glucose levels
   - growth and puberty
5. How to treat newly diagnosed T1DM?
6. What are the effective/safe insulin regimens in T1DM?
   - pre-school children
   - school going children
   - adolescents
7. How is self-adjustment of insulin dose done in T1DM?
8. What are the effective/safe medical nutrition therapies in T1DM?
9. Which are the personal and psychological factors associated with metabolic control and self-care in TIDM?
   What is the appropriate psychosocial support in T1DM?
10. Are physical activities safe/effective in T1DM?
11. What is the safe/effective home or self-monitoring blood glucose in T1DM?
12. What is the safe/effective insulin therapy in special situations?
    - sick day
    - eating out
    - fasting
    - schooling
    - travelling
    - surgery
    - exercise
    - partial remission phase
13. Are supplements/complementary medications safe/effective in T1DM?
14. What are the long-term complications of T1DM?
    How and when to screen for the complications?
15. What are the referral criteria for T1DM?

Appendix 3

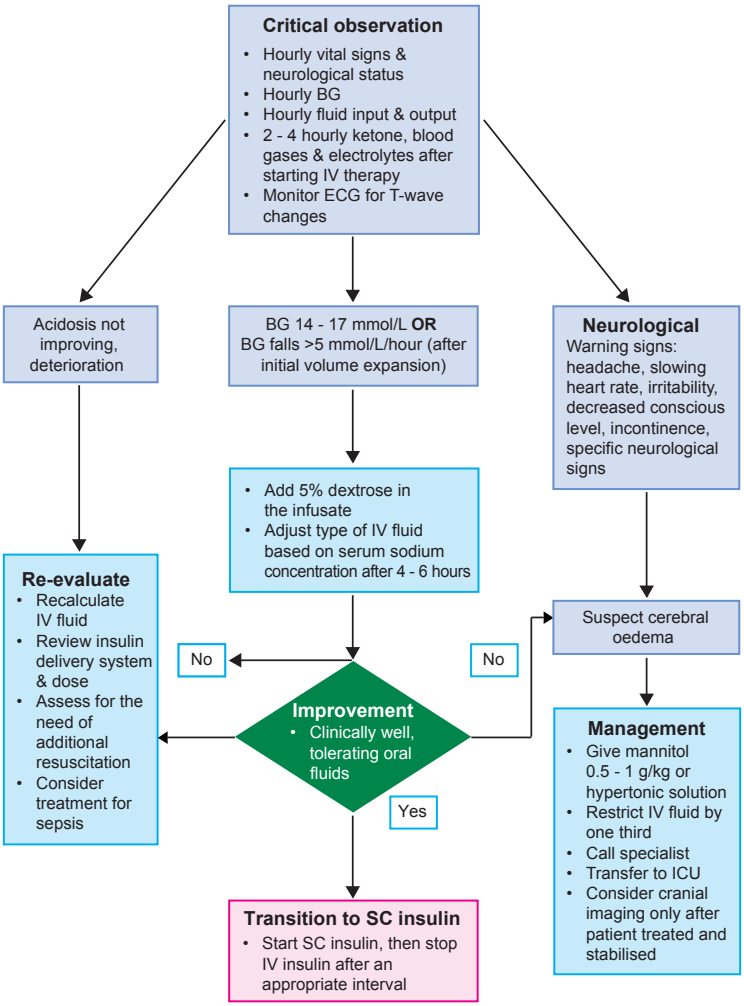
Algorithm 1. Immediate Assessment in DKA



Modified: International Society for Pediatric and Adolescent Diabetes (ISPAD). Pediatic Diabetes. Oxford: Wiley Blackwell; 2014

Appendix 4

Algorithm 2. Critical Observation in DKA



Modified: International Society for Pediatric and Adolescent Diabetes (ISPAD). Pediatic Diabetes. Oxford: Wiley Blackwell; 2014

Appendix 5

Types of Insulin Preparations and their Action Profiles

Generic name	Onset of action	Peak of action (hour)	Duration of action (hour)	Timing of injection
Rapid-acting insulin • Aspart • Lispro • Glulisine	 10 - 20 min 0 - 15 min 5 - 15 min	 1 - 3 1 1 - 2	 3 - 5 3.5 - 4.5 3 - 5	5 - 15 min before or immediately after meals
Short-acting insulin	30 min	1 - 4	6 - 8	30 min before meals
Intermediate-acting insulin [neutral protamine Hagedorn (NPH)]	1 - 1.5 hour	4 - 12	16 - 23	Pre-breakfast/ pre-bed
Long-acting insulin • Glargine • Detemir	 2 - 4 hour 1 hour	 Peakless Peakless	 20 - 24 17 - 23	Same time everyday at anytime of the day
Premixed human (30% short-acting insulin + 70% NPH)	30 min	Dual	16 - 23	30 - 60 min before meals
Premixed analog • 30% aspart + 70% aspart protamine • 25% lispro + 75% lispro protamine	 10 - 20 min 0 - 15 min	 Dual Dual	 18 - 23 16 - 18	5 - 15 min before meals

Source: Perkhidmatan Diabetes dan Endokrinologi, Kementerian Kesihatan Malaysia. Practical Guide to Insulin Therapy in Type 2 Diabetes Mellitus. Putrajaya: MoH; 2010

Insulin Approval by U.S. Food and Drug Administration (FDA), and European Medicines Agency (EMEA)

Type of Insulin	Approved by FDA for (studied from age)	Approved by EMEA from age
Insulin lispro	"adults and children" (3 years)	"adults and children"
Insulin aspart	"adults and children" (2 years)	≥2 years
Insulin glulisine	"adults and children" (4 years)	≥6 years
Insulin detemir	"adults and children" (2 years)	≥1 year
Insulin glargine	"adults and paediatric patients" (6 years)	≥2 years
Insulin degludec	"adults" (18 years)	≥1 year

Source: U.S. Food and Drug Administration (Available at http://www.fda.gov/)
European Medicine Agency (Available at http://www.ema.europa.eu/ema/)

Appendix 6

Dietary Fibre Content of Common Foods

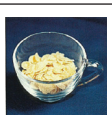
High Fibre (5+ g)	Medium Fibre (2 - 4 g)	Low Fibre (<2g)
Starchy Foods and Cereals Multi whole grain fibre meal bread,1 slice	Rye bread, 1 slice Whole-wheat, 1 slice Whole-wheat pasta, ½ cup	Hamburger/hotdog bun, ½ Plain dinner roll, 1 small White bread, 1 slice
Cereals (ready-to-eat) All bran R, ½ cup 100% bran R, ⅓ cup	Shredded wheat R, 1 biscuit	Rice krispies R, ⅔ cup Special K R, 1 cup Corn flakes, ¾ cup
Cooked cereals Oat bran, 1 cup	Oatmeal, 1 cup	
Grains Barley, cooked, ½ cup	Bran, natural 1 tablespoon (tbsp) Brown rice, cooked, ½ cup Wheat germ, 1 tbsp	White rice, cooked, ½ cup
Cookies/crackers Rye crackers, 1 triple	Oat crackers, 2	Soda crackers, 6 pieces
Pastas Whole-wheat pasta, 1 cup		Macaroni, noodles Spaghetti, cooked, ½ cup
Starchy vegetables Dried beans, peas, legumes, cooked, ½ cup	Corn, canned, whole kernel, ½ cup Corn-on-the-cob, 1 small Potato, whole, cooked, with skin, ½ Sweet potato with skin, ½ Yam, cooked, ½ cup cubes Miso, paste, 3 tbsp	Corn, canned creamed, ½ cup Potato, whipped, no skin, ½ cup Potato, whole, no skin, ½ cup
Fruits Apple, raw with skin, 1 medium Figs/dates, 10 Kiwi fruit, 2 medium Mango, 1 medium Pear, raw, 1 medium Prunes, dried, 5	Apple, raw, no skin, 1 medium Orange, raw, 1 small Raisins, 2 tbsp Prune juice, 1 cup	Grapes, 8 Honeydew melon, 1 slice Pineapple, raw, 1 slice Watermelon, 5" triangle Most fruits and vegetable-based juice (apple, orange) 1 cup
Vegetables Green peas, fresh, frozen or canned, ½ cup Snow peas, 10 pods	Bean sprouts, ½ cup Beans, string, ½ cup Broccoli, ½ cup Carrots, raw, ½ cup Eggplant, ½ cup Ladies fingers, ½ cup Vegetables, mixed, ½ cup	Asparagus, cooked, 6 spears Cabbage, raw, 1 cup Lettuce, iceberg, 1 cup Cauliflower, raw, ½ cup Celery, raw, ½ cup Cucumber, raw, ½ cup Mushrooms, raw, ½ cup Mustard greens, fresh cooked, ½ cup Spinach, raw, 1 cup Tomatoes, raw, 1 cup
Nuts and seeds Almonds, 1 oz	Peanut butter, smooth, crunchy, 2 tbsp Peanuts (15), 1 oz Sunflower seeds, with kernels, 2 tbsp Watermelon seeds, 2 tbsp Sesame seeds, 2 tbsp	Coconut, 2 tbsp Walnuts, 2 tbsp

Source: Malaysian Dietitians' Association. Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus. Kuala Lumpur: MDA; 2013

Appendix 7

Food Group and Exchange Lists for 15 g Carbohydrate
Cereals, Grain Products and Starchy Vegetables

Each item contains 15 g carbohydrate, 2.0 g protein,
0.5 g fat and 75 calories

Cereals, Grain & Bread		
 Rice, white unpolished (cooked), ½ cup or ⅓ chinese rice bowl	 Mee hoon, ½ cup or ⅓ chinese rice bowl	 Biscuits, (plain, unsweetened), 3 pieces
 Rice porridge, 1 cup	 Kuey-teow, ½ cup or ⅓ chinese rice bowl	 Biscuits, (small, thin, salted, 4.5 x 4.5 cm), 6 pieces
 Putu mayam,1 piece (40 g)	 Mee, wet, ½ cup or ⅓ chinese rice bowl	 Bread (wholemeal, high fibre, white/brown), 1 slice (30 g)
 Oats, uncooked, ½ cup or 3 rounded tbsp	 Noodle, laksa, wet, ⅔ cup	 French bread, 2 pieces
 Potato, 1 small	 Macaroni, cooked, ⅔ cup	 Pumpkin, 1 cup (100 g)
 Barley, pearl, uncooked ¼ cup	 Cornflakes, ½ cup	 Sweet potato, ½ cup

Fruits

Each item contains 15 g carbohydrate and 60 calories

Fruits		
 Apple, 1 medium	 Grapes, 8 pieces	 Banana, 1 small (60 g)
 Guava, ½ fruit	 Dates, dried, 3 small pieces	 Sapodilla (ciku), 1 medium
 Limau, 1 medium	 Chestnuts, 7 whole	 Jackfruit, 4 without seeds
 Orange, 1 medium	 Prune, 3 small whole without seeds	 Pineapple, 1 slice
 Pear, 1 medium	 Honeydew, 1 slice	 Pumpkin, 1 cup (100 g)
 Pear, yellow, Chinese, 1 medium	 Duku, 6 whole	 Raisin, 1 dessert spoon, heap (20 g)

Source: Malaysian Dietitians' Association. Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus. Kuala Lumpur: MDA; 2013
Suzana S, Nik Shanita S, Zahara AM, et al. Malaysian Atlas of Food Exchanges and Portion Sizes. Kuala Lumpur: MDC; 2015

Appendix 8

Carbohydrate Exchange for Sugars

Each item contains 15 g carbohydrate

Honey	:	1 tablespoon level (21 g)
Kaya	:	3 tablespoons level (30 g)
Jam	:	1 tablespoon level (21 g)
Sweets	:	1 - 2 pieces
Sugar (brown)	:	3 ½ teaspoons level (18 g)
Sugar (white)	:	3 teaspoons level (15 g)
Rose syrup	:	3 ½ teaspoons level (18 g)
Condensed milk	:	2 tablespoons level (30 g)
Cocoa/malt-based powder	:	1 ½ tablespoon level (21 g)

Source: Malaysian Dietitian's Association. Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus. Kuala Lumpur: MDA; 2013

Glycaemic Index (GI) for Local Malaysian Foods

Food Categories	Low GI (≤55)	Intermediate GI (56 - 70)	High GI (>70)
Rice	Barley	Basmati rice Brown rice Parboiled rice Red rice	Glutinous rice Jasmine rice Instant porridge White rice Sago
Bread and cereals products	All bran breakfast cereals Muesli Wholegrain bread varieties	Capati Idli Oatmeal Pita bread, wholemeal Wholemeal barley flour bread	Cornflakes Rice crackers Roti canai White flour bread Wholemeal (whole wheat) wheat flour bread
Noodle and pasta	Lasagne pasta sheets Spaghetti, white, boiled Spaghetti, wholemeal, boiled	Spaghetti, white, durum wheat semolina Udon noodles, plain Wheat noodles	Fried macaroni Fried meehoon Fried rice noodles Rice noodle *(kuey-teow)*
Milk	Full fat milk Low fat milk Skim milk Soy milk (without added sugar) Yogurt	Ice cream Sweetened condensed milk	*Teh tarik*
Fruit	Apple Mango Oranges Plum	Banana Dates Papaya Pineapples Raisin	Lychee Watermelon
Legumes	Baked beans Chickpeas Lentils Mung bean		
Tuber	Cassava, boiled Sweet potato, boiled	Pumpkins, boiled Sweet corn, boiled	Potato, boiled

Source: Ministry of Health, Malaysia. Management of Type 2 Diabetes Mellitus. Putrajaya: MoH; 2015

LIST OF ABBREVIATIONS

βOHB	β-hydroxybuterate
µg	microgramme
ACEi	angiotensin converting enzyme inhibitor
ACR	albumin:creatinine ratio
ARB	angiotensin receptor blocker
AER	albumin excretion rates
aTPO	anti-thyroid peroxidase antibody
BG	blood glucose
BMI	body mass index
BP	blood pressure
carb	carbohydrate
CI	confidence interval
CGM(S)	Continuous Glucose Monitoring (System)
CPG(s)	clinical practice guidelines
CSII	continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
DG	Development Group
DiCARE	Malaysian Diabetes in Children and Adolescents Registry
DKA	diabetic ketoacidosis
dL	desilitre
ECG	Electrocardiogramme
EDIC	Epidemiology of Diabetes Interventions and Complications
g	gramme
GA	general anaesthesia
GAD	glutamic acid decarboxylase
GI	glycaemic index
HbA1c	glycated haemoglobin
IAA	insulin autoantibodies
ICA	anti-islet antibody
ICA512 or IA2A	protein tyrosine phosphatase antibody
ICR	insulin to carbohydrate ratio
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IM	intramuscular
IQR	interquartile range
ISF	insulin sensitivity factor
ISPAD	International Society for Pediatric and Adolescent Diabetes
IU	international unit
IV	intravenous
kcal	kilocalorie
kg	kilogramme
L	litre
LDL	low-density lipoprotein
LJM	limited joint mobility
MDI	multiple daily injections
mg	milligramme
min	minutes
ml	millilitre
mmol	millimol

MUFA	monounsaturated fatty acids
MoH	Ministry of Health
NaCl	natrium chloride
NPH	neutral protamine Hagedorn
OGTT	oral glucose tolerance test
OR	odds ratio
pCO2	partial pressure of carbon dioxide
PUFA	polyunsaturated fatty acids
RC	Review Committee
RCT(s)	randomised controlled trial(s)
SMBG	self-monitored blood glucose
SC	subcutaneous
SMBG	self-monitoring of blood glucose
SMD	standardised mean difference
T1DM	type 1 diabetes mellitus
tbsp	tablespoon
TDD	total daily insulin dose
TSH	thyroid stimulating hormone
WMD	weighted mean difference
ZnT8	zinc transporter 8

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Malaysia Health Technology
Assessment Section (MaHTAS)
Medical Development Division,
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government
Administrative Centre
62590, Putrajaya, Malaysia