Hyperglycaemia

Definition / Supporting Information

Hyperglycaemia

- A term for describing excess glucose in the blood often associated with diabetes, defined by the World Health Organization [WHO] as:
  - Fasting plasma glucose levels > 7 mmol/L when fasting
  - Plasma glucose levels > 11.1 mmol/L 2 hours after meals
- It is worth noting that hyperglycaemia is also commonly associated with stress and illness in children and neonates

Diabetes mellitus

- Heterogeneous group of conditions with diverse underlying pathophysiological factors that result in elevated blood glucose levels

Type 1 diabetes (T1D)

- Elevated blood glucose level caused by autoimmune destruction of the pancreas leading to an absolute insulin deficiency

Type 2 diabetes (T2D)

- Caused by a relative insulin deficiency, peripheral resistance to the action of insulin, or both

Maturity-onset diabetes of the young (MODY)

- Monogenic inherited defect in pancreatic β-cells secondary to an autosomal dominant mutation [Diabetes UK]
- Diabetes mellitus usually occurs in adolescence or young adulthood

Neonatal diabetes mellitus (NDM)

- Diabetes diagnosed in the first 6 months of life
- May be transient (resolution by 12 months of age) or permanent
- > 90% of cases of permanent neonatal diabetes mellitus are caused by a KCNJ11 *or* ABCC8 genetic change
  - This affects the link between sensing of glucose levels and release of insulin from the pancreatic β-cell

Nonimmune-mediated severe insulin deficiency

- Caused by conditions such as cystic fibrosis or pancreatectomy

Gestational diabetes

- Caused by insulin resistance occurring during pregnancy

Keywords / also known as: high blood sugar, raised glucose levels

Essential History

Ask about:

- Family history
- T1D
  - Polyuria
  - Polydipsia
  - Significant weight loss
  - Fatigue
  - Abdominal pain
  - Nausea
- T2D
  - Patients may be asymptomatic
  - Polyuria
  - Polydipsia
  - Insulin resistance
    - Acanthosis nigricans (eg, areas of thickened, dark, velvety discolouration in body folds and creases particularly nape of neck, axillae and groin)
    - Obesity
    - Hypertension
- MODY
  - Strong family history of diabetes (first degree relative and / or spanning two or more generations)

‘Red Flag’ Symptoms and Signs

Ask about:

- Significant weight loss
- Polydipsia, polyuria, or abdominal pain

Look for:

- Clinical dehydration
- Acidotic ‘Kussmaul’ breathing
- Nausea / vomiting

- Altered mental status

Differential Diagnosis / Conditions

- Hyperglycaemia from any cause can lead to symptoms related to an osmotic diuresis
- Glycosuria
  - Glucose may be seen in the urine of some normoglycaemic individuals
    - Glycosuria alone cannot be used to diagnose diabetes mellitus
- Because of the glycosuria, the child with T1D loses calories
  - This manifests as weight loss although there is increased appetite
- Causes other than T1 or T2 diabetes mellitus that may lead to hyperglycaemia:
  - Other forms of diabetes
    - Neonatal diabetes
    - Gestational diabetes
    - MODY
  - Genetic defects in insulin action
    - Type A insulin resistance
    - Leprechaunism
    - Rabson-Mendenhall syndrome
  - Diseases of the exocrine pancreas
    - Pancreatitis
    - Trauma / pancreatectomy
    - Neoplasia
    - Cystic fibrosis
    - Haemochromatosis
  - Endocrinopathies
    - Aldosteronoma
    - Cushing's syndrome
    - Glucagonoma
    - Growth hormone excess / acromegaly
    - Hyperthyroidism
    - Phaeochromocytoma
    - Somatostatinoma
  - Drug- or chemical-induced
    - Ciclosporin
    - Diazoxide
    - Glucocorticoids
    - Nicotinic acid (in overdose)
    - Pentamidine
    - Sirolimus

        - Tacrolimus
        - Thiazides
    - Stress of illness and sepsis
    - Uncommon forms of immune-mediated diabetes
        - Stiff-person syndrome (SPS)
        - Anti-insulin receptor antibodies
        - Hyperosmolar hyperglycaemic nonketotic syndrome (HHNS)

Investigations

To be undertaken by non-specialist practitioner (eg, General Practitioner (GP) Team(s) / General Paediatrician):

- Diagnostic features
    - Symptoms of diabetes
        - Polyuria, bedwetting, and new daytime incontinence [NICE guideline NG18]
        - Polydipsia
        - Unexplained weight loss
    - Random plasma glucose level ≥ 11.1 mmol/L
    - Fasting (≥ 8 hours) plasma glucose level ≥ 7 mmol/L
    - Glycated haemoglobin (HbA1c) > 48 mmol/mol (6.5%)
    - Glycosuria
    - **If any of the above present, refer to specialist paediatric services immediately (same day)**
    - **If new onset diabetes is suspected, this should be presumed to be type 1 and an emergency referral to paediatric services should be made**
        - **In primary care, point-of-care (POCT) glucose test and / or a urine dipstick, and POCT glucose > 7 OR glycosuria in the presence of suggestive symptoms should prompt same-day referral to paediatrics services**
- Blood test for HbA1c level
- Oral glucose tolerance test (OGTT)
    - May identify some individuals with T2D
    - Usual cut-off values for diagnosis of diabetes are fasting plasma glucose level > 7 mmol/L and 2-hour plasma glucose level ≥ 11.1 mmol/L
    - OGTT is not a standard assessment pathway to diagnose T1D
- Blood and urine ketone levels
    - Traditionally associated with T1D but occasionally present in patients with T2D
- Insulin and C-peptide concentrations
    - Generally low in established T1D

  - Low C-peptide concentrations can be seen in MODY and T2D with glucose toxicity
    - May make it less helpful at time of diagnosis
- Antibody measurements (T1D)
  - Sensitivity and specificity are not sufficient to warrant routine clinical use
  - Antibodies can be elevated in patients who may not develop disease for many years or ever
  - Islet cell autoantibodies (ICA), insulin autoantibodies (IAA) and glutamic acid decarboxylase 65 antibodies (GAD)
    - Screening bloods for coeliac disease
    - Screening test for thyroid disease
    - Simple fundoscopy for cataract

Treatment Approach

To be undertaken by specialist practitioners (eg, Specialist diabetes multidisciplinary team(s) (MDT)):

- Insulin therapy
- **When T1D is suspected, arrange a same-day referral to paediatric services in case diabetic ketoacidosis (DKA) management is required or to manage insulin therapy as part of the multidisciplinary team**
  - Required in patients with T1D
  - May not always be necessary for children with T2D
  - Safe and effective choice if it is not initially clear whether the patient has T1D or T2D
- Therapy must be tailored to the specific underlying pathophysiological condition
  - Individualised patient education and support is imperative for success
- Management of T1D requires an integrated multidisciplinary team approach
  - Physicians
  - Nurses
  - Diabetes educators
  - Dietitians
  - Social workers
  - Psychologists
  - School or day-care personnel
  - Play therapist for inpatients
- Diabetes caused by excess glucocorticoids or other medications
  - Dose reduction or elimination of the drug (if possible) may be all that is required

To be undertaken by specialist practitioners:

- Plasma glucose control (optimal ranges): [NICE guideline NG18]
  - Fasting plasma glucose level of 4–7 mmol/L on waking
  - Plasma glucose level of 4–7 mmol/L before meals and at other times of the day
  - Plasma glucose level of 5–9 mmol/L after meals
- T1DM
  - Safely achieve as near euglycaemia as possible while minimising adverse events, primarily hypoglycaemia
  - Monitor HbA1c levels
    - Target HbA1C of 48 mmol/mol (6.5%) or lower is ideal to minimise the risk of long-term complications [NICE guideline NG18]
    - Agree a lowest achievable HbA1c target for each (individual) patient
      - Consider factors such as daily activities, individual life goals, complications, comorbidities and the risk of hypoglycaemia
- T2DM
  - Therapy must be tailored to fit the clinical situation of the patient
  - Weight loss and exercise
    - Significantly improve insulin sensitivity
    - Appropriate in the asymptomatic patient with a normal or near-normal HbA1c level
    - May be adequate for maintenance of glycaemic goals in patients who will adhere to dietary and exercise guidelines
  - Pharmacological intervention
    - Consider for patient with:
      - Symptomatic hyperglycaemia
      - Presence of ketones or ketoacidosis
      - Significanty elevated HbA1c level > 6.5%
  - Metformin
    - The only oral agent approved for use in children (licensed for children > 10 years)
    - In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial in youths with T2D, metformin alone achieved durable glycaemic control in only about half of adolescents enrolled
    - In addition to lifestyle changes, metformin should be considered first-line pharmacological therapy for children with T2D
    - Gastrointestinal disturbance is the major side-effect
  - Insulin
    - The only medication approved for the treatment of diabetes in children at all ages

        - Most children with T2D can improve glycaemic control with less intensive treatment programmes than are needed for patients with T1D
        - Once- or twice-daily, intermediate- or long-acting insulin may be sufficient
        - When a patient is experiencing symptoms related to hyperglycaemia, and has HbA1C (> 8%–9%), insulin therapy is usually required
    - Patient education
- Specific insulin programmes
    - All patients taking insulin will need to have a tailored plan for:
        - Type and dose of insulin
        - Timing of injections
        - Frequency of home glucose monitoring
            - At least a minimum of 5 times a day, including before breakfast, lunch, supper and bed time
        - Typical doses of insulin in children
            - 0.5–1 unit of insulin per kg per day
            - During puberty, children require higher insulin doses to achieve the same control
            - For patients with T1D
                - Intermediate- or long-acting insulin is used as the basal insulin
                - A short-acting insulin bolus is used to control the post-meal glucose increase (Figure 1)
        - Short-acting (rapid acting) insulins
            - Regular (Actrapid)
                - Onset: 30 minutes
                - Peak: 1.5–3.5 hours
                - Duration: 7–8 hours
            - Lispro
                - Onset: < 15 minutes
                - Peak: 1 hour
                - Duration: 2–5 hours
            - Aspart
                - Onset: < 15 minutes
                - Peak: 1–3 hours
                - Duration: 3–5 hours
            - Glulisine
                - Onset: < 15 minutes
                - Peak: 1 hour
                - Duration: 3–4 hours

    - Intermediate-acting insulins
        - NPH
            - Onset: 2–4 hours
            - Peak: 4–6 hours
            - Duration: 10–16 hours
        - Lente
            - Onset: 3–4 hours
            - Peak: 6–10 hours
            - Duration: 10–20 hours
    - Long-acting insulins
        - Glargine
            - Onset: 2–3 hours
            - Peak: none
            - Duration: ≥ 24 hours
        - Detemir
            - Onset: 1–2 hours
            - Peak: 3–9 hours
            - Duration: 6–23 hours
            - Higher doses result in delayed peak and longer duration of action
        - Degludec (Tresiba)
            - Onset: 1–3 hours
            - Peak: none
            - Duration: over 24 hours
        - Glargine (U-300) (Toujeo)
            - Onset: 6 hours
            - Peak: none
            - Duration: over 24 hours
- Multiple daily injection (MDI) programme
    - Intermediate or long-acting insulin as the basal insulin
    - Basal insulin
        - Constitutes approximately half of the total daily dose
        - Usually given in the evening
    - Short-acting insulin as a bolus with each meal
        - Requires 3–4 (or more) injections each day
        - More flexibility in timing and content of meals than split-mixed programmes
    - The amount of short-acting insulin given with each meal depends on the amount of carbohydrate consumed at that meal

        - If the patient has been prescribed an exchange diet with a fixed amount of carbohydrate for each meal, the dose of insulin will be the same from day to day
        - Patients who vary carbohydrate consumption will need to adjust insulin accordingly, and monitor carbohydrate intake
        - This regimen employs a correction dose of short-acting insulin if the pre-meal glucose is outside the target range
- Continuous subcutaneous insulin injection (CSII) programme delivered using an insulin pump
    - Cartridge filled with short-acting insulin, which serves as both the basal and bolus insulin
        - Insulin is delivered through tubing connected to a flexible plastic cannula, which is inserted subcutaneously
    - Advantages
        - Pump can be concealed under a person's clothing
        - Multiple basal rates can be programmed for patients whose basal insulin requirements are not constant throughout the day
        - Tubing and cannula are changed every 2–3 days, significantly reducing the number of injections required
        - There may be an improvement in HbA_{1c} in patients treated with CSII compared with MDI

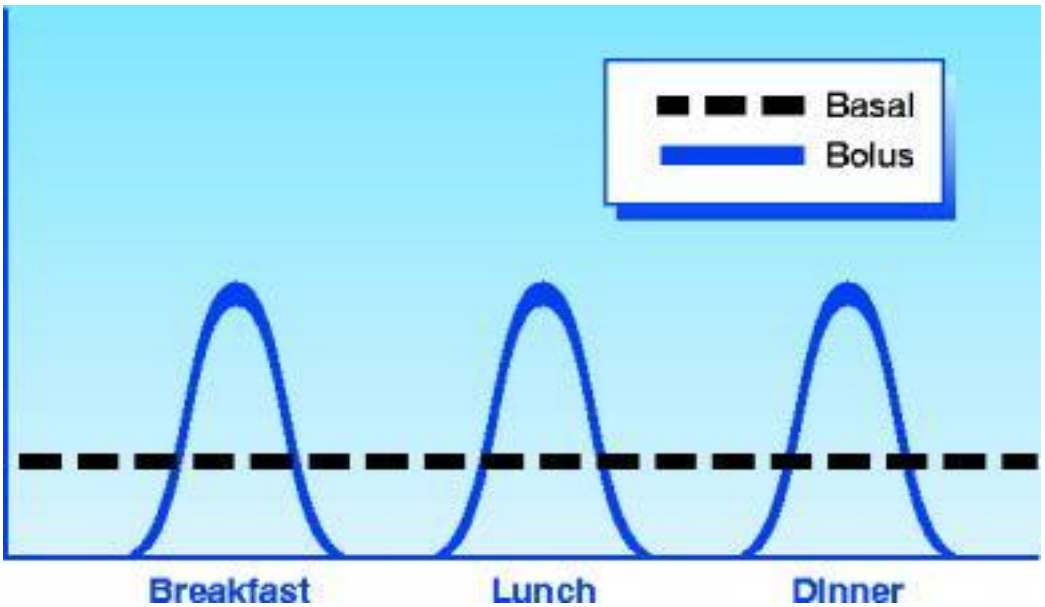

Figure 1: Bolus insulin is used to maintain blood glucose in the goal range after a meal. Basal insulin is used to maintain blood glucose in the goal range between meals and overnight.

Meal plans

- Carbohydrate ingestion is a major determinant of blood glucose concentration
- Matching the amount of food intake with the appropriate amount of insulin requires knowledge of:
  - Onset
  - Peak
  - Duration of action of the various types of insulin available
- Carbohydrate counting
  - More complex than exchange diet, but increasingly popular
    - Patients must be familiar with the carbohydrate content of each food
  - For each unit of carbohydrate taken, a specific amount of insulin must be given to maintain euglycaemia (known as the insulin carbohydrate ratio (ICR))
    - Typical ICR may be 1 unit of short-acting insulin for each 15 g of carbohydrate eaten
    - Ratio is adjusted for each patient
    - Ratio may vary based on time of day for a given individual
  - Advantages
    - Can be used for patients on MDI therapy or CSII regimen
    - Carbohydrate counting allows flexibility in the timing and content of each meal
  - Caveats
    - Patients can take more insulin to maintain glycaemic control while overeating
    - Carbohydrate counting must be part of an overall meal plan so that overeating does not contribute to obesity or hyperlipidaemia
    - Carbohydrate counting requires specific education and a motivated patient and family
    - Recent evidence suggests that protein and fats can also influence postprandial glycaemia
  - Contraindications
    - Patients on a split-mixed insulin programme
    - Insulin doses in a split-mixed programme cannot easily be adjusted to account for the dietary variability of carbohydrate counting

Exercise

- Exercise can be performed safely and should be encouraged as a part of a healthy lifestyle
  - Children should not be discouraged from participating in sports because of diabetes

        - Attention to the effects of activity on glucose levels can assist in preventing hypoglycaemia during or after exercise
        - Hypoglycaemiamay occur if changes are not made in the amount of food eaten or insulin taken
        - The effect of exercise may be sustained and may lead to delayed hypoglycaemia
- Planned activity – 2 methods of preventing hypoglycaemia
    - Reduce the dose of short-acting insulin given at the previous meal
    - A snack can be given just before or during the activity
- Unplanned activity
    - A snack is the only option
- Blood glucose level
    - Should be checked before and after exercise to determine effect of activity on glucose concentrations
    - If activity is prolonged (> 45–60 minutes), glucose level should be checked:
        - Documenting the effect of exercise on the patient's glucose level is the only way to prevent hypoglycaemia
        - Short, intense exercise can have different effects on blood sugar levels from prolonged exercise such as marathon running on blood sugar levels

Illness

- Illness can have a notable effect on blood glucose values
    - Hypoglycaemia or hyperglycaemia may result
        - Dependent on illness severity and the amount of food eaten
- Regardless of food intake, insulin is necessary in health or illness
    - A common error made is the omission of insulin injections because the child is not eating
        - Although the dose may change, some insulin should be given even if the child cannot eat
- Practical guidelines can assist in appropriate care during illness and avoidance of hospitalisation
    - Never completely omit insulin
    - Monitor and record blood glucose concentrations every 2–4 hours
    - Monitor blood ketone concentrations frequently, even if blood glucose level is not significantly elevated
        - Some patients with T1D can develop ketosis in the absence of hyperglycaemia when ill
        - Normal ketones are < 0.6 mmol/L
    - Encourage adequate hydration
    - The presence of ketones may indicate a need for increased insulin treatment

When To Refer

- When T1D or T2D is newly diagnosed, arrange a same-day referral to paediatric specialist services in case diabetes ketoacidosis management is required or to manage insulin therapy as part of the multidisciplinary team

'Safety Netting' Advice

- Children and young people with T1D should be offered clear guidance for the management of diabetes during periods of illness (eg, sick day rules)
- Adequate sick day management at home may reduce the risk of progression to DKA and admission to hospital
- Parents and carers should be provided with the necessary information, and have 24 / 7 access to a paediatric diabetes care team

Patient / Carer Information

Please note: whilst these resources have been developed to a high standard they may not be specific to children.

- Dealing with Hyperglycaemia (High Blood Sugar) (Web page), Patient
- Hyperglycaemia (high blood sugar) (Web page), the NHS website
- Diabetes (Web page), the NHS website
- Diabetes: the basics (Web page), Diabetes UK

Resources

National Clinical Guidance

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (Web page), NICE Technology Appraisal TA151, National Institute for Health and Care Excellence

Diabetes (type 1 and type 2) in children and young people: diagnosis and management (Web page), NICE guideline NG18, National Institute for Health and Care Excellence

Diabetes in children and young people (Web page), NICE Quality Standard QS125, National Institute for Health and Care Excellence

Suggested Resources

Please note: these resources include links to external websites. These resources may not have national accreditation and therefore PCO UK cannot guarantee the accuracy of the content.

Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia (Web page), WHO / IDF Consultation

ACDC Management of Type 1 Diabetes Mellitus during illness in children and young people under 18 years (Sick Day Rules) (Guideline), Association of Children's Diabetes Clinicians

BSPED Recommended Guideline for the Management of Children and Young People under the age of 18 years with Diabetic Ketoacidosis 2015 (Guideline), British Society of Paediatric Endocrinology and Diabetes

ISPAD Clinical Practice Consensus Guidelines 2014 (Guidelines). International Society for Pediatric and Adolescent Diabetes

Gloyn AL, Pearson ER, Antcliff JF, *et al.* eActivating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med*. 2004;350(18):1838–1849 [PubMed]

Metformin for diabetes (Web page), Medicines for Children

Lisinopril for high blood pressure (Web page), Medicines for Children

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