CHAPTER 5

ENDOCRINOLOGY

DIABETES IN CHILDREN

Definition

Diabetes mellitus (DM) is a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, action, or both which leads to abnormalities of carbohydrate, fat, and protein metabolism.

The most common type in children is type 1 DM, usually diagnosed from age 6 months to 36 years.

Risk factors

- Genetics - family history in parent or sibling of type 1 DM
- Age- Type 1 diabetes can appear at any age, but it appears at two noticeable peaks. The first peak occurs in children between 4 and 7 years old. The second is in children between 10 and 14 years old
- Environmental factors
    - The environmental triggers include infections, nutritional, changes in the microbiome and chemicals.
    - Infections include Enterovirus infection (during pregnancy, infancy, childhood, and adulthood), congenital rubella syndrome, CMV, mumps, influenza, rotavirus, and H1N1, possibly SARS-CoV-2

Causes

- Idiopathic and sporadic

Prevention

- Early diagnosis

Promotion

- Health education and advocacy

Signs and symptoms

● Polyuria ● Polydipsia ● Nocturia ● Changing enuresis ● Weight loss ● Polyphagia ● Fatigue ● Frequent UTIs ● Frequent fungal and bacterial infections	● Abdominal pain (pseudo-appendicitis diabetica) ● Behavioral disturbance, including reduced school performance, and blurred vision ● Impairment of growth and susceptibility to perineal candidiasis ● In its most severe form, DKA or (rarer) non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and, in the absence of effective treatment, death

Criteria for the diagnosis of type 1 diabetes mellitus

- Classic symptoms of diabetes or hyperglycemic crisis with plasma glucose concentration ≥11.1 mmol/L (200 mg/dl)
  Or
- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dl). Fasting is defined as no caloric intake for at least 8 hrs
  Or
- Two-hour post-prandial glucose ≥11.1 mmol/L (≥200 mg/dl) during an oral glucose tolerance test (OGTT). The OGTT should be performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g
  Or
    - HbA1c ≥6.5% (important indicator of glycemic control)

Investigations

- Random blood glucose
- Fasting blood sugar
- Oral glucose tolerance test
- HbA1c
- Serum electrolytes
- Urine dipstick (ketones)
- Insulin & C-peptide levels
- Antibodies- Islet cell cytoplasmic autoantibodies (ICA); Glutamic acid decarboxylase (GADA); Insulinoma associate-2 autoantibodies (IA-2A); Insulin autoantibodies (IAA)

Differential diagnosis

Type 2 diabetes mellitus
Maturity onset diabetes of the young (MODY-dm)
Psychogenic polydipsia
Diabetes insipidus

Stress hyperglycemia
Long standing steroid therapy
Renal tubular acidosis type-1
Glucagonoma
Cushing's syndrome
Hypothyroidism

Management

- Diabetes education is a cornerstone.
- Follows a multidisciplinary approach which involves dieticians, nutritionists, psychologists, nurses, doctors and endocrinologists.

PRIMARY HEALTH CARE FACILITY

- Relevant history and physical exam
- Investigations
  - Random blood sugar
  - Fasting blood sugar
  - Urine dipstick (ketones)
- Treatment (stabilize the patient)
  - Check hydration status and manage as per protocol
  - Refer for secondary level care

SECONDARY HEALTH CARE FACILITY

- Relevant history and physical exam
- Investigations
  - Random blood sugar
  - Fasting blood sugar
  - Urine dipstick
- Treatment
  - Rehydrate patient
  - Screen for and treat for DKA. Refer to DKA section of guideline.
  - Prepubertal and pubertal children usually require 0.5 to 1.0 IU/kg/day of insulin. The daily dose is divided and administered as demonstrated below using the glucose- and meal-adjusted injection regimen.

Type of Insulin and dosing ratio	AM	Noon	PM
Soluble (1/3 of total daily insulin dose)	1/3 of total daily dose of soluble insulin	1/3 of total daily dose of soluble insulin	1/3 of total daily dose of soluble insulin

NPH (2/3 of total daily insulin dose)	2/3 of total daily dose of NPH		1/3 of total daily dose of NPH

- Glycemic targets:
  - Achieving target glucose levels assessed through HbA1c, and/or SMBG reduces risks of acute and chronic complications of diabetes. This minimizes the detrimental effects of hypoglycemia and hyperglycemia on brain development, cognitive function, mood and quality of life.
  - Finger capillary glucose should be assessed at least 3 times a day for a person with diabetes taking insulin.
  - Finger capillary glucose- recommended target glucose values are between 4 and 10 mmol (70–180 mg/dl), with a narrower fasting target range of 4–8 mmol/L (70–144 mg/dl).

Short term Follow up

- In patients with new diagnosis of type 1 DM, schedule a 2-weekly visit in which checking of glucose diary and health education are re-enforced
- Thereafter subsequent clinics can be scheduled monthly.

Long term Follow-up

- Dietary education on every visit.
- 3-monthly HbA1c.
- Screen on every visit peripheral neuropathy (3-5years after diagnosis or from age of 9-11 years)
- Screen for diabetic nephropathy annually (3-5years after diagnosis or from age of 9-11).
- Screen for diabetic retinopathy annually (3-5years after diagnosis or from age of 9-11).

TERTIARY HEALTH CARE FACILITY

- Relevant history and physical exam
- Investigations
  - Random blood sugar
  - Fasting blood sugar
  - Urine dipstick
  - HbA1c every 3 months
  - Antibody tests (gold standard for T1D diagnosis) – in new diagnosis
  - Screen for other autoimmune diseases
    - Screen for thyroid disease and celiac disease.
- Treatment
  - Rehydrate patient
  - Screen for and treat for DKA or Honk

- Prepubertal children usually require 0.5 to 1.0 IU/kg/day and during puberty. The daily dose is divided and administered as demonstrated below using the Glucose- and meal-adjusted injection regimen.

Type of Insulin and dosing ratio	**AM**	**Noon**	**PM**
Soluble (1/3 of total daily insulin dose)	1/3 of total daily dose of soluble insulin	1/3 of total daily dose of soluble insulin	1/3 of total daily dose of soluble insulin
NPH (2/3 of total daily insulin dose)	2/3 of total daily dose of NPH		1/3 of total daily dose of NPH

- Glycemic targets:
  - Achieving target glucose levels assessed through HbA1c, and/or SMBG reduces risks of acute and chronic complications of diabetes and minimizes the detrimental effects of hypoglycemia and hyperglycemia on brain development, cognitive function, mood and quality of life.
  - Finger capillary glucose should be assessed at least 3 times a day for a person with diabetes taking insulin.
  - Target HbA1c for young people with diabetes should be <53 mmol/mol (<7.0%)
  - Finger capillary glucose- recommended target glucose values are between 4 and 10 mmol (70–180 mg/dl), with a narrower fasting target range of 4–8 mmol/L (70–144 mg/dl).

Follow up (new diagnosis)

- In patients with new diagnosis of Type 1 DM, schedule a 2-weekly visit in which checking of glucose diary and health education are re-enforced
- Thereafter subsequent clinics can be scheduled monthly.

Long term Follow up

- Dietary education on every visit.
- 3-monthly HbA1c.
- Screen on every visit peripheral neuropathy. (3-5years after diagnosis or from age of 9-11 years)
- Screen for diabetic nephropathy annually (3-5years after diagnosis or from age of 9-11 years).
- Screen for diabetic retinopathy annually (3-5years after diagnosis or from age of 9-11 years).
- Adherence to insulin treatment even on sick days. Do not stop insulin even on sick days. Adjust up by 10 to 20% and taper after recovery to previous dosage before illness.

Diabetic ketoacidosis (DKA)

Definition

A state of absolute or relative insulin deficiency resulting in hyperglycemia, dehydration and metabolic acidosis. Leading cause of morbidity and mortality in children with T1DM but can also occur in patients with type 2 DM.

Risk factors

- New onset T1DM especially due to missed diagnosis
- Omission of insulin or inadequate administration in a known patient with T1DM
- Infection
- Trauma, surgery emotional stress
- Being a young child and/or adolescent

Prevention

- Early diagnosis
- Diagnose and treat underlying infections / triggers early
- Adherence to insulin treatment even on sick days. *Do not stop insulin even on sick days. Adjust up by 10 to 20% and taper after recovery to previous dosage before illness*
- Regular reviews in diabetic clinic
    - Assess for signs of puberty
    - Review insulin dosages
    - Intensify diabetes education (drug storage, drug administration / injection technique, injection site care, nutrition and diet, identifying complications)
- On-going psychosocial counselling

Promotion and advocacy

- Health education and advocacy
- Screening of patients at risk
- Advocate for consistent availability of insulin

Causes

- Missing insulin doses
- New diagnosis of T1DM
- Stress secondary to an acute illness e.g Infection and surgery

Signs and symptoms

- ***Any patient with T1DM who presents with abdominal pain, nausea, fatigue and/or dyspnea should be evaluated for DKA***

Symptoms of hyperglycemia	Symptoms of acidosis and dehydration	Signs
Polyuria	Abdominal pain	Poor skin turgor
Polydipsia	Vomiting, nausea	Dry mucous membranes
Weight loss	Rapid or deep respiration (Kussmaul's)	Fruity smelling breath
Nocturia in a previously continent child	Confusion and coma	
Muscle pains and cramps		

Investigations

- Random blood glucose
- Urinalysis and urine ketones by dipstick
- Full blood count (FBC) with differential
- Serum electrolytes (with calculation of the anion gap), blood urea nitrogen (BUN), and plasma creatinine
- Arterial blood gas
- Plasma osmolality
- Serum beta-hydroxybutyrate (if urine ketones are present)
- Electrocardiogram – to look for signs of hypokalemia/hyperkalemia

Differential diagnosis

- Gastroenteritis
- Sepsis
- Pneumonia
- Encephalitis
- Acute abdomen
- Metabolic acidosis
- Severe malaria
- Meningitis

Management

Principles of DKA management

- Correct dehydration
- Correct acidosis and reverse ketosis (bicarbonate is contraindicated)
- Normalize blood glucose
- Minimize DKA complications
  Provide education for DM

PRIMARY HEALTH CARE FACILITY

- DKA is an emergency, follow ABC approach in managing patient.

- Obtain relevant history and examination.
- Collect relevant investigations: RBS and urine dipstick.
  Assess **airway**
  Assess **breathing** status and support accordingly
  Assess **circulation**- Assess level of dehydration status and start fluid replacement based on the dehydration status.
  Estimate 5% dehydration for mild/moderate dehydration and 7% in severe dehydration
    - Two peripheral intravenous (IV) catheters should be inserted.
      - If unable to give iv rehydration place NGT and use ORS for rehydration (if not vomiting) and for severely dehydrated patients, consider intraosseous fluid replacement if available
    - Fluid replacement should begin before starting insulin therapy.
    - Every patient with DKA is always dehydrated and should get an initial fluid resuscitation of 0.9% **saline/RL** 10ml/kg over 1 hour
    - If in shock one or more boluses of 0.9% **saline/RL** 20ml/kg IV infused as bolus should be given to restore peripheral circulation. Reassess thereafter. Some patients may need more than one bolus to restore normal hydration.
    - Start maintenance fluid 0.9% saline and refer.

  Assess **disability- do AVPU**
- Refer to the next level of care once a patient has stable vital signs, refer whilst on fluid rehydration.

Clearly document amount of fluids given

SECONDARY AND TERTIARY HEALTH CARE FACILITY

- DKA is an emergency, follow ABC approach in managing patients
- Obtain relevant history and examination

Collect relevant investigations: RBS and urine dipstick.

A- Assess **airway**

B- Assess **breathing** status and support accordingly

C- Assess **circulation**- Assess level of dehydration status and start fluid replacement based on the dehydration status:

- Two peripheral intravenous (IV) catheters should be inserted.
  - If unable to give iv rehydration place NGT and use ORS for rehydration
  - Fluid replacement should begin before starting insulin therapy.
  - Every patient with DKA not dehydrated should get an initial fluid resuscitation of 0.9% **saline/RL** 10ml/kg over 1 hour.
  - If in shock or severely dehydrated expand volume using boluses 20mls/kg of 0.9% saline or RL infused over 20–30 min to restore peripheral circulation. **Reassess after every bolus.** If the patient is not responding after 2 boluses consult paediatrician
  - After initial bolus, calculate the subsequent rate of fluid administration which should include maintenance and fluid deficit **(Use 5% deficit for dehydration fluid calculation).** Deficit should be given over 48hrs. SEE EXAMPLE OF FLUID CALCULATION (Box…..).
  - If needing more fluid replacement, discuss with a paediatric consultant). *Refer to fluid replacement chart in the appendix.
  - Monitor for signs of fluid overload.

D- Assess **disability**

- GCS, pupillary exam
- Draw samples: blood glucose, beta-hydroxybutyrate blood or urine ketones, serum electrolytes and blood gases.

Manage the child in an HDU or a designated area where close monitoring can take place.

- Monitor **electrolytes** / arterial blood gas every 6 to 8 hours. Correct accordingly (refer to section I)
- Continue with **fluid replacement**, ensure adequate rate (Refer to fluid replacement chart / calculation)
- **Catheterize**.
- Hourly **glucose** check
- **Insulin therapy**:
  - ➔ Begin with 0.05U/kg/at least 1hr AFTER starting fluid replacement therapy.
  - ➔ Check blood sugars hourly after initiation of insulin.

- ➔ If there is rapid drop of RBS by > 100mg/dl reduce dose of insulin by 10-20% and CONSULT paediatrician.
- ➔ If there is poor response to insulin therapy CONSULT paediatrician.

- **Potassium**: All children with DKA have a relative hypokalemia. Start Potassium therapy after urine void. Begin with 40 mmol potassium added in 1 L of fluid (0.9% NS/RL)
- 6 Hourly **ketones** check.
- Treat underlying cause. i.e. infections
- **Manage other complications or triggers of DKA**
  - ➔ Cerebral oedema is the most common cause of mortality among children with DKA and symptoms include:
    - ◆ Onset of headache or vomiting after beginning treatment or progressively worsening or severe headache,
    - ◆ slowing of heart rate not related to sleep or improved intravascular volume,
    - ◆ change in neurological status (irritability, lethargy, confusion, incontinence),
    - ◆ specific neurological signs (e.g., cranial nerve palsies),
    - ◆ decreased oxygen saturation.
    - ◆ Risk factors for developing cerebral oedema are:
      - elevated blood urea nitrogen (BUN) concentration (>20 mg/dl)
      - severe acidosis (pH < 7.1)
      - severe hypocapnia (pCO2 < 21 mmHg)
      - age < 5 years)
    - ◆ If neurologic status deteriorates acutely, hyperosmolar therapy with mannitol or hypertonic saline should be given immediately
  - ➔ If signs of cerebral edema refer to the management guideline of cerebral edema.

- Transitioning to fixed dosing of insulin:
  - Clearing of beta-hydroxybutyrate (blood ketones) is the gold standard for resolution of DKA.
  - Stable patients with overall improvement of clinical picture should be considered to have resolved DKA, urine ketones take longer to clear therefore should not be the only measure to determine resolution of DKA.
  - Once DKA has resolved subcutaneous insulin should be given ***30 minutes before*** stopping iv insulin.
    REFER TO DIABETES MANAGEMENT SECTION
  - ★ After transitioning, check RBS minimum 3 times daily (before meals) to monitor treatment.

Fluid Calculation In DKA

Formulae for fluid deficit calculation

- Weight in kg x % dehydrated

Percentage dehydrated is 5% for mild dehydration and 7.5% for moderate dehydration and 10% for patients in severe dehydration and shock)

- Total fluid for patients in DKA: Maintenance fluid + Fluid deficit

Note that in DKA fluid calculation, the maintenance volume needs to be doubled as correction occurs over 48hours

Example of fluid calculation

A child weighing 20kg on admission in shock

1 x 20mls/kg bolus needed to correct shock = 400mls
Maintenance = 1500ml/day (1.5L)
Deficit = 20 kg x 5% = 1L
Requirement (over 48 hours) = Maintenance (1.5L + 1.5L) + Deficit (1L) =
4 liters/48hrs = 83mls/hr

THYROID DISORDERS

Congenital Hypothyroidism

Definition

Congenital hypothyroidism (CH) is caused by inadequate thyroid hormone production in newborn infants resulting from an absent or under-developed thyroid gland (a-/dysgenesis) (80-85% of cases) or one that has developed but cannot produce thyroid hormone because of a 'production line' problem (dys-hormonogenesis) (10-15% of cases).

Risk factors/Causes

- Maternal perinatal factors such as advanced maternal age, gestational complications, maternal iodine deficiency, mother on antithyroid drugs, with antithyroid antibodies or excess iodine exposure.
- Neonatal perinatal factors such as female sex, preterm birth, post term birth, low birth weight, presence of other birth defects, and multiple gestation.
- Down's syndrome.
- Predominantly sporadic.
- 2% genetic or familial.

Prevention and promotion

- Newborn screening (TSH): blood (heel prick or cord blood) for screening is collected from full-term infants, the sample is usually collected one to two days after birth.
- Advocate for neonatal screening to prevent intellectual and physical disability.
- Health education.

Signs and symptoms

- Can be asymptomatic.
- Symptoms usually develop over the first few months of life: lethargy, hoarse cry, feeding problems (often needing to be awakened to nurse), constipation, puffy (myxedematous) and/or coarse facies, macroglossia, umbilical hernia, large fontanels, hypotonia, dry skin, hypothermia, and prolonged jaundice (primarily unconjugated hyperbilirubinemia).
- Later problems: profound intellectual disability, growth retardation.
- 3-7% have other birth defects e.g. ASD, VSD, micropenis, undescended testes, hearing loss.

Investigations

- T4 and TSH assays.

Primary hypothyroidism	High TSH, low free T4
Subclinical hypothyroidism	High TSH, normal free T4 or total T4
Central hypothyroidism	Low or normal TSH, low free T4

- Cardiac echo and audiology screening
- Additional testing (may be helpful for selected infants)
    - Thyroid imaging
        - Thyroid ultrasonography and color flow Doppler
        - Thyroid radionuclide uptake and scan
    - Thyroid autoantibodies
    - Serum thyroglobulin concentration
    - Urinary iodine concentration
    - Genetic testing
    - Imaging of left lower extremities: absent distal left femoral epiphysis in 54% of patients.

Differential diagnosis

- Spinal muscular atrophy
- Muscular dystrophies
- TORCH infections
- Hirschsprung's disease
- Panhypopituitarism
- Beckwith-Wiedemann syndrome

Management

PRIMARY HEALTH CARE FACILITY

- Identify key diagnostic indicators (Refer to signs and symptoms above)
- Manage acute illnesses like hypoglycemia as per protocol (See emergency section).
- Refer patient to tertiary level of care.

SECONDARY HEALTH CARE FACILITY

- Proceed as on primary level of care.
- Refer patient to tertiary level of care.

TERTIARY HEALTH CARE FACILITY

- History and Physical exam as above.
- Identify key diagnostic factors as highlighted above
- Carry out baseline tests
    - T4 and TSH assays
    - Random blood sugar
    - Serum electrolytes and liver function tests
    - Manage symptoms of acute illness such as hypoglycemia as per protocol

- Treatment
    - Plot growth chart for length, weight, and head circumference. Follow growth charts on every visit.
    - 0-3 months of age: levothyroxine dose of 10 to 15 µg/kg/day.
        - Administration: The tablet should be crushed and mixed with 5-10mls of breastmilk, formula (except soy protein formula), or water and fed to the infant. Give immediately, do not store. Avoid

administration with Soy formula, supplements with iron or calcium and antacids (aluminum hydroxide) or infant "colic" drops (simethicone) may reduce absorption

- Treatment goals — ensure normal growth and neurodevelopmental outcome. This is achieved by restoring the serum fT4 (or T4) and TSH concentrations to the normal range as rapidly as possible, followed by dose adjustment to ensure continued clinical and biochemical euthyroidism.
  - Target is serum T4 concentration in the upper one-half of the reference range for age.
  - Target for serum TSH should be in the lower end of the reference range.
  - For infants with congenital central hypothyroidism, serum free T4 should be used to guide treatment because measurement of serum TSH is not helpful.
- Monitoring schedule – For infants with congenital primary hypothyroidism, monitor serum T4 and TSH at the following intervals:
  - Two weeks and at 4 weeks after the initiation of levothyroxine treatment.
  - Every one to two months during the first 6 months of life
  - Every three to six months between six months and three years of age.
  - Every 6 to 12 months thereafter until growth is complete.
  - 4 weeks after any change of dose.

Once diagnosis is confirmed and treatment is started refer patient to endocrinologist.

ACQUIRED HYPOTHYROIDISM IN CHILDHOOD AND ADOLESCENCE

Definition

Abnormally low activity of the thyroid gland, resulting in slowing of growth, mental development and metabolic changes in children.

Risk factors/Causes

- A chromosomal disorder such as Down syndrome, Williams syndrome, or Turner syndrome.
- An autoimmune disorder such as type 1 diabetes or celiac disease.
- Too little or too much iodine intake.
- Injury to the thyroid gland.
- Radiation to the head and neck
- Nutritional
    - Iodine Deficiency
    - Excess exposure (eg, nutritional supplements, drugs [amiodarone, expectorants])
- Drugs
    - Antithyroid drugs (eg, methimazole, propylthiouracil)
    - Antiseizure medications (eg, phenytoin, phenobarbital, valproate)

Promotion

Health education

Signs and symptoms

- Initial symptoms: constipation, sluggishness, lethargy, cold intolerance, dry skin, brittle hair, facial puffiness, muscle aches and pains.
- Declining school performance
- Delayed pubertal development.
- Declining growth velocity/short stature.
- Encephalopathy
- Hypothalamic or pituitary disease will cause headaches, visual symptoms, or manifestations of other pituitary hormone deficiencies.

Investigations

- T4 and TSH assays

Primary hypothyroidism	High TSH, low free T4
Subclinical hypothyroidism	High TSH, normal free T4 or total T4
Central hypothyroidism	Low or normal TSH, low free T4

- Additional testing (may be helpful for selected infants)
    - Thyroid imaging
        - Thyroid ultrasonography and color flow Doppler
    - Serum thyroglobulin concentration

- Thyroid autoantibodies - antithyroid peroxidase antibodies (TPO-Ab) and antithyroglobulin antibodies (TrAb)
- Urinary iodine concentration
- Genetic testing

Differential diagnosis

- Autoimmune thyroid disease
- Iodine deficiency/malnutrition
- Constipation
- Growth hormone deficiency

Management

PRIMARY HEALTH CARE FACILITY

- Identify key diagnostic indicators
  - Symptoms and signs: as stated above
  - Manage acute illnesses as per protocol
- Refer patient to next level of care

SECONDARY HEALTH CARE FACILITY

- Identify key diagnostic factors as highlighted above
- Carry out baseline tests
  - Random blood sugar
  - Serum electrolytes and liver function tests
- Stabilize patient, manage acute illness as per protocol.
- Refer patient to next level of care

TERTIARY HEALTH CARE FACILITY

- History and physical exam as above.
- Baseline investigations
  - T4 and TSH assays.
- Treatment
  - Levothyroxine dose — Initial treatment is started with levothyroxine at the following doses, given by mouth, once daily and administered in the morning 30minutes before food and adapt as necessary:
    - Age 1 to 3 years – 4 to 6 µg/kg body weight
    - Age 3 to 10 years – 3 to 5 µg/kg
    - Age 10 to 16 years – 2 to 4 µg/kg
  - Monitoring and dose adjustment — serum TSH and free T4 should be checked six to eight weeks after initiation of treatment and then every 6 to 12 months.
    - Thyroid function tests should be obtained six to eight weeks after any dose change or if the patient develops any clinical manifestations suspicious for hypo- or hyperthyroidism.
    - The levothyroxine dose is adjusted to maintain TSH and free T4 (or T4) in the normal reference range for age.
  - Once levothyroxine therapy is started, Continue treatment until growth and pubertal development are complete.
- Once diagnosis is confirmed and treatment is started refer patient to endocrinologist.

Follow up
Medication review and side effects
Growth and development

Hyperthyroidism
Definition

Hyperthyroidism is defined as an inappropriately high production of thyroid hormones from the thyroid gland leading to various systemic clinical manifestations.

Risk factors/causes

- Drugs (levothyroxine, lithium)
- Having a personal or family history of autoimmune disease
- Viral infections (e.g mumps, influenza)
- Autoimmune dysfunction (eg. Graves' disease)
- Tumours (thyroid carcinoma)
- Excess iodine intake

Prevention

- Early diagnosis in patients at risk

Promotion

- Health education and advocacy

Signs and symptoms

	Symptoms	Signs
Constitutional	Weight loss despite increased appetite; heat-related symptoms (heat intolerance, sweating)	Weight loss
Neuromuscular	Tremor; nervousness; anxiety; fatigue; weakness; disturbed sleep; poor concentration	Tremor of the extremities; hyperactivity; hyperreflexia; pelvic and girdle muscle weakness
Cardiovascular	Palpitations	Tachycardia; systolic hypertension; irregular heartbeat (atrial fibrillation)
Pulmonary	Dyspnoea, shortness of breath	Tachypnoea
Gastrointestinal	Diarrhea; nausea, vomiting	Abdominal tenderness
Skin	Increased perspiration	Warm and moist skin
Reproductive		Menstrual disturbances
Ocular (Graves' disease)	Diplopia; sense of irritation in the eyes; eyelid swelling; retro-orbital pain or discomfort	Proptosis; eyelid retraction and lag; periorbital oedema; conjunctival injection and chemosis; ophthalmoplegia

Investigations

- Full blood count
- Serum thyroid function tests (T4, TSH)
- Serum thyroid antibody tests (TPOs and Trab)
- Ultrasound
- Radionuclide uptake and scan

Differential diagnosis

- Graves' disease
- Subacute thyroiditis
- Hashitoxicosis
- Autonomously functioning thyroid nodule
- Factitious hyperthyroidism (intake of exogenous hormone)
- TSH-secreting pituitary tumor (rare)
- Pituitary resistance to thyroid hormone

Management

PRIMARY CARE HEALTH FACILITY

- Identify key diagnostic indicators
- Symptoms and signs: as stated above
- Manage acute illnesses as per protocol
    - Hypertension-refer to hypertension section for management plan
- Refer patient to next level of care

SECONDARY CARE HEALTH FACILITY

- Identify key diagnostic factors as highlighted above
- Carry out baseline tests
- Random blood sugar
- Serum electrolytes and Liver function tests
- Stabilize patient: manage acute illness as per protocol
- Refer patient to next level of care

TERTIARY CARE HEALTH FACILITY

History and physical exam as above.

- Baseline investigations
- T4 and TSH assays
- Interpretation

Overt hyperthyroidism	Low or undetectable TSH, elevated T4 or T3
Subclinical hyperthyroidism	Normal T4 and T3, clearly low serum TSH

Treatment with antithyroid drugs

- Carbimazole 15mg daily as starting dose

- Once diagnosis is confirmed and treatment is started refer patient to endocrinologist.

Follow up

- FBC-look for evidence of bone marrow suppression
- Blood pressure monitoring
- Nutrition and growth

APPROACH TO DISORDERS OF SEX DEVELOPMENT (AMBIGUOUS GENITALIA)

Definition

Infants born with genitalia that do not appear typically male or female, or that have an appearance discordant with the chromosomal sex, are classified as having a difference (or disorder) of sex development (DSD).

Risk factors/Causes

Autosomal recessive and X-linked.

Caused by mutations of genes associated with sex determination.

Prevention

- Genetic testing of other family members

Promotion

- Advocacy
- Reducing stigma associated with DSD
- Health education for health staff and affected families

Signs and symptoms

General symptoms	
Overt genital ambiguity	
Discordance between genital appearance and (pre-/postnatal) karyotype	
Newborns and infants	
Apparent Male	Apparent female
Largely male appearance of the external genitalia and any of the following: - Bilaterally nonpalpable gonads - Severe hypospadias - Any degree of hypospadias accompanied by unilateral or bilateral cryptorchidism and/or micropenis - Genital appearance discordant with sex chromosomes	Largely female appearance of the external genitalia and any of the following: - Clitoromegaly - Posterior labial fusion - Gonads palpable in the labioscrotal folds or inguinal region - Genital appearance discordant with sex chromosomes
Children and adolescents	
Male	Female

Largely male appearance of the external genitalia and any of the following: - Bilaterally nonpalpable gonads - Severe hypospadias - Any degree of hypospadias accompanied by unilateral or bilateral cryptorchidism and/or micropenis - Breast development - Genital appearance discordant with sex chromosomes	Largely female appearance of the external genitalia and any of the following: - Clitoromegaly - Posterior labial fusion - Gonads palpable in the labioscrotal folds or inguinal region - Lack of breast development - Genital appearance discordant with sex chromosomes

Investigations

- Biochemistry
  - Urea and electrolytes (Sodium and potassium)
  - Blood glucose
  - Hormonal levels, i.e. cortisol, testosterone, estradiol, progesterone, 17-hydroxy-progesterone, LH – luteinizing hormone, FSH – follicle stimulating hormone, and anti-mullerian hormone (AMH)
- Abdomen and pelvic USS
- Karyotyping
- Laparoscopy and gonadal biopsy

Differential diagnosis

- Hypospadias
- Congenital adrenal hyperplasia (CAH)
- Androgen insensitivity
- Oval-Testicular DSD (True hermaphroditism)

Management approach

DO NOT ASSIGN SEX before full evaluation at tertiary level and encourage parents to give unisex name.

PRIMARY HEALTH CARE FACILITY History ● Pregnancy and birth ● Family history of consanguinity Conduct physical examination Management ● Supportive care, correct dehydration and hypoglycemia ● Referral
SECONDARY HEALTH CARE FACILITY History and examination as above Investigations ● Electrolytes ● Abdomen and pelvic USS (if available)

Management
- Supportive care, correct dehydration and hypoglycemia
- Referral

TERTIARY HEALTH CARE FACILITY
History and examination as above
- Thorough investigations (see page…)

Management
- Supportive care, correct dehydration and hypoglycemia
- Specific treatment according to underlying disease

Refer to endocrinologist

Management requires multidisciplinary team that includes: paediatric endocrinologist, geneticist, urologist, gynecologist, psychologist, nurses, social worker.

Follow up
- Medication review and side effects
- Ongoing social counseling

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Definition

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders that occurs because of a defect in adrenal steroidogenesis caused by a mutation in one or more enzyme-encoding genes, leading to dysfunctional cortisol and aldosterone production and excessive levels of androgens.

The most common form is 21-alpha-hydroxylase deficiency (21-OHD) due to mutations in the 21-hydroxylase (CYP21A2) gene which leads to accumulation of androgen precursors and a deficiency of cortisol and aldosterone.

Risk factors/Causes

Factors that increase the risk of having CAH include:

- Parents who both are known to be heterozygous for one of the severe mutations
- Parents who both have CAH
- Having an affected sibling

Prevention/Early diagnosis

- Neonatal screening for elevated 17-hydroxy-progesterone (where screening facilities are available in patients with the above risk factors)
- Genetic testing of other family members
- Early detection and management to prevent complications

Promotion

- Advocacy
- Health education

Signs and symptoms

Symptoms depend on severity of enzyme deficiency, type of enzyme deficiency and are age-dependent.

<table>
<tr><td colspan="2">Infants</td></tr>
<tr><td rowspan="2">Atypical genitalia/ ambiguous genitalia</td><td><u>Females</u>
Clitoral enlargement,
Labial fusion
Formation of a urogenital sinus caused by the effects of in-utero androgen excess on the development of the external genitalia.
Virilization may be so profound that genital atypia is unrecognized, and male sex assignment (with undescended testes) is made at birth in a 46,XX patient.</td></tr>
<tr><td><u>Males</u>
Normal-appearing genitalia at birth but may have subtle findings such as hyperpigmentation of the scrotum or an enlarged phallus.
In some rare enzyme defects, ambiguous genitalia may be present due to impaired androgen production</td></tr>
<tr><td>Adrenal crisis</td><td>Vomiting, diarrhea, hypotension, and hypovolemic shock can occur, typically between 10 to 20 days of age
Laboratory findings suggesting adrenal crisis include hyperkalemia with or without hyponatremia, metabolic acidosis, and hypoglycemia.</td></tr>
<tr><td colspan="2">Children and adolescents</td></tr>
<tr><td></td><td>Pubic hair appears early, acne may be excessive, and the voice may deepen.
Excessive pigmentation may develop.
Signs of virilization in girls, early growth of penis and testicles in boys.
Isosexual central precocious puberty may occur and bone age is significantly advanced if patient is not adequately treated.
Final adult height is often compromised.</td></tr>
</table>

Differential Diagnosis

- Other forms of DSD

- Metabolic diseases of the newborn
- Addison's Disease
- Sepsis

Management

PRIMARY HEALTH CARE FACILITY

- Identify key diagnostic indicators (signs and symptoms).
- Manage acute illnesses like dehydration and hypoglycemia as per protocol.
- Refer patient to the next level of care.

SECONDARY HEALTH CARE FACILITY

- Identify key diagnostic indicators.
- Carry out baseline tests
    - Random blood sugar
    - Serum electrolytes
    - Abdominal and pelvic ultrasound scan
- Stabilize patient, manage dehydration and hypoglycemia.(see section….)
- Refer patient to next level of care.

TERTIARY HEALTH CARE FACILITY

- History and physical exam as above.
- Stabilize patient, manage dehydration and hypoglycemia as per protocol.
- Baseline investigations
    - Random blood sugar (hypoglycemia)
    - Serum electrolytes (hyperkalemia, hyponatremia)
    - Serum 17-hydroxyprogesterone (elevated in CAH)
    - Cortisol at a minimum (decreased)
    - Abdominal and pelvic ultrasound scan
- Other tests
    - ACTH stimulation test
    - Genetic testing
- Medical management
    - Supportive management
        - Treat adrenal crisis (refer to adrenal crisis management)
        - Correct dehydration and manage hypoglycemia
    - Specific management
    - *Newborns*
    - Glucocorticoid therapy should be initiated in newborns with:
        - Confirmed CAH – Initiate treatment with hydrocortisone, fludrocortisone and sodium supplements indefinitely.
        - Suspected CAH (eg, in an infant presenting with a positive newborn screen or atypical genitalia) – After obtaining a blood sample to confirm the diagnosis, initiate treatment with hydrocortisone, fludrocortisone, and sodium chloride supplements at standard starting doses. Continue this treatment until the diagnosis of CAH is either confirmed or excluded.
        - Initial dosing for newborns — In the absence of adrenal crisis, a typical starting regimen for an infant includes:

- Hydrocortisone at 20 to 30 mg/m^2/day, divided three times daily (ie, 2.5 mg three times a day), with rapid dose reduction when target hormone levels are reached.
- Fludrocortisone 100 µg (0.1 mg) once or twice daily and sodium chloride, 1 to 2 g or 17 to 34 mEq/day (2 to 4 mEq/kg/day), divided in several feedings.
- Monitoring and dose adjustment — Follow-up laboratory tests (serum 17-OHP, androstenedione, plasma renin activity, and electrolytes) should be performed no more than 10 to 14 days after starting treatment. The results should be used to guide adjustment of the doses of glucocorticoids and mineralocorticoids. Sufficient glucocorticoid doses are needed to ensure suppression of adrenal androgens, but excessive dosing can impair growth.

  - *Infants and children*
    - Hydrocortisone (cortisol) in a dose of 10 to 15 mg/m^2/day [1,2,4], divided into three doses.
    - Hydrocortisone should be increased 3-5 fold in severe infection, high fever and surgey.
    - Monitoring: see above as for newborns.
- Consult endocrinologist.

Follow up

- Medication review and side effects
- Patients/guardians should be educated on sick day management

PUBERTY DISORDERS

Precocious puberty

Definition

Onset of secondary sexual characteristics before the age of 8 in girls and 9 years in boys.

Much more common in girls than in boys.

Other forms of premature sexual maturation

- Premature thelarche - Premature breast development (as early as first year of life) that can be unilateral or bilateral and is self-limiting usually by age of 4 years.
- Adrenarche - Premature development of pubic hair and axillary hair. Isolated it is not a sign of puberty in either sex.
- Precocious pseudopuberty - When signs of sexual maturation occur due to sex steroid secretion which has a different mechanism from normal puberty eg cysts. Usually recognized by abnormal sequence of events of sexual maturation.

Risk Factors

Factors that increase a child's risk of precocious puberty include:

- Females
- Obesity
- Sex hormone exposure (estrogen or testosterone cream or ointment, or other substances that contain these hormones such as medication or dietary supplements)
- Other medical conditions (McCune-Albright syndrome or congenital adrenal hyperplasia, hypothyroidism and neural tube defects).
- Radiation therapy of the central nervous system.
- Pituitary hamartomas
- Pituitary adenomas

Causes

- Idiopathic
- CNS irradiation
- Females
    - Ovarian cysts
    - Ovarian tumors
- Males
    - Leydig cell tumors
    - Human chorionic gonadotropin secreting germ-cell tumors
- Primary hypothyroidism

- Adrenal pathology

Prevention

Early diagnosis and treatment

Promotion

Health education and advocacy

Signs and symptoms

Male

- Testicular enlargement (=/> 4mls)
- Growth of testis correlates well with growth of penis and pubic hair
- Size of penis (if obese, retract the pubic fat pad to obtain an accurate estimation of size)
- Presence of anatomical variants of the penis e.g. hypospadias
- Foreskin retractability
- Scrotal pain or swelling

Female

- Breast development
- Colour and size of the area around the nipples
- Presence of pubic hair
- Presence of anatomical variants, labial adhesions, vulvar ulcers.
- Vaginal discharge / bleeding (early menarche)

Investigations

- Medical history
- Physical exam
- Plot height, weight, BMI and bone age on growth chart
- Imaging
    - Bone age (x-ray of left hand)
    - Abdominal USS and pelvis USS (r/o cryptorchidism)
    - CT/MRI brain
- Hormones
    - Testosterone and estrogen
    - LH, FSH
    - LH:FSH ratio

Differential diagnosis

- Premature adrenache
- Premature thelarche
- Exogenous androgens
- Testicular mass

Management

PRIMARY LEVEL Identify and refer
SECONDARY LEVEL Identify and refer
TERTIARY LEVEL History, physical exam and i+nvestigations as above. Treatment ● Psychosocial support to the family ● Treat the underlying cause. ● Medical Management ○ Gonadotropin analogues ▪ Luproride acetate ● Refer to endocrinologist

F**ollow up**

- Medication review and side effect
- Growth and development

Delayed Puberty

Definition

Absence of secondary sexual characteristics by 13 years in a girl and 14 years in a boy. Pubertal arrest is considered as delayed puberty.

Risk factors

- Being male
- Family history
- Excessive exercise
- Chronic disease
- Radiation
- Malnutrition
- Eating disorders (eg anorexia nervosa)
- Pituitary surgery
- Pheochromocytoma
- Chemotherapy

Causes

- Chronic disease
- Poor nutrition
- Psychosocial deprivation
- Steroid therapy
- Tumors adjacent to the hypothalamus eg craniopharyngioma
- Congenital anomalies
- Irradiation and trauma
- Testicular torsion, trauma
- Cryptorchidism
- Mumps
- Female DSDs
- PCOS
- Gonadal dygenesis eg Turner syndrome, Klinefelter syndrome
- Chemotherapy

Prevention

Early diagnosis

Promotion

Health education and advocacy

Signs and symptoms

Girls

- No breast development and / or pubic hair by age 14 years
  OR
- No Menstruation by age 16 years
  OR
- First signs of puberty appeared > 5 years before menarche

Boys

- No enlargement of penis or testes by age 15 years
  OR
- No pubic hair by age 15 years

Investigations

- Medical history including family history of delayed puberty
- Physical exam - Plot height, weight, BMI and bone age on the growth chart.
- Imaging studies
    - Bone age
    - Abdominal USS and pelvis USS
    - CT/MRI brain
- Hormones
    - LH, FSH
    - LH:FSH ratio

Differential diagnosis

Constitutional delay of growth and puberty
(Congenital) hypergonadotropic hypogonadism
(Congenital) hypogonadotropic hypogonadism

Management

PRIMARY LEVEL Identify and refer
SECONDARY LEVEL Identify and refer
TERTIARY LEVEL Treatment ● Psychosocial support to the family ● Treat underlying cause ● Medical Management ○ Male - Testosterone ○ Female - Estrogen and Progestin ● Refer to endocrinologist

Follow up

- Medication review and side effects
- Growth and development

OVERWEIGHT AND OBESITY IN CHILDREN AND ADOLESCENTS

Definition

The definition refers to an excess of body fat.

- Overweight – BMI between >85th and 95th percentile for age and sex.
- Obesity – BMI ≥95th percentile for age and sex.
- Severe obesity – Severe (class II or greater) obesity is defined as BMI ≥120 percent of the 95th percentile values or a BMI ≥35 kg/m^2 (whichever is lower).

Risk factors/Causes

Environmental factors

- Glycemic index of foods, sugar-containing beverages, large portion sizes for prepared foods, fast food service, diminishing family presence at meals, decreasing structured physical activity, shortened sleep duration, changes in elements of the built environment (eg, availability of sidewalks and playgrounds).
- Excessive television viewing
- Medications (eg, certain psychoactive drugs, steroids).
- Genetic factors
- Endocrine causes e.g., Hypothyroidism and Cushing syndrome.

Prevention

Lifestyle modification

Promotion

Health education and advocacy

Signs and symptoms

Striae distensae, acanthosis nigricans (darkening of the neck, armpits and groin), sleep apnoeas, joint pains, fatigue, infections in skin folds, shortness of breath, heat intolerance, excessive sweating, depression.

Investigations

- Plot height and weight on a growth chart
- Calculate and plot BMI
- Blood pressure
- Random blood glucose
- Urea and electrolytes
- LFTs

Management

PRIMARY CARE FACILITY
- Relevant history and physical exam
- Plot growth chart
- Calculate and plot BMI
- Measure blood pressure

Management
- Lifestyle modification
- Exercise

- Reduction of intake of food with high glycemic index - Screen for diabetes and hypertension and manage accordingly - Refer to next level of care
SECONDARY CARE FACILITY - Relevant history and physical exam - Plot growth chart - Calculate and plot BMI - Measure blood pressure Management - Lifestyle modification - Exercise - Reduction of intake of food with high glycemic index - Screen for diabetes and hypertension and manage accordingly - Refer to next level of care
TERTIARY CARE FACILITY - Relevant history and physical exam - Plot growth chart - Calculate and plot BMI - Measure blood pressure Management - Lifestyle modification - Exercise - Reduction of intake of food with high glycemic index - Screen for diabetes and hypertension and manage accordingly Psychosocial counseling - Refer to the endocrinologist. Multidisciplinary involvement including nurses, dieticians, nutritionists, paediatricians, psychosocial counselors.

Follow up

- Medication review for side effects
- Monitor growth and development
- Ongoing counselling

GROWTH DISORDERS

Short stature

Definition

Short stature is a term applied to a child whose height is 2 standard deviations (SD) or more below the mean for children of that sex and chronologic age (and ideally of the same racial-ethnic group).

Risk factors/Causes

- Chronic disease
- Chronic malnutrition
- Psychosocial deprivation

- Family history of short stature
- Delayed growth and puberty
- Chronic steroid use

Prevention
Early detection and treatment of underlying causes.

Promotion
Health education.

Signs and symptoms
- Shorter than peers of same age and sex.

Investigations

- Bone age
- Full Blood Count (FBC)
- Erythrocyte Sedimentation Rate (ESR)
- Urea and Electrolytes
- Thyroid-Stimulating Hormone (TSH), free thyroxine (T4)
- If available: IGF-1, IGFBP-3, Transglutaminase IgA

Differential diagnosis

- Familial short stature
- Constitutional delay of growth and puberty
- Undernutrition
- GI disease (especially Crohn disease and celiac disease)
- Renal disease (CKD, renal tubular acidosis)
- Endocrine causes of growth failure (hypothyroidism, isolated growth hormone deficiency, cushings disease)
- Cardiac disease
- Genetic diseases with primary effects on growth eg down's syndrome, Turner syndrome

Management

PRIMARY LEVEL ● History and physical examination Plot height and weight on growth chart ● Random blood Glucose (RBS) and urine dipstick ● Refer to next level of care
SECONDARY LEVEL As above ● RBS, FBC, erythrocyte sedimentation rate (ESR) ● Refer to next level of care
TERTIARY LEVEL ● History and physical exam Calculate height velocity Plot parents' height and calculate mid-parental height

- Investigations
  Bone age
  FBC
  ESR
  Electrolytes, creatinine
  Thyroid-stimulating hormone (TSH), free thyroxine (T4)
  If available: IgF-1, IgFBP-3, IgA, Transglutaminase IgA
- Refer to paediatric endocrinologist

Tall stature

Definition

Tall stature is a term applied to a child whose height is 2 standard deviations (SD) or more above the mean for children of that sex and chronologic age (and ideally of the same racial-ethnic group).

Risk factors/Causes

- Growth hormone excess
- Hyperthyroidism
- Family history of tall stature
- Overweight/obesity
- Accelerated growth and puberty

Prevention

Early detection

Promotion

Health education and advocacy

Signs and symptoms

- Taller than peers of same age and sex.

Investigations

- Bone age
- Complete Blood Count (CBC)
- Erythrocyte Sedimentation Rate (ESR)
- Urea and Electrolytes
- Thyroid-Stimulating Hormone (TSH), free thyroxine (T4)
- If available: IgF-1, IgFBP-3

Differential diagnosis

- Familial tall stature
- Hyperthyroidism
- GH-secreting tumours
- Precocious puberty (temporarily tall stature)
- Genetic diseases with primary effects on growth eg Klinefelter syndrome

Management

PRIMARY LEVEL ● History and physical examination Plot height and weight on growth chart ● Random blood Glucose (RBS) and urine dipstick ● Refer to next level of care
SECONDARY LEVEL As above ● RBS, FBC, erythrocyte sedimentation rate (ESR) ● Refer to next level of care
TERTIARY LEVEL ● History and physical exam Calculate height velocity Plot parents' height and calculate mid-parental height ● Investigations Bone age FBC ESR Electrolytes, creatinine Thyroid-stimulating hormone (TSH), free thyroxine (T4) If available: IgF-1, IgFBP-3 Refer to paediatric endocrinologist

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