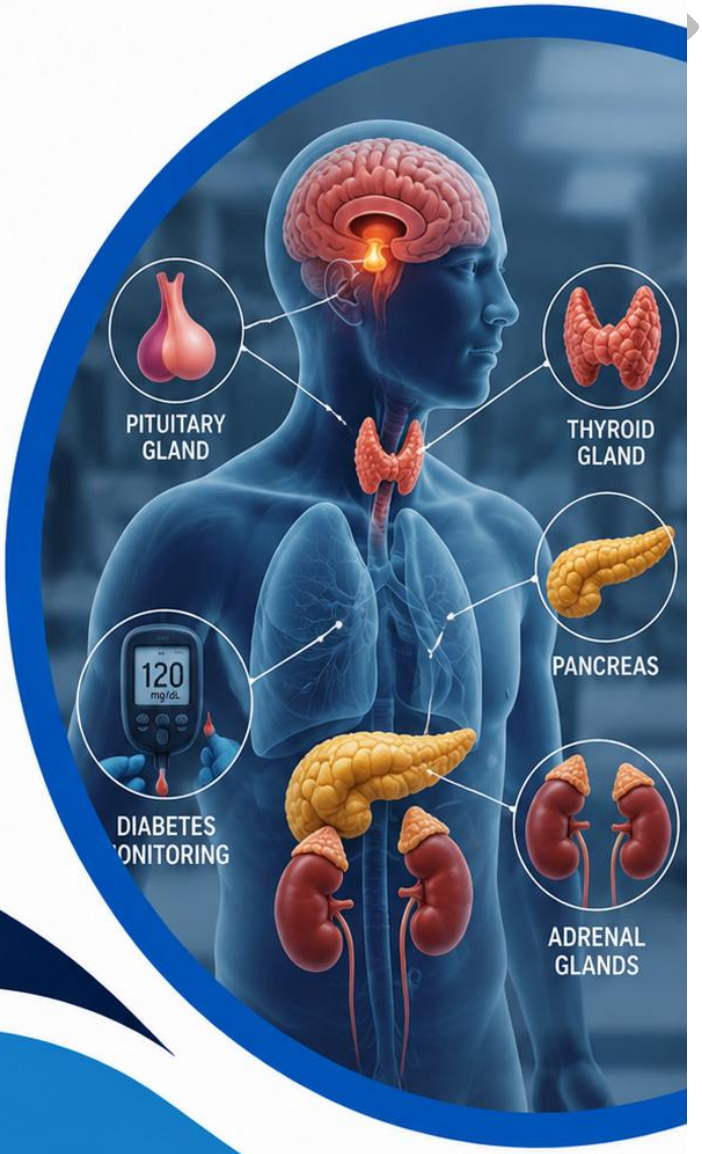
La-Net

PAE 507

ENDOCRINE AND METABOLIC DISORDERS



Download on the App Store

GET IT ON Google Play

Course video is available on our app

lanetonline.com

Course code: PAE 507

Course title: Endocrine and Metabolic Disorders

Course credit load: 2 Units

Series 1: Disorders of Sexual Development

- **Part 1.1: Normal Sexual Differentiation and Definition of DSD**
  - Sub Part 1.1.1: Normal sexual differentiation in the fetus
  - Sub Part 1.1.2: Definition of disorder of sexual development
  - Sub Part 1.1.3: The significance of ambiguous genitalia at birth
- **Part 1.2: Classification of Disorders of Sexual Development**
  - Sub Part 1.2.1: Overview of the classification of DSD
  - Sub Part 1.2.2: 46,XX DSD and 46,XY DSD
  - Sub Part 1.2.3: Sex chromosome DSD
- **Part 1.3: Clinical Evaluation of a Child with Ambiguous Genitalia**
  - Sub Part 1.3.1: Relevant clinical history
  - Sub Part 1.3.2: Physical examination of a child with suspected DSD
  - Sub Part 1.3.3: The importance of sensitive, structured communication
- **Part 1.4: Investigation and Management of Disorders of Sexual Development**
  - Sub Part 1.4.1: Investigations used in evaluating DSD
  - Sub Part 1.4.2: General principles of management
  - Sub Part 1.4.3: Long-term follow up and psychosocial support

Introduction

Picture a newborn whose external genitalia do not appear clearly male or female at birth, leaving the delivery room team uncertain what to tell the anxious parents. Moments such as this, though uncommon, require calm, structured, and sensitive clinical evaluation, since the underlying cause can range from a benign variant to a condition with significant, even life-threatening, hormonal implications. This Series opens the PAE 507 course by introducing disorders of sexual development, building the knowledge required to evaluate and appropriately manage a child presenting with ambiguous genitalia or another indication of atypical sexual differentiation.

The aim of this Series is to equip you with the knowledge required to understand normal sexual differentiation, define and classify disorders of sexual development, and evaluate and understand the management of a child presenting with ambiguous genitalia.

This Series begins with **normal sexual differentiation** and the **definition of disorder of sexual development**, before turning to the **classification** of DSD into its major categories. Next, we examine the **clinical evaluation** of a child with ambiguous genitalia, before concluding with the **investigation and management** of disorders of sexual development.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the normal process of sexual differentiation in the fetus,
- **SLO 1.2:** define disorder of sexual development and list its major categories,
- **SLO 1.3:** classify disorders of sexual development into 46XX DSD, 46XY DSD, and sex chromosome DSD,
- **SLO 1.4:** give examples of conditions within each category of disorder of sexual development,
- **SLO 1.5:** describe the clinical history relevant to a child presenting with ambiguous genitalia,
- **SLO 1.6:** describe the physical examination of a child with suspected disorder of sexual development,
- **SLO 1.7:** describe the investigations used in evaluating a child with disorder of sexual development, and
- **SLO 1.8:** describe the general principles of management of disorder of sexual development.

1.1 Normal Sexual Differentiation and Definition of DSD

1.1.1 normal sexual differentiation in the fetus

Chromosomes set the stage, hormones write the script

Normal sexual differentiation begins with **chromosomal sex**, established at fertilisation as either **46,XX** or **46,XY**, which determines whether the initially **bipotential gonad** develops into a **testis** or an **ovary**, a process termed **gonadal sex**. In a 46,XY fetus, the **SRY gene** on the Y chromosome triggers **testicular development**, and the resulting testis then produces

testosterone and **anti-Mullerian hormone**, which together drive the development of male internal and external genitalia.

In the absence of a Y chromosome and SRY gene expression, the bipotential gonad develops as an **ovary**, and, in the absence of testosterone and anti-Mullerian hormone, the internal and external genitalia develop along the **default female pathway**. This orderly sequence, from chromosomal sex through gonadal sex to the development of internal and external genitalia, is termed **phenotypic sex**, and a disruption at any point in this sequence can result in a disorder of sexual development.

Fill in the blank: In a 46,XY fetus, the _____ gene on the Y chromosome triggers testicular development.

1.1.2 definition of disorder of sexual development

A **disorder of sexual development**, abbreviated DSD, is defined as a **congenital condition** in which the development of **chromosomal**, **gonadal**, or **anatomical sex** is atypical, meaning there is a mismatch or ambiguity somewhere along the normal sequence of chromosomal, gonadal, and phenotypic sex described in the previous sub-Part. DSD encompasses a wide spectrum, from **externally ambiguous genitalia** noted at birth to more subtle presentations identified later in childhood or even adolescence.

The term DSD has largely replaced older, less precise or potentially stigmatising terminology, and its use reflects a broader shift towards a more **structured, biologically grounded classification system**, which in turn supports a more systematic and less anxiety-provoking approach to evaluation and communication with affected families, a theme that will be developed further later in this Series.

Fill in the blank: DSD is defined as a congenital condition in which chromosomal, gonadal, or _____ sex is atypical.

1.1.3 the significance of ambiguous genitalia at birth

Ambiguous genitalia at birth is one of the more striking presentations of DSD, and represents both a **diagnostic** and a significant **communication challenge**, since parents naturally expect to be told clearly whether their baby is a boy or a girl, and a delay or uncertainty in this assignment can be understandably distressing without careful, empathetic explanation.

Beyond the diagnostic and psychosocial dimensions, ambiguous genitalia in a newborn can, in certain underlying conditions, signal a **medical emergency**, particularly where **salt-wasting congenital adrenal hyperplasia** is the underlying cause, since affected infants are at risk of a

life-threatening adrenal crisis within the first weeks of life if the diagnosis is missed, making prompt, structured evaluation genuinely urgent rather than purely of academic interest.

Fill in the blank: Ambiguous genitalia can signal a medical emergency, particularly where salt-wasting congenital adrenal _____ is the underlying cause.

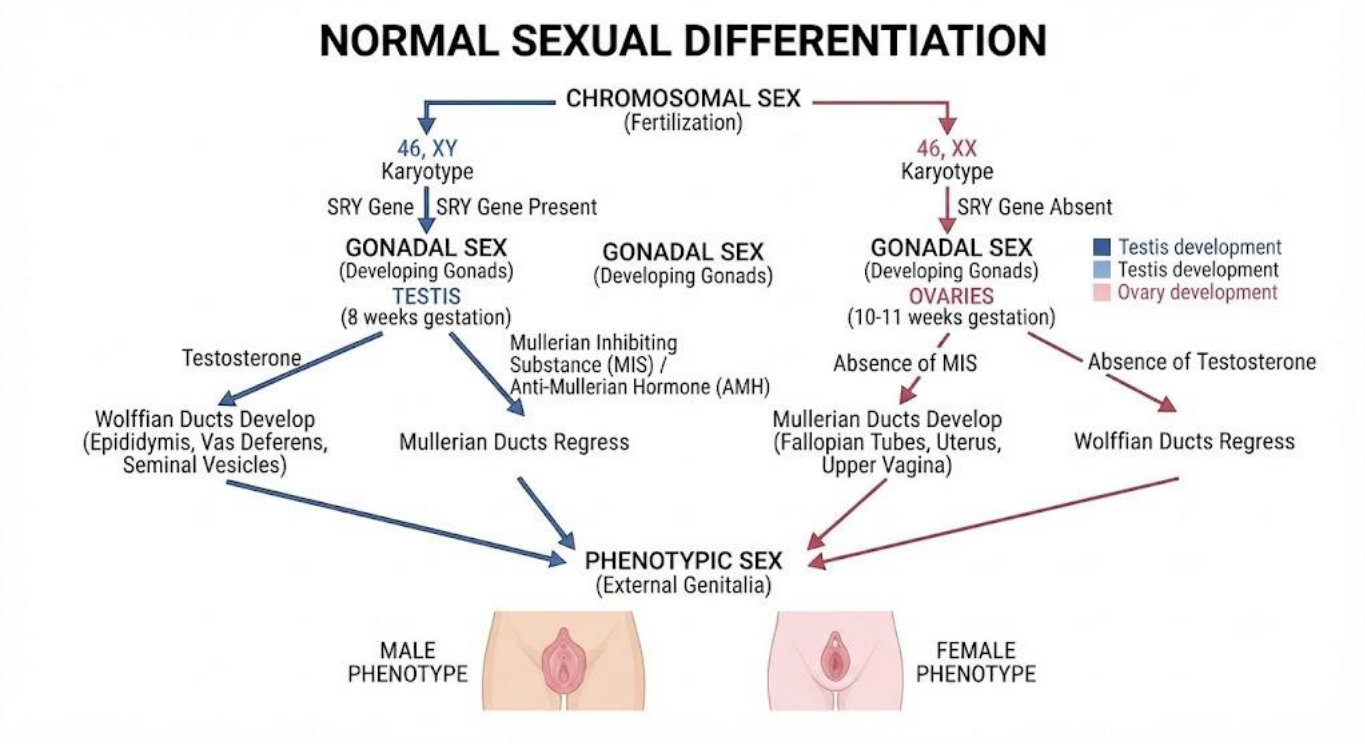


Figure 1.1: The normal sequence from chromosomal sex to phenotypic sex.

Pilot questions 1.1

1. Describe the normal sequence from chromosomal sex to phenotypic sex. (Linked to SLO 1.1)
2. Explain the role of the SRY gene in normal sexual differentiation. (Linked to SLO 1.1)
3. Define disorder of sexual development. (Linked to SLO 1.2)
4. Explain why the term DSD is now preferred to older terminology. (Linked to SLO 1.2)
5. Explain why ambiguous genitalia in a newborn can represent a medical emergency. (Linked to SLO 1.2)

1.2 Classification of Disorders of Sexual Development

1.2.1 overview of the classification of DSD

Classification follows the karyotype

Disorders of sexual development are classified into three major categories based on **karyotype**: **sex chromosome DSD**, in which the sex chromosome complement itself is atypical, **46,XY DSD**, in which the karyotype is male but the gonadal or phenotypic development is atypical, and **46,XX DSD**, in which the karyotype is female but the gonadal or phenotypic development is atypical. This classification system provides a structured starting point for both diagnosis and discussion with families.

Within each of these three broad categories, conditions can be further subdivided according to whether the primary abnormality lies at the level of **gonadal development** itself or at the level of **hormone production or action** further along the differentiation pathway, a distinction that becomes particularly important when selecting appropriate investigations, discussed later in this Series.

Fill in the blank: DSD is classified into three major categories based on _____.

1.2.2 46,XX DSD and 46,XY DSD

46,XX DSD most commonly results from **congenital adrenal hyperplasia**, particularly due to **21-hydroxylase deficiency**, in which excess adrenal androgen production causes **virilisation** of an otherwise chromosomally and gonadally female fetus, producing a spectrum of external genital ambiguity while internal female reproductive structures remain present. This is the single most common identifiable cause of ambiguous genitalia overall and is of particular importance because of its potential to cause salt-wasting adrenal crisis, as discussed earlier.

46,XY DSD encompasses a broader range of underlying mechanisms, including **disorders of testicular development**, such as complete or partial **gonadal dysgenesis**, and **disorders of androgen synthesis or action**, such as **5-alpha reductase deficiency**, which impairs conversion of testosterone to its more potent form, or **androgen insensitivity syndrome**, in which tissues fail to respond normally to circulating androgens despite normal or even elevated levels.

Fill in the blank: The single most common identifiable cause of ambiguous genitalia overall is congenital adrenal _____.

1.2.3 sex chromosome DSD

Sex chromosome DSD includes conditions in which the sex chromosome complement itself deviates from the typical 46,XX or 46,XY pattern, such as **45,X**, associated with **Turner syndrome**, **47,XXY**, associated with **Klinefelter syndrome**, and **mixed gonadal dysgenesis**, in which an individual has a mosaic karyotype with cell lines of differing chromosomal composition, resulting in variable, sometimes asymmetrical, gonadal and genital development.

Unlike many 46,XX and 46,XY DSD conditions, several forms of sex chromosome DSD, particularly **Turner** and **Klinefelter syndrome**, are frequently **not associated with overt genital ambiguity** at birth, and may instead present later in childhood or adolescence with features such as short stature, delayed puberty, or infertility, meaning a normal-appearing genital examination at birth does not entirely exclude an underlying sex chromosome DSD.

Fill in the blank: 45,X karyotype is associated with _____ syndrome.

Table 1.2: Classification of disorders of sexual development with representative examples.

Category	Karyotype pattern	Representative example
46,XX DSD	Female karyotype, atypical development	Congenital adrenal hyperplasia (21-hydroxylase deficiency)
46,XY DSD	Male karyotype, atypical development	Androgen insensitivity syndrome, 5-alpha reductase deficiency
Sex chromosome DSD	Atypical chromosome complement	Turner syndrome (45,X), Klinefelter syndrome (47,XXY)

Pilot questions 1.2

1. List the three major categories used to classify DSD. (Linked to SLO 1.3)
2. Describe the most common cause of 46,XX DSD and its underlying mechanism. (Linked to SLO 1.4)
3. Give two examples of conditions causing 46,XY DSD. (Linked to SLO 1.4)
4. Give two examples of sex chromosome DSD. (Linked to SLO 1.4)
5. Explain why a normal-appearing genital examination at birth does not entirely exclude sex chromosome DSD. (Linked to SLO 1.4)

1.3 Clinical Evaluation of a Child with Ambiguous Genitalia

1.3.1 relevant clinical history

The family and pregnancy history often hold vital clues

A focused history in a child with suspected DSD should include a detailed **antenatal history**, including any maternal **medication or hormone exposure** during pregnancy and any findings on **antenatal ultrasound**, together with a **family history** of similar genital ambiguity, infertility, early infant deaths, which may suggest undiagnosed salt-wasting congenital adrenal hyperplasia in a previous child, or **parental consanguinity**, which increases the likelihood of an autosomal recessive condition such as congenital adrenal hyperplasia.

The **birth history** should also be reviewed for any signs suggestive of an evolving **adrenal crisis**, such as poor feeding, vomiting, or lethargy in the first days of life, since these features, in combination with ambiguous genitalia, should prompt urgent evaluation for salt-wasting congenital adrenal hyperplasia rather than a purely elective work up.

Fill in the blank: Parental _____ increases the likelihood of an autosomal recessive condition such as congenital adrenal hyperplasia.

1.3.2 physical examination of a child with suspected DSD

Physical examination should carefully document the appearance of the **external genitalia**, including **phallus or clitoral size**, the position of the **urethral opening**, the degree of **labioscrotal fold fusion**, and, critically, whether **gonads are palpable**, and if so, their location, since a palpable gonad within a labioscrotal fold strongly suggests the presence of a **testis**, as ovaries do not normally descend into this location.

A general examination should also assess for signs of **hyperpigmentation**, which may suggest excess adrenocorticotrophic hormone associated with congenital adrenal hyperplasia, **blood pressure**, and **hydration status**, together with a careful search for any **dysmorphic features** or other congenital anomalies that might point towards a specific underlying syndrome.

Fill in the blank: A palpable gonad within a labioscrotal fold strongly suggests the presence of a _____.

1.3.3 the importance of sensitive, structured communication

Communication with the family of a newborn with ambiguous genitalia requires particular sensitivity, and current best practice generally recommends **avoiding premature sex**

assignment before an adequate evaluation has been completed, while clearly and honestly explaining to parents that their baby's genital development is still being assessed, using **neutral, non-judgemental language** rather than terms that might feel stigmatising or alarming.

A **multidisciplinary team**, typically including paediatric endocrinology, urology or surgery, clinical genetics, and psychology or counselling support, should be involved as early as possible, both to expedite an accurate diagnosis and to provide the family with **consistent, coordinated support** throughout what is often an emotionally difficult period of uncertainty.

Fill in the blank: Current best practice generally recommends avoiding premature sex _____ before an adequate evaluation has been completed.

Box 1.3: Key elements of history and examination in a child with suspected DSD.

History and examination checklist for suspected DSD
Antenatal history: maternal medication or hormone exposure, antenatal ultrasound findings.
Family history: similar ambiguity, infertility, early infant deaths, parental consanguinity.
Birth history: signs suggestive of evolving adrenal crisis.
Genital examination: phallus or clitoral size, urethral position, labioscrotal fusion, gonadal palpability.
General examination: hyperpigmentation, blood pressure, hydration, dysmorphic features.

Pilot questions 1.3

1. List three components of a focused history in a child with suspected DSD. (Linked to SLO 1.5)
2. Why is parental consanguinity relevant when evaluating a child with suspected DSD? (Linked to SLO 1.5)
3. Describe the key components of genital examination in a child with suspected DSD. (Linked to SLO 1.6)
4. What is the significance of a palpable gonad in a labioscrotal fold? (Linked to SLO 1.6)
5. Describe the recommended approach to communicating with parents of a newborn with ambiguous genitalia. (Linked to SLO 1.6)

1.4 Investigation and Management of Disorders of Sexual Development

1.4.1 investigations used in evaluating DSD

Building a diagnosis from chromosomes to hormones to anatomy

Investigation of suspected DSD begins with **karyotyping**, or rapid chromosomal analysis where urgently required, to establish the chromosomal sex and guide the subsequent diagnostic pathway, together with **serum electrolytes**, since hyponatraemia and hyperkalaemia may indicate an evolving salt-wasting adrenal crisis requiring urgent treatment even before the underlying diagnosis is fully confirmed.

Further hormonal investigations are selected according to the clinical picture and karyotype result, and may include **17-hydroxyprogesterone**, markedly elevated in 21-hydroxylase deficiency congenital adrenal hyperplasia, **testosterone** and related androgen precursors, and **anti-Mullerian hormone**, which provides information about the presence and function of testicular tissue, while **pelvic ultrasound** assesses for the presence of a **uterus** and helps localise the **gonads**.

Fill in the blank: Rapid _____ is performed urgently where required to establish chromosomal sex.

1.4.2 general principles of management

Management of DSD is highly individualised according to the specific underlying diagnosis, but several general principles apply broadly: urgent recognition and treatment of any **salt-wasting adrenal crisis**, using **hydrocortisone**, **fludrocortisone**, and, where needed, **intravenous fluid and glucose**, takes priority over any other consideration when clinically suspected, since this can be immediately life-threatening if missed or delayed.

Beyond the acute management of any emergency, **sex of rearing** decisions, where relevant, together with any consideration of **surgical management** of genital anatomy, should be made carefully, by the multidisciplinary team together with the family, and, wherever developmentally appropriate, the child themselves as they grow older, reflecting a shift away from historical practice towards a more individualised, less rushed approach to these significant decisions.

Fill in the blank: Urgent treatment of salt-wasting adrenal crisis using hydrocortisone and _____ takes priority over other considerations.

1.4.3 long-term follow up and psychosocial support

Children with DSD require **long-term, coordinated follow up**, including monitoring of **growth and pubertal development**, ongoing **hormone replacement** where required, such as glucocorticoid and mineralocorticoid replacement in congenital adrenal hyperplasia, and periodic reassessment as the child matures and their own understanding, questions, and preferences develop.

Psychosocial support for both the child and family is an essential, ongoing component of care, since children with DSD and their families can face particular challenges around identity, disclosure, and social acceptance, and access to **psychology or counselling services**, together with connection to relevant **peer support networks** where available, meaningfully improves long-term wellbeing and should be considered a core, not optional, part of comprehensive DSD care.

Fill in the blank: Psychosocial support should be considered a core, not _____, part of comprehensive DSD care.

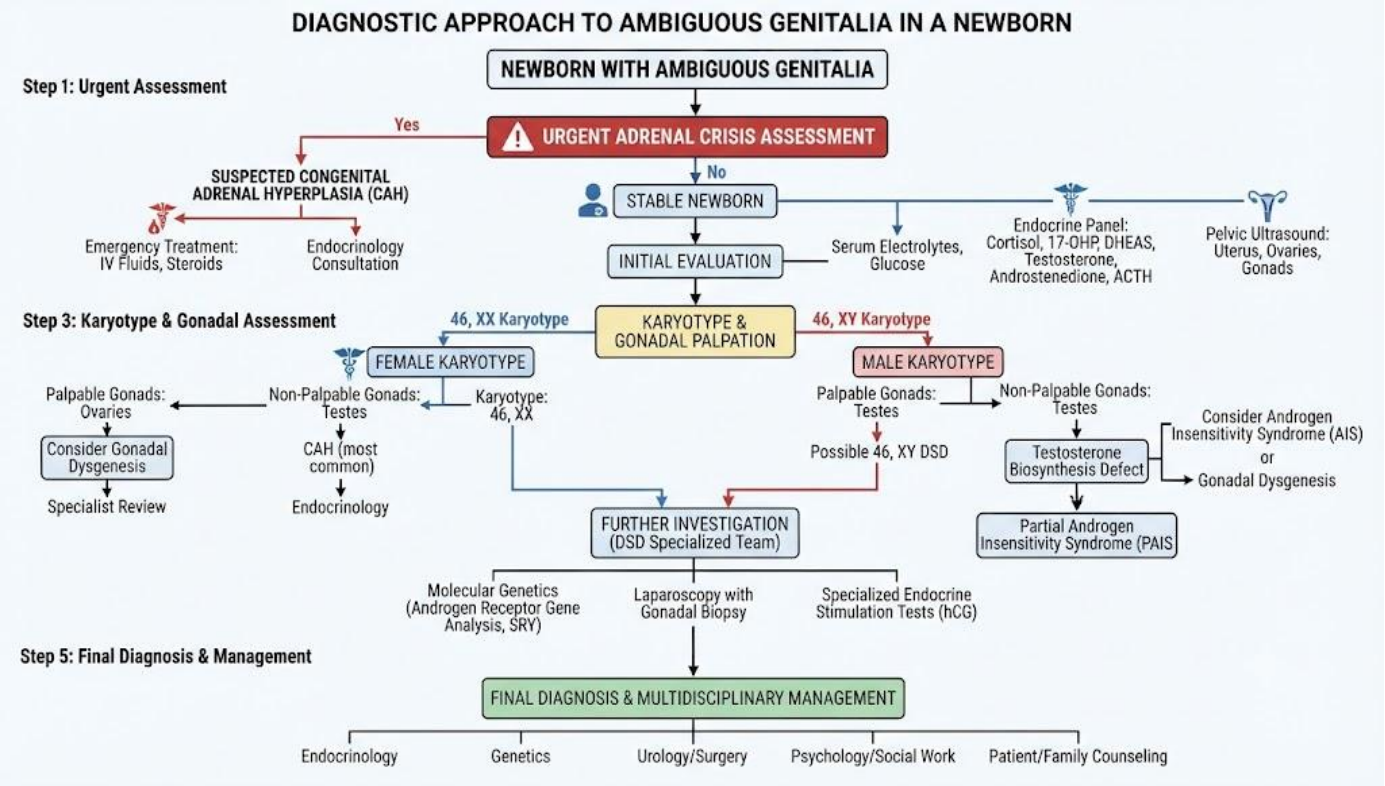


Figure 1.4: A structured diagnostic approach to a newborn with ambiguous genitalia.

Pilot questions 1.4

1. Describe the first investigations performed in a newborn with suspected DSD. (Linked to SLO 1.7)
2. Explain why serum electrolytes are checked urgently in a newborn with ambiguous genitalia. (Linked to SLO 1.7)
3. Which hormone is markedly elevated in 21-hydroxylase deficiency congenital adrenal hyperplasia? (Linked to SLO 1.7)
4. Describe the emergency management of suspected salt-wasting adrenal crisis. (Linked to SLO 1.8)
5. Explain the importance of psychosocial support in the long-term management of DSD. (Linked to SLO 1.8)

Series Summary

This Series introduced **disorders of sexual development**, beginning with normal sexual differentiation and the definition of DSD, before turning to its **classification** into 46,XX DSD, 46,XY DSD, and sex chromosome DSD.

We then examined the **clinical evaluation** of a child with ambiguous genitalia, before concluding with the **investigation and management** of DSD, including the urgent recognition of salt-wasting adrenal crisis and the importance of long-term, multidisciplinary follow up. Having worked through this Series, you should now be able to evaluate and understand the management of a child with a suspected disorder of sexual development. The next Series turns to **thyroid gland physiology and thyroid disorders**.

Glossary of Terms

- **Disorder of sexual development:** a congenital condition in which chromosomal, gonadal, or anatomical sex is atypical.
- **SRY gene:** a gene on the Y chromosome that triggers testicular development in normal male sexual differentiation.
- **46,XX DSD:** a disorder of sexual development in an individual with a female karyotype, most commonly due to congenital adrenal hyperplasia.
- **46,XY DSD:** a disorder of sexual development in an individual with a male karyotype, including disorders of testicular development or androgen action.
- **Sex chromosome DSD:** a disorder of sexual development in which the sex chromosome complement itself is atypical.
- **Congenital adrenal hyperplasia:** the most common identifiable cause of 46,XX DSD, most often due to 21-hydroxylase deficiency.
- **Androgen insensitivity syndrome:** a form of 46,XY DSD in which tissues fail to respond normally to circulating androgens.
- **Turner syndrome:** a sex chromosome DSD associated with a 45,X karyotype.
- **Klinefelter syndrome:** a sex chromosome DSD associated with a 47,XXY karyotype.
- **Salt-wasting adrenal crisis:** a life-threatening complication of severe congenital adrenal hyperplasia requiring urgent treatment.
- **Karyotyping:** chromosomal analysis used to establish chromosomal sex in a child with suspected DSD.
- **17-hydroxyprogesterone:** a hormone markedly elevated in 21-hydroxylase deficiency congenital adrenal hyperplasia.

Concept Check Questions [Series 1]

Objective questions

1. In a 46,XY fetus, the _____ gene on the Y chromosome triggers testicular development.
2. The single most common identifiable cause of ambiguous genitalia overall is congenital adrenal _____.
3. 45,X karyotype is associated with _____ syndrome.
4. A palpable gonad within a labioscrotal fold strongly suggests the presence of a _____.
5. Rapid _____ is performed urgently where required to establish chromosomal sex.

Short-answer questions

6. Describe the normal sequence from chromosomal sex to phenotypic sex.
7. List the three major categories used to classify DSD.
8. Describe the key components of genital examination in a child with suspected DSD.
9. Explain why serum electrolytes are checked urgently in a newborn with ambiguous genitalia.
10. Describe the emergency management of suspected salt-wasting adrenal crisis.

Long-answer questions

11. Discuss normal sexual differentiation and the definition of disorder of sexual development. (Linked to SLO 1.1, SLO 1.2)
12. Discuss the classification of disorders of sexual development with examples of each category. (Linked to SLO 1.3, SLO 1.4)
13. Discuss the clinical history and examination relevant to a child with suspected DSD. (Linked to SLO 1.5, SLO 1.6)
14. Discuss the investigations used in evaluating a child with disorder of sexual development. (Linked to SLO 1.7)
15. Discuss the general principles of management of disorder of sexual development. (Linked to SLO 1.8)

Answers to Concept Check Questions [Series 1]

Objective questions

1. SRY.

2. Hyperplasia.
3. Turner.
4. Testis.
5. Karyotyping.

Short-answer questions

6. Chromosomal sex determines gonadal sex, which through hormone production determines phenotypic sex.
7. 46,XX DSD, 46,XY DSD, and sex chromosome DSD.
8. Phallus or clitoral size, urethral position, labioscrotal fusion, and gonadal palpability.
9. Hyponatraemia and hyperkalaemia may indicate an evolving salt-wasting adrenal crisis requiring urgent treatment.
10. Hydrocortisone, fludrocortisone, and intravenous fluid and glucose as needed.

Long-answer questions

11. **Basic response:** Chromosomal sex determines gonadal sex through SRY gene expression, and gonadal hormone production then determines phenotypic sex; DSD is a congenital condition in which this sequence is atypical.

Value-added response: The term DSD reflects a structured, biologically grounded classification that supports more systematic evaluation and less stigmatising communication with families than older terminology.

12. **Basic response:** DSD is classified into 46,XX DSD, most commonly congenital adrenal hyperplasia, 46,XY DSD, including androgen insensitivity syndrome, and sex chromosome DSD, including Turner and Klinefelter syndrome.

Value-added response: This karyotype-based classification provides a structured starting point for diagnosis, though further subdivision by whether the abnormality lies at gonadal development or hormone production or action guides specific investigation choices.

13. **Basic response:** History should cover antenatal exposures, family history including consanguinity, and birth history, while examination assesses genital anatomy, gonadal palpability, and general signs such as hyperpigmentation.

Value-added response: Sensitive, structured communication avoiding premature sex assignment is essential, with early multidisciplinary team involvement supporting both accurate diagnosis and family support.

14. **Basic response:** Investigation begins with karyotyping and serum electrolytes, followed by hormonal tests such as 17-hydroxyprogesterone and anti-Mullerian hormone, and pelvic ultrasound to assess internal anatomy.

Value-added response: Electrolytes are checked urgently since salt-wasting adrenal crisis can be immediately life-threatening and must be identified and treated even before the underlying diagnosis is fully confirmed.

15. **Basic response:** Management prioritises urgent treatment of any salt-wasting adrenal crisis, followed by individualised decisions on sex of rearing and surgical management made with the multidisciplinary team and family.

Value-added response: Long-term follow up includes monitoring growth and puberty, hormone replacement where needed, and ongoing psychosocial support, which should be considered a core part of comprehensive DSD care.

Answers to Pilot Questions [Series 1]

Part 1.1

1. Chromosomal sex determines gonadal sex, which through hormone production determines phenotypic sex.
2. The SRY gene on the Y chromosome triggers testicular development from the bipotential gonad.
3. DSD is a congenital condition in which chromosomal, gonadal, or anatomical sex is atypical.
4. DSD reflects a more structured, biologically grounded, and less stigmatising classification system.
5. It can signal salt-wasting congenital adrenal hyperplasia, risking a life-threatening adrenal crisis.

Part 1.2

1. 46,XX DSD, 46,XY DSD, and sex chromosome DSD are the three major categories.
2. Congenital adrenal hyperplasia, due to 21-hydroxylase deficiency, is the most common cause of 46,XX DSD.
3. Androgen insensitivity syndrome and 5-alpha reductase deficiency are examples of 46,XY DSD.
4. Turner syndrome (45,X) and Klinefelter syndrome (47,XXY) are examples of sex chromosome DSD.
5. Several sex chromosome DSD conditions are not associated with overt genital ambiguity at birth and may present later.

Part 1.3

1. Antenatal history, family history, and birth history are key components.
2. Consanguinity increases the likelihood of an autosomal recessive condition such as congenital adrenal hyperplasia.
3. Phallus or clitoral size, urethral position, labioscrotal fusion, and gonadal palpability.
4. A palpable gonad in a labioscrotal fold strongly suggests the presence of a testis.
5. Avoid premature sex assignment, use neutral language, and involve a multidisciplinary team early.

Part 1.4

1. Karyotyping and serum electrolytes are the first investigations performed.
2. They may indicate an evolving salt-wasting adrenal crisis requiring urgent treatment.

3. 17-hydroxyprogesterone is markedly elevated in 21-hydroxylase deficiency congenital adrenal hyperplasia.
4. Hydrocortisone, fludrocortisone, and intravenous fluid and glucose as needed.
5. It supports identity, disclosure, and social acceptance, meaningfully improving long-term wellbeing.

- Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
- Lee, P. A. et al. (2016). Global disorders of sex development update since 2006. Hormone Research in Paediatrics, 85(3), 158 to 180.
- Hughes, I. A. et al. (2006). Consensus statement on management of intersex disorders. Archives of Disease in Childhood, 91(7), 554 to 563.
- Speiser, P. W. et al. (2018). Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism, 103(11), 4043 to 4088.

Figures, Plates, Tables, and Boxes

- Figure 1.1: The normal sequence from chromosomal sex to phenotypic sex. AI-generated using the prompt: "Create a professional educational diagram titled Normal Sexual Differentiation, showing the sequence from chromosomal sex to gonadal sex to phenotypic sex with hormone influences labelled. Clean clinical educational diagram style."
- Table 1.2: Classification of disorders of sexual development with representative examples. AI-generated using the prompt: "Create a clean reference table titled Classification of Disorders of Sexual Development, listing category, karyotype pattern, and representative example. Simple clinical reference table style with outside border."
- Box 1.3: Key elements of history and examination in a child with suspected DSD. AI-generated using the prompt: "Create a simple single-column reference box titled History and Examination Checklist for Suspected DSD. Clean clinical reference box style."
- Figure 1.4: A structured diagnostic approach to a newborn with ambiguous genitalia. AI-generated using the prompt: "Create a professional medical flowchart titled Diagnostic Approach to Ambiguous Genitalia in a Newborn, branching from urgent adrenal crisis assessment through karyotyping to further investigation. Clean clinical educational diagram style."

Series 2: Thyroid Gland Physiology and Thyroid Disorders

- **Part 2.1: Normal Thyroid Gland Physiology**
    - Sub Part 2.1.1: Anatomy of the thyroid gland
    - Sub Part 2.1.2: Synthesis and regulation of thyroid hormone
    - Sub Part 2.1.3: Thyroid hormone action at the cellular level
- **Part 2.2: Functions of Thyroid Hormone and Classification of Thyroid Disorders**
    - Sub Part 2.2.1: Functions of thyroid hormone
    - Sub Part 2.2.2: Classification of thyroid disorders
    - Sub Part 2.2.3: Goitre and its significance
- **Part 2.3: Hypothyroidism and Hyperthyroidism: Clinical Features**
    - Sub Part 2.3.1: Clinical features of congenital hypothyroidism
    - Sub Part 2.3.2: Clinical features of acquired hypothyroidism
    - Sub Part 2.3.3: Clinical features of hyperthyroidism
- **Part 2.4: Work Up and Management of Thyroid Disorders**
    - Sub Part 2.4.1: Laboratory investigation of thyroid disorders
    - Sub Part 2.4.2: Imaging in the evaluation of thyroid disorders
    - Sub Part 2.4.3: General management of thyroid disorders

Introduction

In the last Series, we explored disorders of sexual development. We now turn to another important endocrine gland, the thyroid. Picture a newborn who appears well at birth but, if a thyroid disorder present from birth is missed, may go on to develop irreversible intellectual impairment entirely preventable with timely treatment. This Series introduces normal thyroid physiology and the common thyroid disorders encountered in paediatric practice, building the knowledge required to recognise and manage them promptly.

The aim of this Series is to equip you with the knowledge required to understand normal thyroid physiology, recognise the clinical features of common thyroid disorders, and understand their appropriate work up and management.

This Series begins with **normal thyroid gland physiology**, before turning to the **functions of thyroid hormone and classification of thyroid disorders**. Next, we examine the **clinical features of hypothyroidism and hyperthyroidism**, before concluding with the **work up and management** of thyroid disorders.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** describe the normal anatomy and physiology of the thyroid gland,
- **SLO 1.2:** describe the hypothalamic-pituitary-thyroid axis and its regulation,
- **SLO 1.3:** list the functions of thyroid hormone in the body,
- **SLO 1.4:** enumerate the different types of thyroid disorders encountered in children,
- **SLO 1.5:** describe the clinical features of congenital and acquired hypothyroidism,
- **SLO 1.6:** describe the clinical features of hyperthyroidism in children,
- **SLO 1.7:** describe the work up of thyroid disorders, including relevant laboratory and imaging investigations, and
- **SLO 1.8:** outline the general management of thyroid disorders in children.

2.1 Normal Thyroid Gland Physiology

2.1.1 anatomy of the thyroid gland

A small gland with a large metabolic reach

The **thyroid gland** is a butterfly-shaped gland situated in the anterior neck, straddling the trachea just below the **thyroid cartilage**, and consists of two lobes connected by a central **isthmus**. Microscopically, the gland is composed of numerous **follicles**, each lined by **follicular cells** that synthesise and secrete **thyroid hormone**, and containing a central store of **colloid**, the protein matrix within which thyroid hormone is stored prior to release.

Scattered between the follicles are **parafollicular cells**, also called **C cells**, which produce **calcitonin**, a hormone involved in calcium regulation, distinct from the main hormone-producing function of the follicular cells, and this dual cellular population within a single gland is a useful anatomical detail to remember when considering thyroid pathology, since it explains why certain thyroid tumours arise specifically from calcitonin-producing tissue.

Fill in the blank: Thyroid hormone is stored within a central protein matrix called _____ inside each follicle.

2.1.2 synthesis and regulation of thyroid hormone

Thyroid hormone synthesis begins with active **uptake of iodide** from the bloodstream into follicular cells, followed by **organification**, the incorporation of iodide into **thyroglobulin**, and coupling to form **thyroxine**, abbreviated **T4**, and **triiodothyronine**, abbreviated **T3**, the two principal thyroid hormones, with T4 produced in much greater quantity but T3 being the more biologically active form at the tissue level.

Thyroid hormone production is regulated by the **hypothalamic-pituitary-thyroid axis**: the hypothalamus secretes **thyrotropin-releasing hormone**, which stimulates the anterior pituitary to secrete **thyroid-stimulating hormone**, abbreviated **TSH**, which in turn stimulates the thyroid gland to produce and release T4 and T3. Circulating thyroid hormone then exerts **negative feedback** on both the hypothalamus and pituitary, completing a tightly regulated control loop that maintains thyroid hormone levels within a narrow normal range.

Fill in the blank: Circulating thyroid hormone exerts negative _____ on the hypothalamus and pituitary.

2.1.3 thyroid hormone action at the cellular level

Most circulating thyroid hormone is bound to carrier proteins, particularly **thyroxine-binding globulin**, with only the small **free fraction** of T4 and T3 being biologically active. At the tissue level, T4 is converted to the more active T3 by the enzyme **deiodinase**, and T3 then binds to **nuclear thyroid hormone receptors**, altering gene transcription and ultimately influencing **metabolic rate**, **growth**, and **development** across virtually every organ system in the body.

This wide-ranging cellular action explains why thyroid dysfunction, whether excess or deficiency, produces such a broad range of clinical effects, and why thyroid hormone is of particular importance in **early childhood**, since adequate thyroid hormone is essential for normal **brain development**, particularly during fetal life and the first few years after birth.

Fill in the blank: T4 is converted to the more biologically active T3 by the enzyme _____.

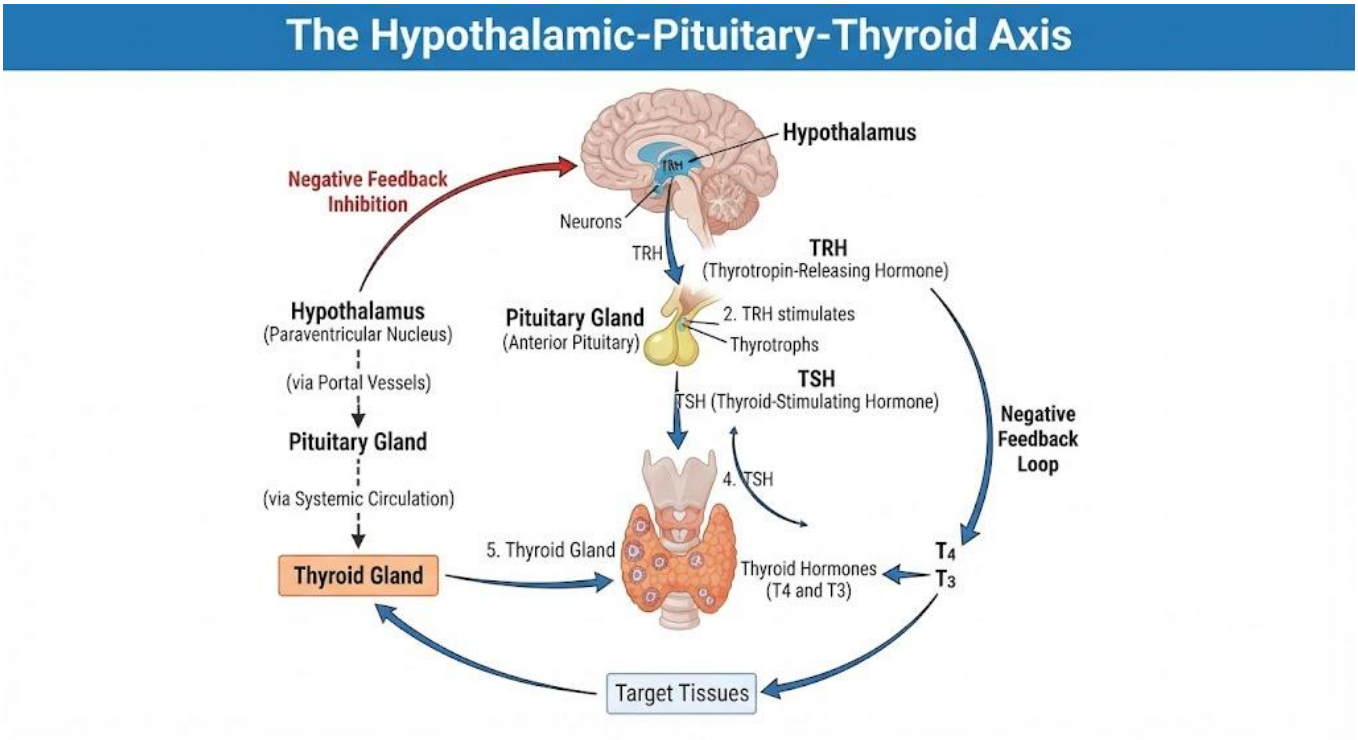


Figure 2.1: The hypothalamic-pituitary-thyroid axis and its negative feedback loop.

Pilot questions 2.1

- Describe the basic anatomy of the thyroid gland. (Linked to SLO 2.1)
- Distinguish the function of follicular cells from parafollicular cells. (Linked to SLO 2.1)
- Describe the steps involved in thyroid hormone synthesis. (Linked to SLO 2.2)
- Describe the hypothalamic-pituitary-thyroid axis and its feedback regulation. (Linked to SLO 2.2)
- Explain why adequate thyroid hormone is particularly important in early childhood. (Linked to SLO 2.2)

2.2 Functions of Thyroid Hormone and Classification of Thyroid Disorders

2.2.1 functions of thyroid hormone

Thyroid hormone touches nearly every organ system

Thyroid hormone has wide-ranging effects across the body, most notably regulating **basal metabolic rate**, influencing **oxygen consumption** and **heat production** in nearly all tissues, and playing an essential role in **growth and skeletal development** throughout childhood, meaning

untreated thyroid dysfunction in a growing child can significantly impair linear growth if not identified and corrected.

Thyroid hormone also has important effects on the **cardiovascular system**, increasing **heart rate** and **cardiac output**, the **nervous system**, where it is essential for normal **brain development** in early life and continues to influence mood, cognition, and reflexes throughout life, and the **gastrointestinal system**, where it influences **gut motility**, explaining why both hypothyroidism and hyperthyroidism can present with altered bowel habit in opposite directions.

Fill in the blank: Thyroid hormone plays an essential role in growth and skeletal _____ throughout childhood.

2.2.2 classification of thyroid disorders

Thyroid disorders in children are broadly classified into **hypothyroidism**, insufficient thyroid hormone production or action, and **hyperthyroidism**, excess thyroid hormone production or action, each further subdivided by **timing** and **cause**. Hypothyroidism may be **congenital**, present from birth, most commonly due to **thyroid dysgenesis**, an abnormality of thyroid gland development, or **acquired**, developing later in childhood, most commonly due to **autoimmune thyroiditis**, also known as **Hashimoto's thyroiditis**.

Hyperthyroidism in children is less common than hypothyroidism and is most frequently caused by **Graves' disease**, an autoimmune condition in which antibodies stimulate the TSH receptor, driving excess thyroid hormone production, while other causes, such as **thyroiditis** or a **toxic nodule**, are considerably less common in the paediatric age group than in adults.

Fill in the blank: Congenital hypothyroidism is most commonly due to thyroid _____.

2.2.3 goitre and its significance

A **goitre**, or visible or palpable enlargement of the thyroid gland, can occur in the context of **hypothyroidism**, **hyperthyroidism**, or, notably, with **normal thyroid function**, termed a **euthyroid goitre**, meaning the presence of a goitre alone does not indicate the direction of any underlying thyroid dysfunction and must always be interpreted alongside thyroid function testing.

Common causes of goitre in children include **autoimmune thyroiditis**, whether associated with hypo- or hyperthyroidism, **iodine deficiency**, historically an important cause globally though now less common where iodised salt programmes are well established, and, less commonly, **thyroid nodules** or, rarely, **thyroid malignancy**, which should be considered particularly where a goitre is asymmetrical, firm, or associated with lymphadenopathy.

Fill in the blank: A goitre occurring alongside normal thyroid function is termed a _____ goitre.

Table 2.2: Classification of thyroid disorders with typical hormone patterns.

Disorder	Typical TSH	Typical free T4	Common cause
Congenital hypothyroidism	High	Low	Thyroid dysgenesis
Acquired hypothyroidism	High	Low or low-normal	Hashimoto's thyroiditis
Hyperthyroidism	Low	High	Graves' disease

Pilot questions 2.2

1. List three body systems influenced by thyroid hormone. (Linked to SLO 2.3)
2. Distinguish congenital from acquired hypothyroidism by typical cause. (Linked to SLO 2.4)
3. Name the most common cause of hyperthyroidism in children. (Linked to SLO 2.4)
4. Define goitre and explain why its presence alone does not indicate the direction of thyroid dysfunction. (Linked to SLO 2.4)
5. List two causes of goitre in children. (Linked to SLO 2.4)

2.3 Hypothyroidism and Hyperthyroidism: Clinical Features

2.3.1 clinical features of congenital hypothyroidism

Early features are often subtle, which is why screening matters

Congenital hypothyroidism is frequently **clinically silent** in the newborn period, since some maternal thyroid hormone crosses the placenta and provides partial protection in the first weeks of life, which is precisely why routine **newborn screening** for congenital hypothyroidism is so important in settings where it is available, allowing detection and treatment before symptoms become apparent.

When clinical features do become apparent, they include **prolonged jaundice**, **poor feeding**, **lethargy**, **hypotonia**, a **hoarse cry**, **large fontanelles**, **umbilical hernia**, and **macroglossia**, or an enlarged tongue, and, critically, if the diagnosis is missed and treatment delayed, **irreversible intellectual impairment** can result, making this one of the most important preventable causes of intellectual disability in children when screening and treatment are not available or are delayed.

Fill in the blank: If congenital hypothyroidism is missed and treatment delayed, _____ intellectual impairment can result.

2.3.2 clinical features of acquired hypothyroidism

Acquired hypothyroidism in an older child typically presents more insidiously than the congenital form, with features including **growth deceleration** or **short stature**, often the presenting feature noticed by a parent or on routine growth monitoring, together with **fatigue**, **cold intolerance**, **constipation**, **dry skin**, and **delayed puberty**, though paradoxically some children can present with **precocious puberty** in severe, longstanding untreated hypothyroidism.

A **goitre** may or may not be present depending on the underlying cause, and school performance can decline as **concentration** and **cognitive processing speed** are affected, meaning acquired hypothyroidism should be actively considered in any child presenting with unexplained growth deceleration or declining school performance, even in the absence of more classic symptoms.

Fill in the blank: Growth _____ or short stature is often the presenting feature of acquired hypothyroidism in a child.

2.3.3 clinical features of hyperthyroidism

Hyperthyroidism in children presents with features reflecting an increased metabolic rate, including **weight loss** despite a normal or increased appetite, **heat intolerance**, **tremor**, **tachycardia** or **palpitations**, **irritability** or **emotional lability**, and **difficulty concentrating**, which can be mistaken for a primary behavioural or attention disorder if the underlying thyroid cause is not considered.

Specific features of **Graves' disease** may also be present, including a **goitre**, often with an audible **bruit** reflecting increased vascularity, and, in some children, **exophthalmos**, or protrusion of the eyes, though this ophthalmic finding is somewhat less common and often less pronounced in children than in adults with the same underlying condition.

Fill in the blank: Difficulty concentrating in a hyperthyroid child can be mistaken for a primary behavioural or _____ disorder.

Box 2.3: Comparing the clinical features of hypothyroidism and hyperthyroidism.

Hypothyroidism versus hyperthyroidism: key clinical features
Hypothyroidism: growth deceleration, cold intolerance, constipation, fatigue, dry skin.
Hyperthyroidism: weight loss, heat intolerance, tremor, tachycardia, irritability.

Both: goitre may be present in either condition and does not indicate the direction of dysfunction.
Congenital hypothyroidism specifically: prolonged jaundice, hypotonia, macroglossia, hoarse cry.
Graves' disease specifically: goitre with bruit, possible exophthalmos.

Pilot questions 2.3

1. Explain why congenital hypothyroidism is often clinically silent in the newborn period. (Linked to SLO 2.5)
2. List four clinical features of congenital hypothyroidism. (Linked to SLO 2.5)
3. Describe the typical presenting feature of acquired hypothyroidism in an older child. (Linked to SLO 2.5)
4. List four clinical features of hyperthyroidism in children. (Linked to SLO 2.6)
5. Describe two features specific to Graves' disease. (Linked to SLO 2.6)

2.4 Work Up and Management of Thyroid Disorders

2.4.1 laboratory investigation of thyroid disorders

TSH usually gives the first clue

The initial investigation of suspected thyroid dysfunction is **thyroid function testing**, comprising **serum TSH** and **free T4**, which together allow classification of thyroid dysfunction as **primary**, arising from the thyroid gland itself, in which TSH and free T4 move in opposite directions, or, much less commonly, **central**, arising from pituitary or hypothalamic dysfunction, in which TSH may be inappropriately low or normal despite a low free T4.

Where **autoimmune thyroid disease** is suspected, **thyroid autoantibodies**, including **thyroid peroxidase antibodies** and **thyroglobulin antibodies** in Hashimoto's thyroiditis, or **TSH receptor antibodies** in Graves' disease, provide supportive diagnostic evidence, and **newborn screening** programmes, where available, use a **heel-prick TSH** measurement to detect congenital hypothyroidism before clinical features become apparent.

Fill in the blank: Newborn screening programmes use a heel-prick _____ measurement to detect congenital hypothyroidism.

2.4.2 imaging in the evaluation of thyroid disorders

Thyroid ultrasound is useful for assessing **gland size**, **structure**, and the presence of any **nodules**, and is particularly helpful in evaluating congenital hypothyroidism, where it can help distinguish thyroid dysgenesis, such as an absent or ectopic gland, from other causes such as dyshormonogenesis, in which the gland is present but hormone synthesis is impaired.

Radionuclide thyroid scanning, using a small dose of radioactive iodine or technetium, provides additional information about **gland location** and **functional activity**, and can be particularly useful in confirming the specific underlying cause of congenital hypothyroidism, though in practice, given the urgency of starting treatment, imaging should never delay prompt initiation of thyroid hormone replacement once the diagnosis is biochemically confirmed.

Fill in the blank: Imaging should never delay prompt initiation of thyroid hormone replacement once the diagnosis is biochemically _____.

2.4.3 general management of thyroid disorders

Management of **hypothyroidism**, whether congenital or acquired, is with **levothyroxine replacement**, dosed according to age and weight and titrated based on regular monitoring of **TSH** and **free T4**, with the treatment goal of maintaining these values within the normal range to support normal growth and, in infancy, normal neurodevelopment, making early diagnosis and consistent treatment adherence particularly important in this age group.

Management of **hyperthyroidism**, most commonly Graves' disease in children, typically begins with **antithyroid medication**, such as **methimazole**, to reduce thyroid hormone production, with **beta blockers** sometimes used additionally for symptomatic control of tachycardia and tremor in the initial period, while **radioactive iodine ablation** or **surgical thyroidectomy** are reserved as definitive treatment options for children who do not achieve remission with medication or who experience significant side effects.

Fill in the blank: Management of hypothyroidism is with _____ replacement, titrated based on TSH and free T4 monitoring.

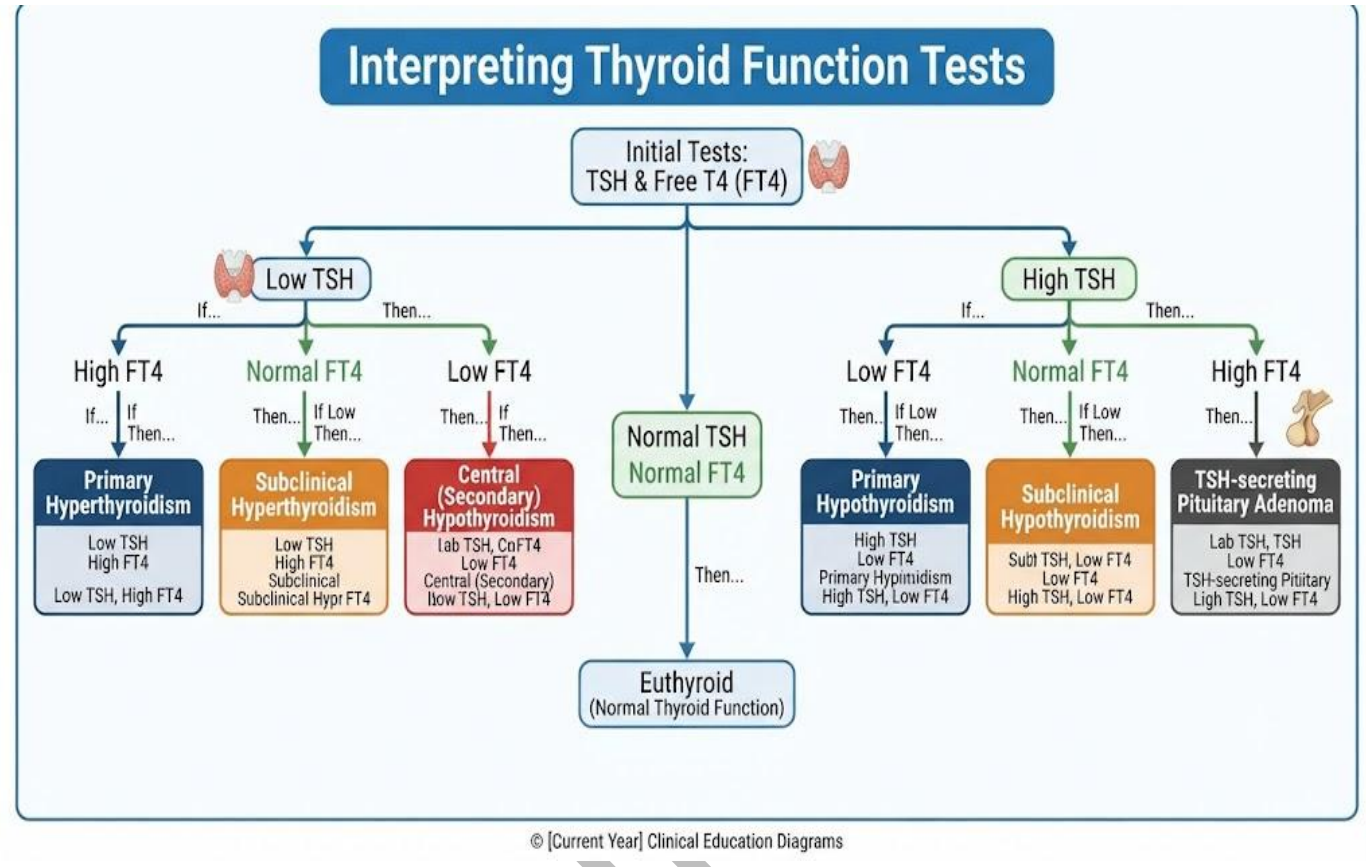


Figure 2.4: A diagnostic algorithm for interpreting thyroid function tests.

Pilot questions 2.4

1. Describe the initial laboratory investigation of suspected thyroid dysfunction. (Linked to SLO 2.7)
2. Distinguish primary from central thyroid dysfunction based on TSH and free T4 patterns. (Linked to SLO 2.7)
3. Describe the role of thyroid ultrasound in evaluating congenital hypothyroidism. (Linked to SLO 2.7)
4. Describe the management of hypothyroidism in children. (Linked to SLO 2.8)
5. Describe the initial medical management of hyperthyroidism due to Graves' disease. (Linked to SLO 2.8)

Series Summary

This Series introduced **thyroid gland physiology**, beginning with normal anatomy, hormone synthesis, and the hypothalamic-pituitary-thyroid axis, before turning to the **functions of thyroid hormone and classification of thyroid disorders**.

We then examined the **clinical features of hypothyroidism and hyperthyroidism**, before concluding with the **work up and management** of thyroid disorders. Having worked through this Series, you should now be able to recognise and understand the management of common thyroid disorders in children. The next Series turns to **vitamin D metabolism and metabolic rickets**.

Glossary of Terms

1. **Thyroid follicle:** the basic structural unit of the thyroid gland, lined by hormone-producing follicular cells surrounding a colloid store.
2. **Thyroxine (T4):** the principal thyroid hormone produced in greatest quantity by the thyroid gland.
3. **Triiodothyronine (T3):** the more biologically active thyroid hormone, largely produced by peripheral conversion from T4.
4. **Hypothalamic-pituitary-thyroid axis:** the regulatory feedback loop controlling thyroid hormone production.
5. **Congenital hypothyroidism:** hypothyroidism present from birth, most commonly due to thyroid dysgenesis.
6. **Hashimoto's thyroiditis:** autoimmune thyroiditis, the most common cause of acquired hypothyroidism in children.
7. **Graves' disease:** an autoimmune condition and the most common cause of hyperthyroidism in children.
8. **Goitre:** visible or palpable enlargement of the thyroid gland, which may occur with hypo-, hyper-, or euthyroid function.
9. **TSH:** thyroid-stimulating hormone, produced by the pituitary gland to stimulate thyroid hormone production.
10. **Thyroid autoantibodies:** antibodies, such as thyroid peroxidase antibodies, used to support diagnosis of autoimmune thyroid disease.
11. **Levothyroxine:** the synthetic thyroid hormone used to treat hypothyroidism.

12. **Methimazole:** an antithyroid medication used to reduce thyroid hormone production in hyperthyroidism.

Concept Check Questions [Series 2]

Objective questions

- Thyroid hormone is stored within a central protein matrix called _____ inside each follicle.
- Circulating thyroid hormone exerts negative _____ on the hypothalamus and pituitary.
- Congenital hypothyroidism is most commonly due to thyroid _____.
- If congenital hypothyroidism is missed and treatment delayed, _____ intellectual impairment can result.
- Management of hypothyroidism is with _____ replacement, titrated based on TSH and free T4 monitoring.

Short-answer questions

1. Describe the hypothalamic-pituitary-thyroid axis and its feedback regulation.
2. Distinguish congenital from acquired hypothyroidism by typical cause.
3. List four clinical features of congenital hypothyroidism.
4. List four clinical features of hyperthyroidism in children.
5. Distinguish primary from central thyroid dysfunction based on TSH and free T4 patterns.

Long-answer questions

6. Discuss the normal physiology of thyroid hormone synthesis and regulation. (Linked to SLO 2.1, SLO 2.2)
7. Discuss the classification of thyroid disorders and the significance of goitre. (Linked to SLO 2.4)
8. Discuss the clinical features of congenital and acquired hypothyroidism. (Linked to SLO 2.5)
9. Discuss the clinical features of hyperthyroidism in children. (Linked to SLO 2.6)
10. Discuss the work up and management of thyroid disorders in children. (Linked to SLO 2.7, SLO 2.8)

Answers to Concept Check Questions [Series 2]

Objective questions

11. Colloid.
12. Feedback.
13. Dysgenesis.
14. Irreversible.
15. Levothyroxine.

Short-answer questions

16. The hypothalamus secretes TRH, stimulating pituitary TSH secretion, which stimulates thyroid hormone production, with thyroid hormone providing negative feedback on both.
17. Congenital hypothyroidism is most commonly due to thyroid dysgenesis, while acquired hypothyroidism is most commonly due to Hashimoto's thyroiditis.
18. Prolonged jaundice, poor feeding, hypotonia, and macroglossia.
19. Weight loss, heat intolerance, tremor, and tachycardia.
20. In primary dysfunction, TSH and free T4 move in opposite directions; in central dysfunction, TSH is inappropriately low or normal despite a low free T4.

Long-answer questions

21. **Basic response:** Thyroid hormone synthesis involves iodide uptake, organification, and coupling to form T4 and T3, regulated by the hypothalamic-pituitary-thyroid axis through negative feedback.

Value-added response: T4 is converted peripherally to the more active T3 by deiodinase, and thyroid hormone is essential for normal brain development, particularly in early childhood.

22. **Basic response:** Thyroid disorders are classified as hypothyroidism or hyperthyroidism, each subdivided by timing and cause; goitre may occur with either or with normal thyroid function.

Value-added response: The presence of a goitre alone does not indicate the direction of dysfunction and must always be interpreted alongside thyroid function testing.

23. **Basic response:** Congenital hypothyroidism is often clinically silent at birth but presents with prolonged jaundice, hypotonia, and macroglossia if untreated, while acquired hypothyroidism presents with growth deceleration and fatigue.

Value-added response: Missed congenital hypothyroidism can cause irreversible intellectual impairment, making newborn screening critically important where available.

24. **Basic response:** Hyperthyroidism presents with weight loss, heat intolerance, tremor, and tachycardia, most commonly due to Graves' disease, which may also cause goitre and exophthalmos.

Value-added response: Irritability and difficulty concentrating can be mistaken for a primary behavioural disorder if the underlying thyroid cause is not actively considered.

25. **Basic response:** Work up begins with TSH and free T4, supported by thyroid autoantibodies and imaging such as ultrasound, and management uses levothyroxine for hypothyroidism or antithyroid medication for hyperthyroidism.

Value-added response: Imaging should never delay treatment once the diagnosis is biochemically confirmed, and definitive treatments such as radioactive iodine or surgery are reserved for hyperthyroidism not controlled with medication.

Answers to Pilot Questions [Series 2]

Part 2.1

1. The thyroid is a butterfly-shaped gland with two lobes connected by an isthmus, located in the anterior neck.
2. Follicular cells produce thyroid hormone, while parafollicular cells produce calcitonin.
3. Iodide uptake, organification into thyroglobulin, and coupling to form T4 and T3.
4. Hypothalamic TRH stimulates pituitary TSH, which stimulates thyroid hormone production, with negative feedback from circulating hormone.
5. Thyroid hormone is essential for normal brain development, particularly during fetal life and early childhood.

Part 2.2

6. Metabolic rate, cardiovascular system, and nervous system are influenced by thyroid hormone.
7. Congenital hypothyroidism is most commonly due to thyroid dysgenesis, while acquired is most commonly due to Hashimoto's thyroiditis.
8. Graves' disease is the most common cause of hyperthyroidism in children.
9. A goitre is thyroid gland enlargement, which can occur with hypo-, hyper-, or normal thyroid function.

10. Autoimmune thyroiditis and iodine deficiency are causes of goitre.

Part 2.3

11. Maternal thyroid hormone crosses the placenta, providing partial protection in the first weeks of life.
12. Prolonged jaundice, poor feeding, hypotonia, and macroglossia are features of congenital hypothyroidism.
13. Growth deceleration or short stature is often the presenting feature of acquired hypothyroidism.
14. Weight loss, heat intolerance, tremor, and tachycardia are features of hyperthyroidism.
15. Goitre with a bruit and exophthalmos are features specific to Graves' disease.

Part 2.4

1. Serum TSH and free T4 are the initial investigations of suspected thyroid dysfunction.
2. In primary dysfunction, TSH and free T4 move in opposite directions; in central dysfunction, TSH is inappropriately low or normal.
3. Thyroid ultrasound helps distinguish thyroid dysgenesis from other causes of congenital hypothyroidism.
4. Hypothyroidism is managed with levothyroxine replacement, titrated with TSH and free T4 monitoring.
5. Hyperthyroidism is initially managed with antithyroid medication such as methimazole, sometimes with beta blockers.

References and Attributions [Series 2]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. Rastogi, M. V. and LaFranchi, S. H. (2010). Congenital hypothyroidism. Orphanet Journal of Rare Diseases, 5(1), 17.
3. Bauer, A. J. and Wassner, A. J. (2019). Thyroid disorders in children. In Nelson Textbook of Pediatrics (21st ed.). Elsevier.
4. Ross, D. S. et al. (2016). American Thyroid Association guidelines for diagnosis and management of hyperthyroidism. Thyroid, 26(10), 1343 to 1421.

Figures, Plates, Tables, and Boxes

1. Figure 2.1: The hypothalamic-pituitary-thyroid axis and its negative feedback loop. AI-generated using the prompt: "Create a professional educational diagram titled The Hypothalamic-Pituitary-Thyroid Axis, showing the feedback loop between hypothalamus, pituitary, and thyroid gland. Clean clinical educational diagram style."
2. Table 2.2: Classification of thyroid disorders with typical hormone patterns. AI-generated using the prompt: "Create a clean reference table titled Classification of Thyroid Disorders and Hormone Patterns, listing disorder, TSH, free T4, and common cause. Simple clinical reference table style with outside border."
3. Box 2.3: Comparing the clinical features of hypothyroidism and hyperthyroidism. AI-generated using the prompt: "Create a simple single-column reference box titled Hypothyroidism versus Hyperthyroidism: Key Clinical Features. Clean clinical reference box style."
4. Figure 2.4: A diagnostic algorithm for interpreting thyroid function tests. AI-generated using the prompt: "Create a professional medical flowchart titled Interpreting Thyroid Function Tests, branching by TSH and free T4 patterns into primary and central thyroid dysfunction. Clean clinical educational diagram style."

Series 3: Vitamin D Metabolism and Metabolic Rickets

- **Part 3.1: Types, Sources, and Metabolism of Vitamin D**
    - Sub Part 3.1.1: Types of vitamin D
    - Sub Part 3.1.2: Sources of vitamin D
    - Sub Part 3.1.3: Metabolism of vitamin D
- **Part 3.2: Action of Vitamin D and Aetiology of Vitamin D Deficiency**
    - Sub Part 3.2.1: Action of vitamin D on calcium and phosphate homeostasis
    - Sub Part 3.2.2: Action of vitamin D on bone
    - Sub Part 3.2.3: Aetiology of vitamin D deficiency
- **Part 3.3: Definition, Aetiology, and Pathogenesis of Rickets**
    - Sub Part 3.3.1: Definition of rickets
    - Sub Part 3.3.2: Aetiology of rickets
    - Sub Part 3.3.3: Pathogenesis of rickets
- **Part 3.4: Clinical Features, Investigation, and Treatment of Rickets**
    - Sub Part 3.4.1: Clinical features of rickets
    - Sub Part 3.4.2: Investigation of rickets
    - Sub Part 3.4.3: Treatment of rickets

Introduction

In the last Series, we explored thyroid gland physiology and thyroid disorders. We now turn to vitamin D and its most important clinical consequence in childhood, rickets. Picture an eighteen month old brought to clinic because his mother has noticed his legs appear increasingly bowed as he has begun to walk. Understanding vitamin D metabolism and how its deficiency produces this and other clinical features is the focus of this Series.

The aim of this Series is to equip you with the knowledge required to understand vitamin D metabolism and action, the causes of vitamin D deficiency, and the clinical features, investigation, and treatment of rickets.

This Series begins with the **types, sources, and metabolism** of vitamin D, before turning to its **action and the aetiology of vitamin D deficiency**. Next, we examine the **definition, aetiology, and pathogenesis of rickets**, before concluding with its **clinical features, investigation, and treatment**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** list the types of vitamin D,
- **SLO 1.2:** describe the metabolism of vitamin D, from skin synthesis to its active hormonal form,
- **SLO 1.3:** list the sources of vitamin D,
- **SLO 1.4:** describe the action of vitamin D on calcium, phosphate, and bone,
- **SLO 1.5:** discuss the aetiology of vitamin D deficiency,
- **SLO 1.6:** define rickets and discuss its aetiology and pathogenesis,
- **SLO 1.7:** enumerate the clinical features of rickets, and
- **SLO 1.8:** describe the investigation and treatment of rickets.

3.1 Types, Sources, and Metabolism of Vitamin D

3.1.1 types of vitamin D

Two forms, one shared final pathway

Vitamin D exists in two principal forms: **vitamin D2**, or **ergocalciferol**, derived from plant and fungal sources, and **vitamin D3**, or **cholecalciferol**, synthesised in the skin on exposure to **ultraviolet B radiation** from sunlight, or obtained from animal-derived dietary sources. Both forms are biologically inert as ingested or synthesised and must undergo the same sequence of hepatic and renal activation before becoming functionally active within the body.

While vitamin D2 and D3 are handled similarly by the body's activation pathway, **vitamin D3** is generally considered somewhat more effective at raising and maintaining serum vitamin D levels than vitamin D2, a distinction that has practical relevance when selecting a supplementation product for treatment or prevention of vitamin D deficiency.

Fill in the blank: Vitamin D3, or cholecalciferol, is synthesised in the skin on exposure to ultraviolet _____ radiation.

3.1.2 sources of vitamin D

Cutaneous synthesis following sunlight exposure is the principal source of vitamin D for most children, meaning factors that reduce skin exposure to sunlight, such as **extensive clothing coverage**, consistent **sunscreen use**, **darker skin pigmentation**, which reduces cutaneous vitamin D synthesis efficiency, or simply living at **higher latitudes** with less intense year-round sunlight, all reduce this primary source and increase reliance on dietary intake.

Dietary sources of vitamin D are relatively limited, and include **oily fish**, **egg yolk**, **liver**, and, in many countries, **fortified foods** such as fortified milk, margarine, or infant formula, and **breast milk**, while nutritionally excellent for infants in almost every other respect, contains relatively **low concentrations of vitamin D**, meaning exclusively breastfed infants, particularly those with limited sunlight exposure, are at particular risk of deficiency without supplementation.

Fill in the blank: Breast milk contains relatively _____ concentrations of vitamin D.

3.1.3 metabolism of vitamin D

Vitamin D synthesised in the skin or absorbed from the diet undergoes a first hydroxylation step in the **liver**, converting it to **25-hydroxyvitamin D**, also called **calcidiol**, which is the major circulating form of vitamin D and the form typically measured in blood tests to assess a child's vitamin D status, since it reflects both cutaneous synthesis and dietary intake and has a relatively long half-life.

A second hydroxylation step then occurs in the **kidney**, converting 25-hydroxyvitamin D to **1,25-dihydroxyvitamin D**, also called **calcitriol**, the biologically **active hormonal form** of vitamin D, and this final activation step is tightly regulated, particularly by **parathyroid hormone** and serum **phosphate** concentration, meaning renal disease can significantly impair vitamin D activation even when 25-hydroxyvitamin D levels themselves are adequate.

Fill in the blank: The second hydroxylation of vitamin D occurs in the _____, producing the active hormonal form.

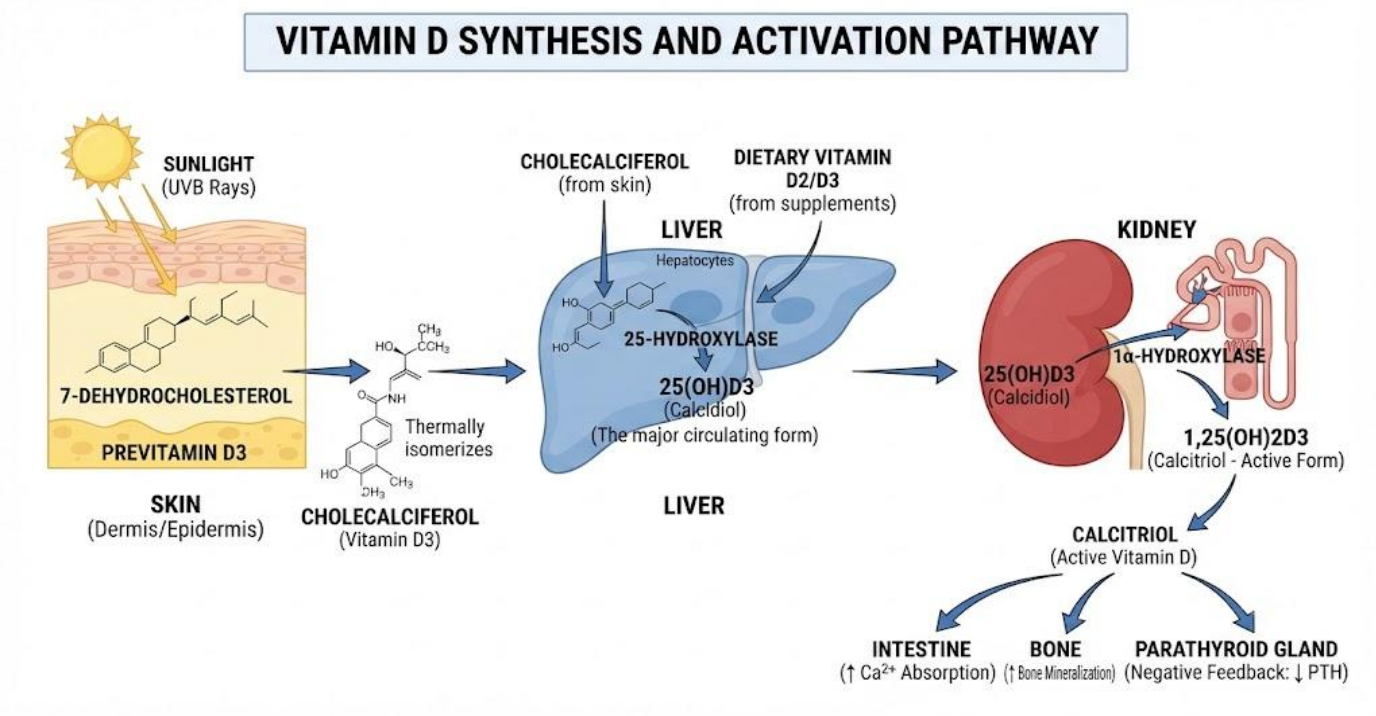


Figure 3.1: The pathway of vitamin D synthesis and activation.

Pilot questions 3.1

- Distinguish vitamin D2 from vitamin D3 by source. (Linked to SLO 3.1)
- List two factors that reduce cutaneous vitamin D synthesis. (Linked to SLO 3.1)
- Explain why exclusively breastfed infants are at particular risk of vitamin D deficiency. (Linked to SLO 3.1)
- Describe the two hydroxylation steps involved in vitamin D activation and where each occurs. (Linked to SLO 3.2)
- Name the major circulating form of vitamin D measured to assess vitamin D status. (Linked to SLO 3.2)

3.2 Action of Vitamin D and Aetiology of Vitamin D Deficiency

3.2.1 action of vitamin D on calcium and phosphate homeostasis

Vitamin D works together with parathyroid hormone

The primary action of **1,25-dihydroxyvitamin D**, or calcitriol, is to maintain normal **serum calcium** and **phosphate** concentrations, principally by increasing **intestinal absorption of**

calcium and phosphate from dietary sources, an effect that is essential since the body cannot maintain adequate calcium levels through diet alone without adequate active vitamin D to support its absorption.

Vitamin D also acts on **bone**, together with **parathyroid hormone**, to regulate **bone mineralisation** and, when necessary, to promote **calcium release from bone** to maintain serum calcium levels when dietary calcium absorption is insufficient, and has additional effects on the **kidney**, promoting **renal calcium reabsorption**, all working together to maintain calcium homeostasis within a narrow, tightly regulated range.

Fill in the blank: Calcitriol principally increases intestinal absorption of calcium and _____ from dietary sources.

3.2.2 action of vitamin D on bone

Beyond its role in calcium and phosphate homeostasis, adequate vitamin D is essential for normal **bone mineralisation**, the process by which the **osteoid**, the organic collagen matrix of bone, becomes hardened through deposition of **calcium and phosphate crystals**. When vitamin D is deficient, calcium and phosphate availability is insufficient to adequately mineralise newly formed osteoid, resulting in the accumulation of **unmineralised osteoid** at the growth plate and throughout the skeleton.

This failure of mineralisation is the fundamental pathological process underlying the skeletal manifestations of vitamin D deficiency in a growing child, and explains why the clinical and radiographic features of vitamin D deficiency are most pronounced at sites of **rapid bone growth**, such as the growth plates of the long bones and the costochondral junctions of the ribs, discussed further later in this Series.

Fill in the blank: Vitamin D deficiency results in accumulation of unmineralised _____ at the growth plate and throughout the skeleton.

3.2.3 aetiology of vitamin D deficiency

Vitamin D deficiency arises from an imbalance between **vitamin D requirements** and the combination of **cutaneous synthesis** and **dietary intake**, and common contributing factors in children include **inadequate sunlight exposure**, whether from cultural clothing practices, indoor lifestyles, or geographic and seasonal factors, **exclusive breastfeeding without supplementation**, **dietary restriction**, including certain vegan diets without adequate fortified food intake, and **darker skin pigmentation**, which reduces the efficiency of cutaneous synthesis for a given amount of sun exposure.

Less common causes include **malabsorption**, since vitamin D is fat-soluble and requires normal intestinal fat absorption, and, less commonly, **chronic liver or kidney disease**, which impairs the hepatic or renal hydroxylation steps required for activation, and certain **anticonvulsant medications**, which can accelerate vitamin D breakdown through induction of hepatic enzymes, meaning children on long-term anticonvulsant therapy warrant particular attention to vitamin D status.

Fill in the blank: Certain anticonvulsant medications can accelerate vitamin D breakdown through induction of hepatic _____.

Table 3.2: Common contributing factors to vitamin D deficiency in children.

Category	Example contributing factors
Reduced cutaneous synthesis	Limited sunlight exposure, extensive clothing coverage, darker skin pigmentation
Inadequate intake	Exclusive breastfeeding without supplementation, restrictive diets
Impaired absorption or activation	Malabsorption, chronic liver or kidney disease
Increased breakdown	Certain anticonvulsant medications

Pilot questions 3.2

1. Describe the primary action of calcitriol on calcium and phosphate homeostasis. (Linked to SLO 3.4)
2. Explain the role of vitamin D in bone mineralisation. (Linked to SLO 3.4)
3. List three factors contributing to reduced cutaneous vitamin D synthesis. (Linked to SLO 3.5)
4. Explain why exclusively breastfed infants without supplementation are at risk of vitamin D deficiency. (Linked to SLO 3.5)
5. Describe how anticonvulsant medications can contribute to vitamin D deficiency. (Linked to SLO 3.5)

3.3 Definition, Aetiology, and Pathogenesis of Rickets

3.3.1 definition of rickets

A disease of the growing skeleton specifically

Rickets is defined as a disorder of **defective mineralisation** of the **growth plate** and the newly formed bone, or **osteoid**, in a growing child, resulting from inadequate available calcium and

phosphate at the site of bone formation. Because rickets specifically affects the **growth plate**, it occurs only in children with **open growth plates**, and the equivalent defective mineralisation of already-formed, mature bone in an adult is instead termed **osteomalacia**.

While **vitamin D deficiency** is by far the most common underlying cause of rickets globally, it is important to recognise that rickets can also result from **primary calcium deficiency** even with adequate vitamin D status, or from **phosphate deficiency**, whether due to dietary insufficiency or, less commonly, an underlying **renal phosphate wasting disorder**, meaning not every case of rickets is attributable to vitamin D deficiency alone.

Fill in the blank: Defective mineralisation of already-formed, mature bone in an adult is termed _____.

3.3.2 aetiology of rickets

The most common cause of rickets worldwide is **nutritional vitamin D deficiency**, arising from the combination of factors discussed in the previous Part of this Series, and this remains an important, largely preventable cause of childhood morbidity in many settings, including parts of Nigeria, despite abundant year-round sunlight, reflecting the importance of cultural, dietary, and lifestyle factors beyond simple geographic sun exposure.

Less common causes include **calcium-deficient rickets**, arising from severely inadequate dietary calcium intake even with normal vitamin D status, and **hereditary hypophosphataemic rickets**, a genetic condition causing excessive renal phosphate wasting independent of vitamin D or dietary calcium status, which characteristically does **not respond** to standard vitamin D treatment alone and requires specific phosphate supplementation and specialist management.

Fill in the blank: Hereditary hypophosphataemic rickets characteristically does not respond to standard _____ treatment alone.

3.3.3 pathogenesis of rickets

The pathogenesis of nutritional rickets begins with **vitamin D deficiency**, leading to reduced intestinal calcium absorption and a resulting tendency towards **hypocalcaemia**. In response, the body increases **parathyroid hormone** secretion, termed **secondary hyperparathyroidism**, which acts to normalise serum calcium by increasing bone calcium release and increasing renal phosphate excretion, but this compensatory response comes at the cost of worsening **hypophosphataemia**.

This combination of insufficient calcium and, particularly, insufficient phosphate at the growth plate impairs normal **mineralisation** of newly formed osteoid, leading to the characteristic

widening and disorganisation of the growth plate and the accumulation of soft, unmineralised bone that underlies the clinical and radiographic features of rickets discussed in the next Part of this Series.

Fill in the blank: Reduced intestinal calcium absorption in vitamin D deficiency triggers secondary _____.

Box 3.3: Key steps in the pathogenesis of nutritional rickets.

Pathogenesis of nutritional rickets, step by step
Vitamin D deficiency reduces intestinal calcium absorption.
Resulting tendency towards hypocalcaemia triggers secondary hyperparathyroidism.
Parathyroid hormone raises serum calcium but increases renal phosphate excretion.
The resulting hypophosphataemia impairs mineralisation of the growth plate.
Unmineralised osteoid accumulates, producing the features of rickets.

Pilot questions 3.3

1. Define rickets and explain why it occurs only in children with open growth plates. (Linked to SLO 3.6)
2. Distinguish rickets from osteomalacia. (Linked to SLO 3.6)
3. List two causes of rickets other than vitamin D deficiency. (Linked to SLO 3.6)
4. Describe the role of secondary hyperparathyroidism in the pathogenesis of nutritional rickets. (Linked to SLO 3.6)
5. Explain why hereditary hypophosphataemic rickets does not respond to vitamin D treatment alone. (Linked to SLO 3.6)

3.4 Clinical Features, Investigation, and Treatment of Rickets

3.4.1 clinical features of rickets

Features cluster at sites of rapid growth

Clinical features of rickets reflect the underlying defective mineralisation at sites of active bone growth, and include **craniotabes**, a softening of the skull bones palpable in young infants, **widened wrists and ankles**, reflecting growth plate widening, a **rachitic rosary**, the palpable enlargement of the costochondral junctions along the anterior chest wall, and, in older, walking children, **bowing of the legs**, either **genu varum** or, less commonly, **genu valgum**.

Additional features include **delayed closure of the anterior fontanelle**, **delayed tooth eruption**, **frontal bossing** of the skull, and, since hypocalcaemia can also directly affect neuromuscular function, features such as **muscle weakness** or, in severe cases, **hypocalcaemic seizures** or **tetany**, meaning rickets should also be considered in a child presenting with these neuromuscular features even in the absence of the more classic skeletal deformities.

Fill in the blank: Palpable enlargement of the costochondral junctions along the anterior chest wall is called the rachitic _____.

3.4.2 investigation of rickets

Laboratory investigation of suspected rickets typically shows a **low or low-normal serum calcium**, a **low serum phosphate**, reflecting the renal phosphate wasting driven by secondary hyperparathyroidism, and a markedly **elevated alkaline phosphatase**, reflecting increased osteoblastic activity attempting to mineralise bone, together with a **low 25-hydroxyvitamin D** level confirming vitamin D deficiency as the underlying cause in most cases, and an **elevated parathyroid hormone** confirming the expected secondary hyperparathyroidism.

Radiographic imaging, typically of the wrist, is a key diagnostic investigation, characteristically showing **widening**, **cupping**, and **fraying** of the growth plate at the distal radius and ulna, findings that provide strong supporting evidence for the diagnosis and can also be used to monitor the radiographic response to treatment over subsequent weeks and months.

Fill in the blank: Radiographic imaging of the wrist in rickets characteristically shows widening, cupping, and _____ of the growth plate.

3.4.3 treatment of rickets

Treatment of nutritional rickets centres on **vitamin D replacement**, typically given as a high dose course of oral **cholecalciferol** to rapidly correct the deficiency, followed by an ongoing **maintenance dose** to prevent recurrence, together with adequate **calcium supplementation**, particularly important where dietary calcium intake is likely to be insufficient, since correcting vitamin D deficiency alone without adequate calcium intake can occasionally precipitate a transient worsening of hypocalcaemia, sometimes called **hungry bone syndrome**.

With appropriate treatment, most **biochemical abnormalities** normalise within weeks, and **radiographic healing** is typically evident within a few months, though established **skeletal deformities**, such as significant leg bowing, may take considerably longer to improve or may persist and require **orthopaedic assessment** in severe or longstanding cases, underscoring the importance of early recognition and treatment to prevent this longer-term consequence wherever possible.

Fill in the blank: Correcting vitamin D deficiency without adequate calcium intake can occasionally precipitate hungry bone _____.

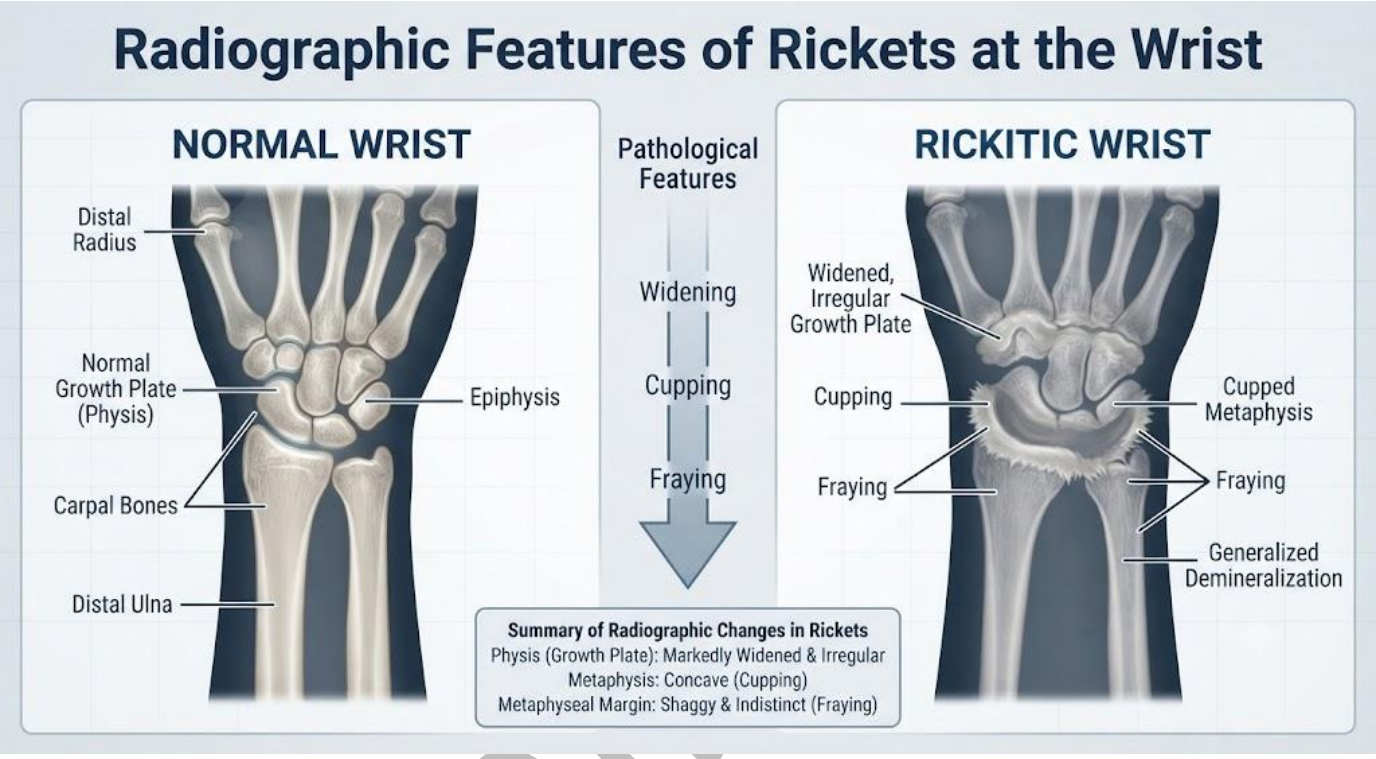


Figure 3.4: Characteristic radiographic features of rickets at the wrist.

Pilot questions 3.4

1. List four clinical features of rickets. (Linked to SLO 3.7)
2. Describe the typical laboratory findings in nutritional rickets. (Linked to SLO 3.8)
3. Describe the characteristic radiographic findings of rickets at the wrist. (Linked to SLO 3.8)
4. Describe the treatment of nutritional rickets. (Linked to SLO 3.8)
5. Explain what is meant by hungry bone syndrome. (Linked to SLO 3.8)

Series Summary

This Series examined **vitamin D metabolism**, beginning with its types, sources, and activation pathway, before turning to its **action on calcium and phosphate homeostasis and the aetiology of vitamin D deficiency**.

We then examined the **definition, aetiology, and pathogenesis of rickets**, before concluding with its **clinical features, investigation, and treatment**. Having worked through this Series, you should now be able to understand vitamin D metabolism and recognise and manage a child with rickets. The next Series turns to the **diagnosis and treatment of diabetes mellitus**.

Glossary of Terms

1. **Cholecalciferol:** vitamin D3, synthesised in the skin on exposure to ultraviolet B radiation.
2. **Ergocalciferol:** vitamin D2, derived from plant and fungal sources.
3. **25-hydroxyvitamin D:** calcidiol, the major circulating form of vitamin D used to assess vitamin D status.
4. **1,25-dihydroxyvitamin D:** calcitriol, the biologically active hormonal form of vitamin D.
5. **Osteoid:** the organic collagen matrix of bone prior to mineralisation.
6. **Secondary hyperparathyroidism:** increased parathyroid hormone secretion in response to hypocalcaemia, a key step in the pathogenesis of rickets.
7. **Rickets:** a disorder of defective mineralisation of the growth plate and newly formed bone in a growing child.
8. **Osteomalacia:** defective mineralisation of already-formed, mature bone, the adult equivalent of rickets.
9. **Craniotabes:** softening of the skull bones, palpable in young infants with rickets.
10. **Rachitic rosary:** palpable enlargement of the costochondral junctions along the anterior chest wall in rickets.
11. **Genu varum:** bow-legged deformity, a clinical feature seen in walking children with rickets.
12. **Hungry bone syndrome:** a transient worsening of hypocalcaemia that can occur when vitamin D deficiency is corrected without adequate calcium intake.

Concept Check Questions [Series 3]

Objective questions

- Vitamin D3, or cholecalciferol, is synthesised in the skin on exposure to ultraviolet _____ radiation.
- The second hydroxylation of vitamin D occurs in the _____, producing the active hormonal form.
- Vitamin D deficiency results in accumulation of unmineralised _____ at the growth plate.
- Defective mineralisation of already-formed, mature bone in an adult is termed _____.
- Palpable enlargement of the costochondral junctions along the anterior chest wall is called the rachitic _____.

Short-answer questions

1. Distinguish vitamin D2 from vitamin D3 by source.
2. Describe the two hydroxylation steps involved in vitamin D activation and where each occurs.
3. List three factors contributing to reduced cutaneous vitamin D synthesis.
4. List four clinical features of rickets.
5. Describe the characteristic radiographic findings of rickets at the wrist.

Long-answer questions

6. Discuss the types, sources, and metabolism of vitamin D. (Linked to SLO 3.1, SLO 3.2)
7. Discuss the action of vitamin D and the aetiology of vitamin D deficiency. (Linked to SLO 3.4, SLO 3.5)
8. Discuss the pathogenesis of nutritional rickets, from vitamin D deficiency to skeletal changes. (Linked to SLO 3.6)
9. Discuss the clinical features of rickets. (Linked to SLO 3.7)
10. Discuss the investigation and treatment of nutritional rickets. (Linked to SLO 3.8)

Answers to Concept Check Questions [Series 3]

Objective questions

11. B.
12. Kidney.

13. Osteoid.
14. Osteomalacia.
15. Rosary.

Short-answer questions

16. Vitamin D2 is derived from plant and fungal sources, while vitamin D3 is synthesised in the skin or obtained from animal sources.
17. The liver converts vitamin D to 25-hydroxyvitamin D, and the kidney converts this to the active 1,25-dihydroxyvitamin D.
18. Limited sunlight exposure, extensive clothing coverage, and darker skin pigmentation.
19. Craniotabes, widened wrists, rachitic rosary, and leg bowing.
20. Widening, cupping, and fraying of the growth plate, typically assessed at the distal radius and ulna.

Long-answer questions

21. **Basic response:** Vitamin D exists as D2 and D3, obtained from cutaneous synthesis or diet, and is activated by hepatic hydroxylation to 25-hydroxyvitamin D and renal hydroxylation to the active 1,25-dihydroxyvitamin D.

Value-added response: 25-hydroxyvitamin D is the form measured to assess vitamin D status because of its long half-life, while the renal step is tightly regulated by parathyroid hormone and phosphate.

22. **Basic response:** Vitamin D increases intestinal calcium and phosphate absorption and supports bone mineralisation; deficiency arises from inadequate sunlight exposure, inadequate intake, malabsorption, or increased breakdown.

Value-added response: Exclusively breastfed infants without supplementation and children on long-term anticonvulsant therapy are particular risk groups requiring active attention to vitamin D status.

23. **Basic response:** Vitamin D deficiency reduces intestinal calcium absorption, triggering secondary hyperparathyroidism, which raises calcium but worsens phosphate loss, impairing mineralisation of the growth plate.

Value-added response: This connected cascade explains why rickets results in unmineralised osteoid accumulation specifically at sites of active bone growth in children with open growth plates.

24. **Basic response:** Clinical features of rickets include craniotabes, widened wrists and ankles, rachitic rosary, and leg bowing, reflecting defective mineralisation at sites of rapid growth.

Value-added response: Neuromuscular features such as hypocalcaemic seizures or tetany can also occur and should prompt consideration of rickets even without classic skeletal deformity.

25. **Basic response:** Investigation shows low calcium and phosphate, elevated alkaline phosphatase and parathyroid hormone, low 25-hydroxyvitamin D, and characteristic wrist radiograph changes.

Value-added response: Treatment with vitamin D and calcium supplementation resolves biochemical abnormalities within weeks, though established skeletal deformities may persist and require orthopaedic assessment.

Answers to Pilot Questions [Series 3]

Part 3.1

1. Vitamin D2 is plant and fungal derived, while vitamin D3 is synthesised in skin or obtained from animal sources.
2. Extensive clothing coverage, sunscreen use, and darker skin pigmentation reduce cutaneous synthesis.
3. Breast milk contains relatively low concentrations of vitamin D, so exclusively breastfed infants are at particular risk without supplementation.
4. Hepatic hydroxylation produces 25-hydroxyvitamin D, and renal hydroxylation produces the active 1,25-dihydroxyvitamin D.
5. 25-hydroxyvitamin D is the major circulating form measured to assess vitamin D status.

Part 3.2

6. Calcitriol increases intestinal absorption of calcium and phosphate, essential for maintaining adequate serum levels.
7. Vitamin D supports mineralisation of osteoid; deficiency leads to accumulation of unmineralised osteoid.
8. Limited sunlight exposure, clothing coverage, and darker skin pigmentation reduce cutaneous synthesis.
9. Breast milk has low vitamin D content, so infants without supplementation are at risk of deficiency.

10. Anticonvulsants can induce hepatic enzymes that accelerate vitamin D breakdown.

Part 3.3

11. Rickets is defective mineralisation of the growth plate, occurring only where growth plates remain open.
12. Rickets affects the growing skeleton, while osteomalacia affects already-formed, mature bone.
13. Calcium-deficient rickets and hereditary hypophosphataemic rickets are causes other than vitamin D deficiency.
14. Secondary hyperparathyroidism raises serum calcium but worsens phosphate loss, impairing mineralisation.
15. It results from renal phosphate wasting independent of vitamin D status, so vitamin D alone cannot correct it.

Part 3.4

1. Craniotabes, widened wrists and ankles, rachitic rosary, and leg bowing are clinical features.
2. Low calcium, low phosphate, elevated alkaline phosphatase, low 25-hydroxyvitamin D, and elevated parathyroid hormone.
3. Widening, cupping, and fraying of the growth plate at the distal radius and ulna.
4. Treatment is with vitamin D replacement and adequate calcium supplementation.
5. Hungry bone syndrome is a transient worsening of hypocalcaemia when vitamin D deficiency is corrected without adequate calcium intake.

References and Attributions [Series 3]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. Munns, C. F. et al. (2016). Global consensus recommendations on prevention and management of nutritional rickets. Journal of Clinical Endocrinology and Metabolism, 101(2), 394 to 415.
3. Holick, M. F. et al. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism, 96(7), 1911 to 1930.
4. Thacher, T. D. and Clarke, B. L. (2011). Vitamin D insufficiency. Mayo Clinic Proceedings, 86(1), 50 to 60.

Figures, Plates, Tables, and Boxes

1. Figure 3.1: The pathway of vitamin D synthesis and activation. AI-generated using the prompt: "Create a professional educational diagram titled Vitamin D Synthesis and Activation Pathway, showing skin, liver, and kidney steps with hormone names labelled. Clean clinical educational diagram style."
2. Table 3.2: Common contributing factors to vitamin D deficiency in children. AI-generated using the prompt: "Create a clean reference table titled Contributing Factors to Vitamin D Deficiency, listing category and example factors. Simple clinical reference table style with outside border."
3. Box 3.3: Key steps in the pathogenesis of nutritional rickets. AI-generated using the prompt: "Create a simple single-column reference box titled Pathogenesis of Nutritional Rickets, listing sequential steps. Clean clinical reference box style."
4. Figure 3.4: Characteristic radiographic features of rickets at the wrist. AI-generated using the prompt: "Create a professional medical illustration titled Radiographic Features of Rickets at the Wrist, comparing a normal growth plate with widening, cupping, and fraying seen in rickets. Clean clinical educational diagram style."

Series 4: Diagnosis and Treatment of Diabetes Mellitus

- **Part 4.1: Definition, Types, and Clinical Presentation of Diabetes Mellitus**
  - Sub Part 4.1.1: Definition and types of diabetes mellitus
  - Sub Part 4.1.2: Clinical history suggesting diabetes mellitus
  - Sub Part 4.1.3: Clinical examination findings in diabetes mellitus
- **Part 4.2: Risk Factors, Diagnosis, and Confirmatory Testing**
  - Sub Part 4.2.1: Risk factors for type 1 and type 2 diabetes
  - Sub Part 4.2.2: Diagnostic criteria for diabetes mellitus
  - Sub Part 4.2.3: Confirmatory serum and urine tests
- **Part 4.3: Insulin Preparations and Treatment of Type 1 Diabetes**
  - Sub Part 4.3.1: Types of insulin preparations
  - Sub Part 4.3.2: Basal-bolus and other insulin regimens for type 1 diabetes
  - Sub Part 4.3.3: Practical considerations in insulin therapy
- **Part 4.4: Treatment of Type 2 Diabetes**
  - Sub Part 4.4.1: Lifestyle management of type 2 diabetes
  - Sub Part 4.4.2: Pharmacological treatment of type 2 diabetes
  - Sub Part 4.4.3: Monitoring and long-term follow up in type 2 diabetes

Introduction

In the last Series, we explored vitamin D metabolism and metabolic rickets. We now turn to diabetes mellitus, one of the most important chronic endocrine conditions in paediatric practice. Picture a nine year old brought to clinic with several weeks of increasing thirst, frequent urination, and unintentional weight loss despite a normal appetite. Recognising this presentation promptly, and understanding how diabetes mellitus is diagnosed and treated, is the focus of this Series.

The aim of this Series is to equip you with the knowledge required to recognise the clinical presentation of diabetes mellitus, understand its diagnostic criteria and confirmatory testing, and understand the treatment regimens used for type 1 and type 2 diabetes.

This Series begins with the **definition, types, and clinical presentation** of diabetes mellitus, before turning to its **risk factors, diagnosis, and confirmatory testing**. Next, we examine **insulin preparations and treatment of type 1 diabetes**, before concluding with **treatment of type 2 diabetes**.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** define diabetes mellitus and describe its major types,
- **SLO 1.2:** explain the clinical history and examination findings that suggest a diagnosis of diabetes mellitus,
- **SLO 1.3:** list the risk factors for developing type 1 and type 2 diabetes,
- **SLO 1.4:** outline the diagnostic criteria for diabetes mellitus,
- **SLO 1.5:** explain how to order appropriate confirmatory serum and urine tests for diabetes mellitus,
- **SLO 1.6:** describe the insulin preparations available for treatment,
- **SLO 1.7:** enumerate the treatment regimens used for patients with type 1 diabetes, and
- **SLO 1.8:** enumerate the treatment regimens used for patients with type 2 diabetes.

4.1 Definition, Types, and Clinical Presentation of Diabetes Mellitus

4.1.1 definition and types of diabetes mellitus

One label, several distinct underlying processes

Diabetes mellitus is defined as a group of metabolic disorders characterised by **chronic hyperglycaemia**, resulting from defects in **insulin secretion**, **insulin action**, or both. The most common form in children is **type 1 diabetes**, resulting from **autoimmune destruction** of the insulin-producing **beta cells** of the pancreas, leading to **absolute insulin deficiency**, meaning affected children require lifelong **insulin replacement** from diagnosis onward.

Type 2 diabetes, historically considered an adult-onset condition, is increasingly recognised in children and adolescents, particularly in the context of **obesity**, and results from a combination of **insulin resistance** and **relative insulin deficiency**, rather than the absolute deficiency seen in type 1 diabetes. Less common forms include **monogenic diabetes**, resulting from a single gene defect, and diabetes secondary to other conditions, such as **cystic fibrosis-related diabetes**.

Fill in the blank: Type 1 diabetes results from autoimmune destruction of the insulin-producing _____ cells of the pancreas.

4.1.2 clinical history suggesting diabetes mellitus

The classic clinical history suggestive of diabetes mellitus includes **polyuria**, increased frequency and volume of urination, **polydipsia**, increased thirst, **polyphagia**, increased appetite, often paradoxically accompanied by **unintentional weight loss**, and, in younger children who had previously achieved bladder control, new-onset **secondary enuresis**, or bedwetting, which can be an important early clue in a toilet-trained child.

A history of **recurrent infections**, particularly **candidal infections** or slow-healing skin infections, and, in more advanced or missed presentations, symptoms of **diabetic ketoacidosis**, including **abdominal pain**, **vomiting**, and **altered consciousness**, should also be actively sought, since diabetes mellitus in children not infrequently first presents at this more advanced, acutely unwell stage rather than with the classic gradual symptom onset described above.

Fill in the blank: New-onset bedwetting in a previously toilet-trained child is termed secondary _____.

4.1.3 clinical examination findings in diabetes mellitus

Physical examination in a child with suspected diabetes mellitus should assess **hydration status**, since significant dehydration can accompany prolonged osmotic diuresis, **weight and growth trend**, since unexplained weight loss is an important supporting feature, and **respiratory pattern**, since deep, sighing **Kussmaul breathing** is a sign of significant metabolic acidosis and should prompt urgent evaluation for diabetic ketoacidosis.

In children with suspected **type 2 diabetes**, examination should also assess for **acanthosis nigricans**, a velvety, hyperpigmented skin change typically found at the neck or axillae reflecting significant insulin resistance, and features of the broader **metabolic syndrome**, including **obesity** and, where relevant, **hypertension**, since these findings support a type 2, rather than type 1, underlying process.

Fill in the blank: Deep, sighing Kussmaul breathing is a sign of significant metabolic _____ and should prompt urgent evaluation for DKA.

Table 4.1: Comparing type 1 and type 2 diabetes mellitus in children.

Feature	Type 1 diabetes	Type 2 diabetes

Underlying mechanism	Autoimmune beta cell destruction	Insulin resistance with relative deficiency
Typical body habitus	Often normal weight or underweight at diagnosis	Often overweight or obese
Onset	Usually acute, over days to weeks	Often more insidious
Associated skin finding	Not typical	Acanthosis nigricans may be present
Initial treatment	Insulin required from diagnosis	May respond to lifestyle measures and oral agents initially

Pilot questions 4.1

- Define diabetes mellitus and distinguish type 1 from type 2 by underlying mechanism. (Linked to SLO 4.1)
- List the classic symptoms suggestive of diabetes mellitus. (Linked to SLO 4.2)
- Explain why secondary enuresis can be a clue to diabetes mellitus in a toilet-trained child. (Linked to SLO 4.2)
- Describe the significance of Kussmaul breathing on examination. (Linked to SLO 4.2)
- Describe acanthosis nigricans and its clinical significance. (Linked to SLO 4.2)

4.2 Risk Factors, Diagnosis, and Confirmatory Testing

4.2.1 risk factors for type 1 and type 2 diabetes

Genetics and environment interact differently in each type

Risk factors for **type 1 diabetes** include a **family history** of type 1 diabetes, though most affected children have no affected first-degree relative, certain **HLA genotypes** conferring increased genetic susceptibility, and, though less clearly established, certain **environmental triggers**, such as viral infections, that may precipitate the autoimmune process in a genetically susceptible child.

Risk factors for **type 2 diabetes** are more clearly linked to **modifiable lifestyle factors**, including **obesity**, **physical inactivity**, and a diet high in **refined carbohydrates**, alongside **non-modifiable factors** such as a strong **family history** of type 2 diabetes, certain **ethnic backgrounds** with higher population prevalence, and a history of **gestational diabetes** in the child's mother or **low birth weight**, both of which are associated with increased later risk.

Fill in the blank: Risk factors for type 2 diabetes include obesity, physical inactivity, and a diet high in refined _____.

4.2.2 diagnostic criteria for diabetes mellitus

The diagnosis of diabetes mellitus is based on demonstrating **hyperglycaemia** using one of several accepted criteria: a **fasting plasma glucose** of 7.0 millimoles per litre or greater, a **random plasma glucose** of 11.1 millimoles per litre or greater in the presence of classic symptoms, a **2 hour plasma glucose** of 11.1 millimoles per litre or greater during an **oral glucose tolerance test**, or a **glycated haemoglobin**, or HbA1c, of 6.5 percent or greater.

In a child presenting with **classic symptoms and a clearly elevated random glucose**, a single confirmatory test is generally sufficient to establish the diagnosis without delay, given the urgency of starting treatment, whereas in an **asymptomatic child**, such as one identified through incidental testing, **repeat testing** on a separate day is generally recommended before confirming the diagnosis, to avoid a false positive result from a single abnormal value.

Fill in the blank: A glycated haemoglobin, or HbA1c, of _____ percent or greater supports a diagnosis of diabetes mellitus.

4.2.3 confirmatory serum and urine tests

Once diabetes mellitus is diagnosed, further testing helps confirm the **type** and assess for **complications** at presentation. **Urinalysis** for **glycosuria** and **ketonuria** provides rapid supporting evidence and helps identify children who may already be in or developing **diabetic ketoacidosis**, requiring urgent further evaluation and management discussed in the next Series of this course.

Serum autoantibodies, including **glutamic acid decarboxylase antibodies** and **islet cell antibodies**, support a diagnosis of type 1 diabetes when positive, while a **C-peptide** level, reflecting the child's own residual insulin production, is typically **low** in type 1 diabetes and **preserved or elevated** in type 2 diabetes, providing additional evidence to help distinguish between the two types when the clinical picture is not entirely clear-cut.

Fill in the blank: A C-peptide level is typically _____ in type 1 diabetes, reflecting minimal residual insulin production.

Box 4.2: Diagnostic criteria for diabetes mellitus.

Diagnostic criteria for diabetes mellitus (any one of the following)
Fasting plasma glucose of 7.0 mmol/L or greater.

Random plasma glucose of 11.1 mmol/L or greater with classic symptoms.
2 hour plasma glucose of 11.1 mmol/L or greater during an oral glucose tolerance test.
Glycated haemoglobin (HbA1c) of 6.5 percent or greater.
In asymptomatic children, repeat testing on a separate day is recommended before confirming diagnosis.

Pilot questions 4.2

1. List two risk factors for type 1 diabetes and two for type 2 diabetes. (Linked to SLO 4.3)
2. State the fasting and random plasma glucose thresholds used to diagnose diabetes mellitus. (Linked to SLO 4.4)
3. Explain when repeat confirmatory testing is recommended before diagnosing diabetes mellitus. (Linked to SLO 4.4)
4. Describe the role of urinalysis in a child with suspected diabetes mellitus. (Linked to SLO 4.5)
5. Explain how C-peptide level helps distinguish type 1 from type 2 diabetes. (Linked to SLO 4.5)

4.3 Insulin Preparations and Treatment of Type 1 Diabetes

4.3.1 types of insulin preparations

Different insulins are designed to mimic different parts of the day

Insulin preparations are classified by their **onset**, **peak**, and **duration of action**. **Rapid-acting insulin analogues**, such as insulin lispro or aspart, have an onset within 10 to 20 minutes and are typically given with meals to cover the glucose rise from food intake, while **short-acting** regular insulin has a somewhat slower onset and longer duration, though it has now been largely superseded by rapid-acting analogues in routine paediatric practice.

Intermediate-acting insulin, such as NPH insulin, and **long-acting** insulin analogues, such as insulin glargine or detemir, are designed to provide a steady **background, or basal, insulin level** throughout the day and night, distinct from the **bolus** doses of rapid-acting insulin given at mealtimes, together forming the basis of the **basal-bolus regimen** widely used in the management of type 1 diabetes.

Fill in the blank: Rapid-acting insulin analogues are typically given with meals to cover the glucose rise from food _____.

4.3.2 basal-bolus and other insulin regimens for type 1 diabetes

The **basal-bolus regimen**, combining a once or twice daily long-acting basal insulin with rapid-acting bolus doses given before each meal, is now the most widely recommended approach for children with type 1 diabetes, since it most closely mimics normal physiological insulin secretion and allows greater **flexibility** in meal timing and content compared with older, more rigid regimens.

Continuous subcutaneous insulin infusion, delivered via an **insulin pump**, provides an alternative to multiple daily injections, delivering a programmable, continuous basal insulin rate with additional bolus doses given at mealtimes, and, increasingly, is used together with **continuous glucose monitoring** in an integrated system, allowing for more precise glucose control, though access to pump therapy varies considerably depending on the healthcare setting and available resources.

Fill in the blank: Continuous subcutaneous insulin infusion is delivered via an insulin _____.

4.3.3 practical considerations in insulin therapy

Insulin doses in children require regular **adjustment**, since insulin requirements change with **growth**, **pubertal development**, **physical activity**, and intercurrent **illness**, meaning ongoing, structured follow up with a paediatric diabetes team is essential rather than a fixed dose being prescribed once and left unchanged. **Injection site rotation** is also important to prevent **lipohypertrophy**, a localised fatty swelling at repeatedly used injection sites that can impair insulin absorption if not avoided.

Education of the child and family in **insulin administration technique**, **blood glucose monitoring**, and **recognition and management of hypoglycaemia** is an essential, ongoing component of care from the point of diagnosis, since insulin therapy, while lifesaving, carries an inherent risk of hypoglycaemia if not matched carefully to food intake and activity level.

Fill in the blank: Localised fatty swelling at repeatedly used insulin injection sites is called _____.

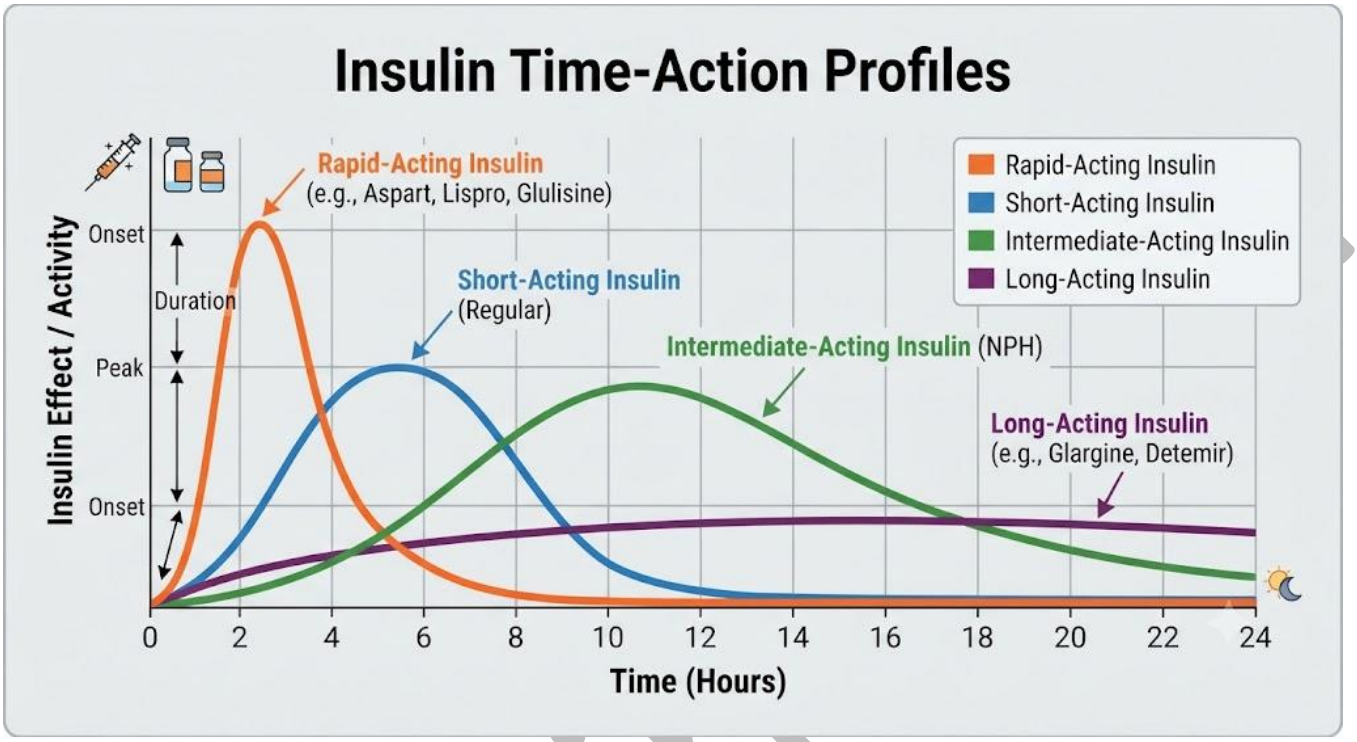


Figure 4.3: Onset, peak, and duration of action of common insulin preparation categories.

Pilot questions 4.3

1. Distinguish rapid-acting from long-acting insulin by onset and purpose. (Linked to SLO 4.6)
2. Describe the basal-bolus insulin regimen. (Linked to SLO 4.7)
3. Describe continuous subcutaneous insulin infusion. (Linked to SLO 4.7)
4. Explain why insulin doses require regular adjustment in a growing child. (Linked to SLO 4.7)
5. Describe lipohypertrophy and how it is prevented. (Linked to SLO 4.7)

4.4 Treatment of Type 2 Diabetes

4.4.1 lifestyle management of type 2 diabetes

Lifestyle change is the foundation, not an afterthought

The foundation of management for a child with type 2 diabetes is **lifestyle modification**, including structured advice on **healthy eating**, reducing intake of refined carbohydrates and energy-dense processed foods, and increasing **regular physical activity**, both to improve insulin

sensitivity directly and to support gradual, sustainable **weight management** where relevant, since even modest, sustained improvements in these areas can meaningfully improve glycaemic control.

Family-based intervention is generally more effective than targeting the child alone, since dietary and activity patterns are typically shared across the household, and involving parents and siblings in lifestyle changes both improves the child's own adherence and models healthier behaviour more broadly, an approach that also helps avoid singling out or stigmatising the affected child within the family.

Fill in the blank: Family-based intervention is generally more effective than targeting the _____ alone.

4.4.2 pharmacological treatment of type 2 diabetes

Where lifestyle measures alone are insufficient to achieve adequate glycaemic control, **metformin** is generally the first-line pharmacological treatment for type 2 diabetes in children, working principally by reducing **hepatic glucose production** and improving peripheral **insulin sensitivity**, and is generally well tolerated, though gastrointestinal side effects such as nausea or diarrhoea are relatively common, particularly if the dose is increased too rapidly.

Insulin therapy may also be required in type 2 diabetes, particularly at initial presentation if the child is significantly symptomatic or in ketosis, or later in the disease course if oral therapy alone becomes insufficient to maintain adequate control, meaning the distinction between type 1 and type 2 diabetes does not always neatly predict whether a given child will ultimately require insulin.

Fill in the blank: _____ is generally the first-line pharmacological treatment for type 2 diabetes in children.

4.4.3 monitoring and long-term follow up in type 2 diabetes

Children with type 2 diabetes require regular monitoring of **glycaemic control**, typically through periodic **HbA1c** measurement, together with screening for **associated comorbidities** that frequently accompany type 2 diabetes in the paediatric population, including **hypertension**, **dyslipidaemia**, and **non-alcoholic fatty liver disease**, all of which share underlying links to obesity and insulin resistance.

Given the strong association between paediatric type 2 diabetes and later **cardiovascular and renal complications**, often occurring earlier in life than in adults diagnosed with type 2 diabetes, **long-term, structured follow up** with regular screening for early complications is an essential,

non-negotiable component of comprehensive care, alongside the ongoing lifestyle and pharmacological management already discussed.

Fill in the blank: Children with type 2 diabetes should be screened for associated comorbidities including hypertension and _____.

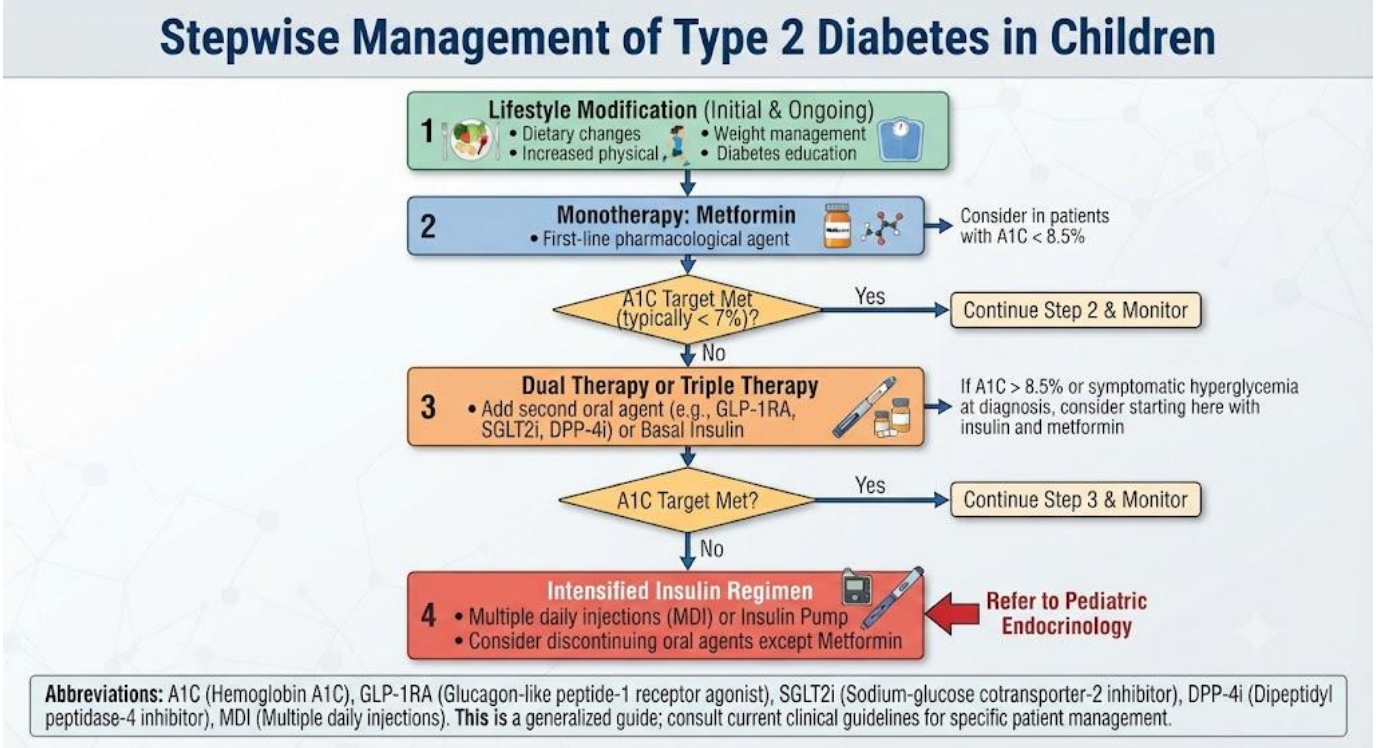


Figure 4.4: A stepwise approach to the management of type 2 diabetes in children.

Pilot questions 4.4

1. Describe the foundation of management for a child with type 2 diabetes. (Linked to SLO 4.8)
2. Explain why family-based intervention is generally more effective than targeting the child alone. (Linked to SLO 4.8)
3. Name the first-line pharmacological treatment for type 2 diabetes in children. (Linked to SLO 4.8)
4. Describe when insulin therapy may be required in a child with type 2 diabetes. (Linked to SLO 4.8)
5. List two comorbidities that should be screened for in a child with type 2 diabetes. (Linked to SLO 4.8)

Series Summary

This Series examined the **diagnosis and treatment of diabetes mellitus**, beginning with its definition, types, and clinical presentation, before turning to **risk factors, diagnostic criteria, and confirmatory testing**.

We then examined **insulin preparations and treatment of type 1 diabetes**, before concluding with the **treatment of type 2 diabetes**. Having worked through this Series, you should now be able to recognise, diagnose, and understand the treatment of diabetes mellitus in children. The next Series turns to **diabetic ketoacidosis, complications, and monitoring of diabetes**.

Glossary of Terms

1. **Type 1 diabetes:** diabetes mellitus resulting from autoimmune destruction of pancreatic beta cells, causing absolute insulin deficiency.
2. **Type 2 diabetes:** diabetes mellitus resulting from insulin resistance with relative insulin deficiency.
3. **Polyuria:** increased frequency and volume of urination, a classic symptom of diabetes mellitus.
4. **Acanthosis nigricans:** a velvety, hyperpigmented skin change reflecting insulin resistance.
5. **Kussmaul breathing:** deep, sighing breathing that is a sign of significant metabolic acidosis.
6. **HbA1c:** glycated haemoglobin, used both to diagnose diabetes and monitor long-term glycaemic control.
7. **C-peptide:** a marker of residual endogenous insulin production, typically low in type 1 diabetes.
8. **Basal-bolus regimen:** an insulin regimen combining long-acting basal insulin with rapid-acting mealtime bolus doses.
9. **Insulin pump:** a device delivering continuous subcutaneous insulin infusion as an alternative to multiple daily injections.
10. **Lipohypertrophy:** a localised fatty swelling at repeatedly used insulin injection sites.
11. **Metformin:** the first-line pharmacological treatment for type 2 diabetes in children.
12. **Gestational diabetes:** diabetes occurring during pregnancy, associated with increased later risk of type 2 diabetes in the child.

Concept Check Questions [Series 4]

Objective questions

- Type 1 diabetes results from autoimmune destruction of the insulin-producing _____ cells of the pancreas.
- New-onset bedwetting in a previously toilet-trained child is termed secondary _____.
- A glycated haemoglobin, or HbA1c, of _____ percent or greater supports a diagnosis of diabetes mellitus.
- A C-peptide level is typically _____ in type 1 diabetes, reflecting minimal residual insulin production.
- _____ is generally the first-line pharmacological treatment for type 2 diabetes in children.

Short-answer questions

1. List the classic symptoms suggestive of diabetes mellitus.
2. List two risk factors for type 1 diabetes and two for type 2 diabetes.
3. State the fasting and random plasma glucose thresholds used to diagnose diabetes mellitus.
4. Distinguish rapid-acting from long-acting insulin by onset and purpose.
5. Describe when insulin therapy may be required in a child with type 2 diabetes.

Long-answer questions

6. Discuss the definition, types, and clinical presentation of diabetes mellitus. (Linked to SLO 4.1, SLO 4.2)
7. Discuss the risk factors and diagnostic criteria for diabetes mellitus. (Linked to SLO 4.3, SLO 4.4)
8. Discuss the confirmatory serum and urine tests used in diagnosing diabetes mellitus. (Linked to SLO 4.5)
9. Discuss the insulin preparations and treatment regimens used for type 1 diabetes. (Linked to SLO 4.6, SLO 4.7)
10. Discuss the treatment regimens used for type 2 diabetes. (Linked to SLO 4.8)

Answers to Concept Check Questions [Series 4]

Objective questions

11. Beta.
12. Enuresis.
13. 6.5.
14. Low.
15. Metformin.

Short-answer questions

16. Polyuria, polydipsia, polyphagia, and unintentional weight loss.
17. Type 1: family history and HLA genotype; Type 2: obesity and physical inactivity.
18. Fasting plasma glucose of 7.0 mmol/L or greater, and random plasma glucose of 11.1 mmol/L or greater with symptoms.
19. Rapid-acting insulin has onset within 10 to 20 minutes and is given with meals, while long-acting insulin provides steady basal coverage over 24 hours.
20. Insulin may be required at presentation if the child is significantly symptomatic or in ketosis, or later if oral therapy becomes insufficient.

Long-answer questions

21. **Basic response:** Diabetes mellitus is characterised by chronic hyperglycaemia; type 1 results from autoimmune beta cell destruction and type 2 from insulin resistance, presenting with polyuria, polydipsia, and weight loss.

Value-added response: Kussmaul breathing on examination suggests significant metabolic acidosis and should prompt urgent evaluation for diabetic ketoacidosis, while acanthosis nigricans supports a type 2 process.

22. **Basic response:** Risk factors for type 1 diabetes include family history and HLA genotype, while type 2 is linked to obesity, inactivity, and family history; diagnosis requires meeting fasting, random, OGTT, or HbA1c thresholds.

Value-added response: Asymptomatic children require repeat confirmatory testing on a separate day before diagnosis is confirmed, to avoid a false positive result from a single abnormal value.

23. **Basic response:** Urinalysis for glycosuria and ketonuria provides rapid supporting evidence, while autoantibodies and C-peptide help distinguish type 1 from type 2 diabetes.

Value-added response: A low C-peptide supports type 1 diabetes, reflecting minimal residual insulin production, while a preserved or elevated C-peptide supports type 2 diabetes.

24. **Basic response:** Insulin preparations range from rapid-acting to long-acting, forming the basis of the basal-bolus regimen, or can be delivered via continuous subcutaneous insulin infusion.

Value-added response: Insulin doses require ongoing adjustment for growth, puberty, activity, and illness, and injection site rotation prevents lipohypertrophy, which can impair absorption.

25. **Basic response:** Type 2 diabetes management begins with lifestyle modification, adding metformin if needed, with insulin reserved for significant symptoms, ketosis, or inadequate control on oral therapy.

Value-added response: Family-based intervention improves adherence, and regular screening for comorbidities such as hypertension and dyslipidaemia is essential given the risk of early cardiovascular and renal complications.

Answers to Pilot Questions [Series 4]

Part 4.1

1. Diabetes mellitus is chronic hyperglycaemia from defects in insulin secretion or action; type 1 is autoimmune beta cell destruction, type 2 is insulin resistance with relative deficiency.
2. Polyuria, polydipsia, polyphagia, and unintentional weight loss are classic symptoms.
3. It can be an early clue to diabetes in a previously toilet-trained child developing new-onset bedwetting.
4. Kussmaul breathing suggests significant metabolic acidosis and should prompt urgent evaluation for DKA.
5. Acanthosis nigricans is a velvety, hyperpigmented skin change reflecting insulin resistance, supporting a type 2 process.

Part 4.2

6. Type 1: family history and HLA genotype; Type 2: obesity and physical inactivity are examples.
7. Fasting plasma glucose of 7.0 mmol/L or greater, and random plasma glucose of 11.1 mmol/L or greater with symptoms.
8. Repeat testing on a separate day is recommended in asymptomatic children before confirming the diagnosis.

9. Urinalysis for glycosuria and ketonuria provides rapid supporting evidence and identifies possible DKA.
10. A low C-peptide supports type 1 diabetes, while a preserved or elevated level supports type 2 diabetes.

Part 4.3

11. Rapid-acting insulin has onset within 10 to 20 minutes for mealtime coverage; long-acting provides steady basal coverage.
12. The basal-bolus regimen combines long-acting basal insulin with rapid-acting mealtime bolus doses.
13. Continuous subcutaneous insulin infusion delivers programmable basal insulin with mealtime boluses via a pump.
14. Insulin requirements change with growth, puberty, activity, and illness, requiring ongoing adjustment.
15. Lipohypertrophy is fatty swelling at repeatedly used injection sites, prevented by injection site rotation.

Part 4.4

1. The foundation of management is lifestyle modification, including healthy eating and regular physical activity.
2. Dietary and activity patterns are shared across the household, so family involvement improves adherence.
3. Metformin is the first-line pharmacological treatment for type 2 diabetes in children.
4. Insulin may be required at presentation with significant symptoms or ketosis, or later if oral therapy is insufficient.
5. Hypertension and dyslipidaemia, or non-alcoholic fatty liver disease, are comorbidities to screen for.

References and Attributions [Series 4]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. International Society for Pediatric and Adolescent Diabetes (2022). ISPAD Clinical Practice Consensus Guidelines.
3. American Diabetes Association (2023). Standards of Care in Diabetes. Diabetes Care, 46(Supplement 1).
4. Zeitler, P. et al. (2018). ISPAD Clinical Practice Consensus Guidelines: Type 2 diabetes mellitus in youth. Pediatric Diabetes, 19(Supplement 27), 28 to 46.

Figures, Plates, Tables, and Boxes

1. Table 4.1: Comparing type 1 and type 2 diabetes mellitus in children. AI-generated using the prompt: "Create a clean reference table titled Type 1 versus Type 2 Diabetes Mellitus in Children, comparing mechanism, body habitus, onset, and treatment. Simple clinical reference table style with outside border."
2. Box 4.2: Diagnostic criteria for diabetes mellitus. AI-generated using the prompt: "Create a simple single-column reference box titled Diagnostic Criteria for Diabetes Mellitus. Clean clinical reference box style."
3. Figure 4.3: Onset, peak, and duration of action of common insulin preparation categories. AI-generated using the prompt: "Create a professional educational graph titled Insulin Time-Action Profiles, comparing rapid-acting, short-acting, intermediate-acting, and long-acting insulin on a shared time axis. Clean clinical educational diagram style."
4. Figure 4.4: A stepwise approach to the management of type 2 diabetes in children. AI-generated using the prompt: "Create a professional medical flowchart titled Stepwise Management of Type 2 Diabetes in Children, showing progression from lifestyle modification to metformin to insulin. Clean clinical educational diagram style."

Series 5: Diabetic Ketoacidosis, Complications, and Monitoring of Diabetes

- **Part 5.1: Definition and Diagnosis of Diabetic Ketoacidosis**
  - Sub Part 5.1.1: Definition and pathophysiology of diabetic ketoacidosis
  - Sub Part 5.1.2: Precipitating factors and clinical features
  - Sub Part 5.1.3: Diagnostic criteria for diabetic ketoacidosis
- **Part 5.2: Laboratory Investigation and Treatment of Diabetic Ketoacidosis**
  - Sub Part 5.2.1: Laboratory investigations for diabetic ketoacidosis
  - Sub Part 5.2.2: Fluid and insulin management in the treatment of DKA
  - Sub Part 5.2.3: Electrolyte correction and cerebral oedema
- **Part 5.3: Complications of Diabetes Mellitus**
  - Sub Part 5.3.1: Acute complications of diabetes mellitus
  - Sub Part 5.3.2: Chronic microvascular complications
  - Sub Part 5.3.3: Chronic macrovascular and other complications
- **Part 5.4: Monitoring of Patients with Diabetes**
  - Sub Part 5.4.1: Glycaemic monitoring
  - Sub Part 5.4.2: Periodic monitoring and complication screening
  - Sub Part 5.4.3: Education and psychosocial support in ongoing monitoring

Introduction

In the last Series, we explored the diagnosis and treatment of diabetes mellitus. We now turn to its most dangerous acute complication, diabetic ketoacidosis, together with the longer-term complications of diabetes and the ongoing monitoring required for good control. Picture a twelve year old with known type 1 diabetes admitted with vomiting, abdominal pain, and deep, laboured breathing after missing several days of insulin doses during an intercurrent illness. Recognising and appropriately treating this presentation, and understanding how to prevent both acute and long-term complications through structured monitoring, is the focus of this final Series of the course.

The aim of this Series is to equip you with the knowledge required to diagnose and treat diabetic ketoacidosis, recognise the complications of diabetes mellitus, and understand the plan for ongoing monitoring of a child with diabetes.

This Series begins with the **definition and diagnosis of diabetic ketoacidosis**, before turning to its **laboratory investigation and treatment**. Next, we examine the **complications of diabetes mellitus**, before concluding with the **plan for monitoring** patients with diabetes.

Series Learning Outcomes

At the end of this Series, you should be able to:

- **SLO 1.1:** define diabetic ketoacidosis and describe its underlying pathophysiology,
- **SLO 1.2:** describe the clinical features and diagnosis of diabetic ketoacidosis,
- **SLO 1.3:** enumerate the laboratory investigations required for diabetic ketoacidosis,
- **SLO 1.4:** explain the treatment of diabetic ketoacidosis, including fluid, insulin, and electrolyte management,
- **SLO 1.5:** describe the potential complications of diabetic ketoacidosis and its treatment,
- **SLO 1.6:** enumerate the acute and chronic complications of diabetes mellitus,
- **SLO 1.7:** describe the plan for monitoring patients with diabetes, and
- **SLO 1.8:** discuss the education and psychosocial support required for effective diabetes self-management.

5.1 Definition and Diagnosis of Diabetic Ketoacidosis

5.1.1 definition and pathophysiology of diabetic ketoacidosis

Absolute insulin deficiency drives the entire cascade

Diabetic ketoacidosis, abbreviated DKA, is a life-threatening acute complication of diabetes mellitus, defined biochemically by the triad of **hyperglycaemia**, **ketosis**, and **metabolic acidosis**, arising from a state of **absolute or severe relative insulin deficiency**. Without adequate insulin, cells are unable to take up and utilise glucose effectively, and the body responds as though in a state of starvation, mobilising alternative fuel sources despite the paradoxically high blood glucose.

This insulin deficiency drives **lipolysis**, the breakdown of fat stores, releasing **free fatty acids** that are converted in the liver to **ketone bodies**, which accumulate in the blood and cause a

metabolic acidosis. Simultaneously, unchecked **hepatic glucose production** and impaired peripheral glucose uptake worsen the hyperglycaemia, which in turn causes an **osmotic diuresis**, leading to significant fluid and electrolyte losses that compound the overall clinical picture.

Fill in the blank: Insulin deficiency drives lipolysis, releasing free fatty acids converted in the liver to _____ bodies.

5.1.2 precipitating factors and clinical features

DKA most commonly occurs either as the **initial presentation** of previously undiagnosed type 1 diabetes, or in a child with **established diabetes** who has missed insulin doses, whether deliberately or inadvertently, or who has an **intercurrent illness**, such as infection, which increases insulin requirements beyond the usual dose and can precipitate DKA even with generally good background diabetes management.

Clinical features include the classic symptoms of hyperglycaemia, **polyuria** and **polydipsia**, together with **vomiting**, **abdominal pain**, which can occasionally mimic an acute surgical abdomen, **dehydration**, **Kussmaul breathing** as discussed in the previous Series, and a characteristic **fruity or acetone odour** to the breath from exhaled ketones, progressing, in severe cases, to **drowsiness** and, ultimately, **coma** if not promptly recognised and treated.

Fill in the blank: Abdominal pain in DKA can occasionally mimic an acute surgical _____.

5.1.3 diagnostic criteria for diabetic ketoacidosis

The diagnosis of DKA requires demonstrating all three components of the defining triad: **hyperglycaemia**, generally a blood glucose above 11 millimoles per litre, **ketosis**, demonstrated by significant **ketonaemia** or **ketonuria**, and **acidosis**, demonstrated by a **venous pH below 7.3** or a **serum bicarbonate below 15 millimoles per litre**, with the severity of DKA further graded as **mild**, **moderate**, or **severe** based primarily on the degree of acidosis present.

This severity grading has important practical implications, since it guides the intensity of monitoring required during treatment and helps anticipate the child's likely clinical trajectory, with more severe acidosis at presentation generally associated with a more prolonged treatment course and a correspondingly higher level of clinical vigilance required throughout.

Fill in the blank: DKA severity is graded as mild, moderate, or severe based primarily on the degree of _____.

Table 5.1: Classification of diabetic ketoacidosis severity.

Severity	Venous pH	Serum bicarbonate (mmol/L)
Mild	7.2 to less than 7.3	10 to less than 15
Moderate	7.1 to less than 7.2	5 to less than 10
Severe	Less than 7.1	Less than 5

Pilot questions 5.1

- Define diabetic ketoacidosis by its defining biochemical triad. (Linked to SLO 5.1)
- Explain the pathophysiological link between insulin deficiency and ketone body production. (Linked to SLO 5.1)
- List two common precipitating factors for diabetic ketoacidosis. (Linked to SLO 5.2)
- Describe the clinical features of diabetic ketoacidosis. (Linked to SLO 5.2)
- State the diagnostic criteria used to confirm diabetic ketoacidosis. (Linked to SLO 5.2)

5.2 Laboratory Investigation and Treatment of Diabetic Ketoacidosis

5.2.1 laboratory investigations for diabetic ketoacidosis

Testing must confirm the diagnosis and guide safe treatment

Initial laboratory investigation of suspected DKA includes **blood glucose**, **venous blood gas** to assess pH and bicarbonate, **blood or urine ketones**, and **serum electrolytes**, particularly **sodium** and **potassium**, since total body potassium is typically significantly **depleted** in DKA despite the serum level often appearing normal or even elevated at presentation, a discrepancy explained by the shift of potassium out of cells in the acidotic state.

Additional investigations include **serum urea and creatinine** to assess renal function and hydration status, **full blood count**, since a raised white cell count can occur even without underlying infection due to the stress response, and, where an infective precipitant is suspected, appropriate **cultures** and other investigations to identify and treat any underlying trigger alongside the DKA itself.

Fill in the blank: Total body potassium is typically significantly depleted in DKA despite the serum level often appearing normal or even _____.

5.2.2 fluid and insulin management in the treatment of DKA

Treatment of DKA begins with careful **fluid resuscitation**, using **isotonic crystalloid**, administered cautiously and calculated to correct the fluid deficit **gradually over 24 to 48 hours**

rather than rapidly, since overly rapid fluid administration is a recognised risk factor for the most feared complication of DKA treatment, **cerebral oedema**, discussed further in the next sub-Part.

Insulin therapy, typically as a **continuous intravenous infusion** of short-acting insulin, is generally started after initial fluid resuscitation has begun, rather than as an immediate bolus, since insulin drives glucose and potassium into cells and can precipitate a dangerous fall in serum potassium or a too-rapid fall in osmolality if given before adequate fluid and, where needed, potassium replacement is underway.

Fill in the blank: Insulin therapy in DKA is generally given as a continuous intravenous _____ rather than a bolus.

5.2.3 electrolyte correction and cerebral oedema

Potassium replacement is a critical component of DKA management, generally added to intravenous fluids once the serum potassium and urine output are confirmed adequate, and closely monitored throughout treatment with repeated blood testing, since both **hypokalaemia** and **hyperkalaemia** can cause dangerous cardiac arrhythmias if potassium correction is not managed carefully alongside the ongoing insulin infusion.

Cerebral oedema is a rare but potentially devastating complication of DKA treatment, more common in children than adults, presenting with **headache**, **altered consciousness**, or **focal neurological signs**, typically within the first several hours of treatment, and risk is reduced by adhering to gradual fluid correction protocols, avoiding overly rapid changes in serum osmolality, and maintaining close clinical monitoring throughout the treatment period to allow prompt recognition and management should it occur.

Fill in the blank: Cerebral oedema during DKA treatment typically presents within the first several hours with headache and altered _____.

Box 5.2: Key principles in the treatment of diabetic ketoacidosis.

Key principles of DKA treatment
Fluid resuscitation with isotonic crystalloid, correcting the deficit gradually over 24 to 48 hours.
Insulin as a continuous intravenous infusion, generally started after fluid resuscitation begins.
Potassium replacement once serum level and urine output are confirmed adequate, with close monitoring.
Frequent reassessment of glucose, electrolytes, and neurological status throughout treatment.

Vigilance for cerebral oedema, particularly in the first several hours of treatment.

Pilot questions 5.2

1. List the key laboratory investigations required in suspected diabetic ketoacidosis. (Linked to SLO 5.3)
2. Explain why total body potassium is depleted in DKA despite a normal or elevated serum level. (Linked to SLO 5.3)
3. Describe the general approach to fluid resuscitation in DKA treatment. (Linked to SLO 5.4)
4. Explain why insulin infusion is generally started after fluid resuscitation has begun. (Linked to SLO 5.4)
5. Describe cerebral oedema as a complication of DKA treatment, including its typical presentation. (Linked to SLO 5.5)

5.3 Complications of Diabetes Mellitus

5.3.1 acute complications of diabetes mellitus

Hypoglycaemia is the most immediate everyday risk

Beyond DKA, the most important **acute complication** of diabetes mellitus in day-to-day management is **hypoglycaemia**, most commonly resulting from a **mismatch** between insulin dose, food intake, and physical activity, presenting with **shakiness**, **sweating**, **hunger**, and **irritability** in mild cases, progressing to **confusion**, **seizures**, or **loss of consciousness** in severe, untreated episodes, making prompt recognition and treatment with fast-acting oral glucose, or, if severe, glucagon or intravenous glucose, an essential skill for the child, family, and school.

Hyperglycaemic hyperosmolar state, a less common acute complication seen predominantly in type 2 diabetes, involves severe hyperglycaemia and dehydration without significant ketosis, and, while less frequent in children than DKA, requires similarly urgent recognition and careful, gradual fluid correction given its own distinct risk of neurological complications if treated too rapidly.

Fill in the blank: Hypoglycaemia most commonly results from a mismatch between insulin dose, food intake, and physical _____.

5.3.2 chronic microvascular complications

Chronic, longstanding **hyperglycaemia** drives a range of **microvascular complications** affecting the small blood vessels, including **diabetic retinopathy**, damage to the blood vessels of the retina that can progress to visual impairment if unrecognised, **diabetic nephropathy**, progressive kidney damage that can eventually lead to chronic kidney disease, and **diabetic neuropathy**, nerve damage that can affect sensation, particularly in the feet, and, less commonly in children, autonomic nerve function.

While these microvascular complications typically take **many years** to develop and are therefore relatively uncommon during childhood itself, the duration of diabetes and the degree of glycaemic control throughout childhood significantly influence the risk of their later development in adulthood, underscoring why consistent, well-supported diabetes management from diagnosis onward matters for long-term, not just immediate, health outcomes.

Fill in the blank: Diabetic retinopathy, nephropathy, and neuropathy are collectively termed _____ complications.

5.3.3 chronic macrovascular and other complications

Longstanding diabetes also increases the risk of **macrovascular complications**, affecting larger blood vessels and including an increased long-term risk of **cardiovascular disease**, such as ischaemic heart disease and stroke, a risk that begins to accumulate from the duration of diabetes exposure even though clinical events themselves typically occur much later in adult life.

Additional complications relevant to children and adolescents with diabetes include an increased risk of certain **autoimmune conditions**, particularly relevant in type 1 diabetes, such as **autoimmune thyroid disease** and **coeliac disease**, both of which are more common in children with type 1 diabetes than in the general population, and **psychosocial complications**, including an increased risk of anxiety, depression, and disordered eating behaviour related to the chronic burden of diabetes self-management.

Fill in the blank: Children with type 1 diabetes have an increased risk of certain autoimmune conditions, including autoimmune thyroid disease and _____ disease.

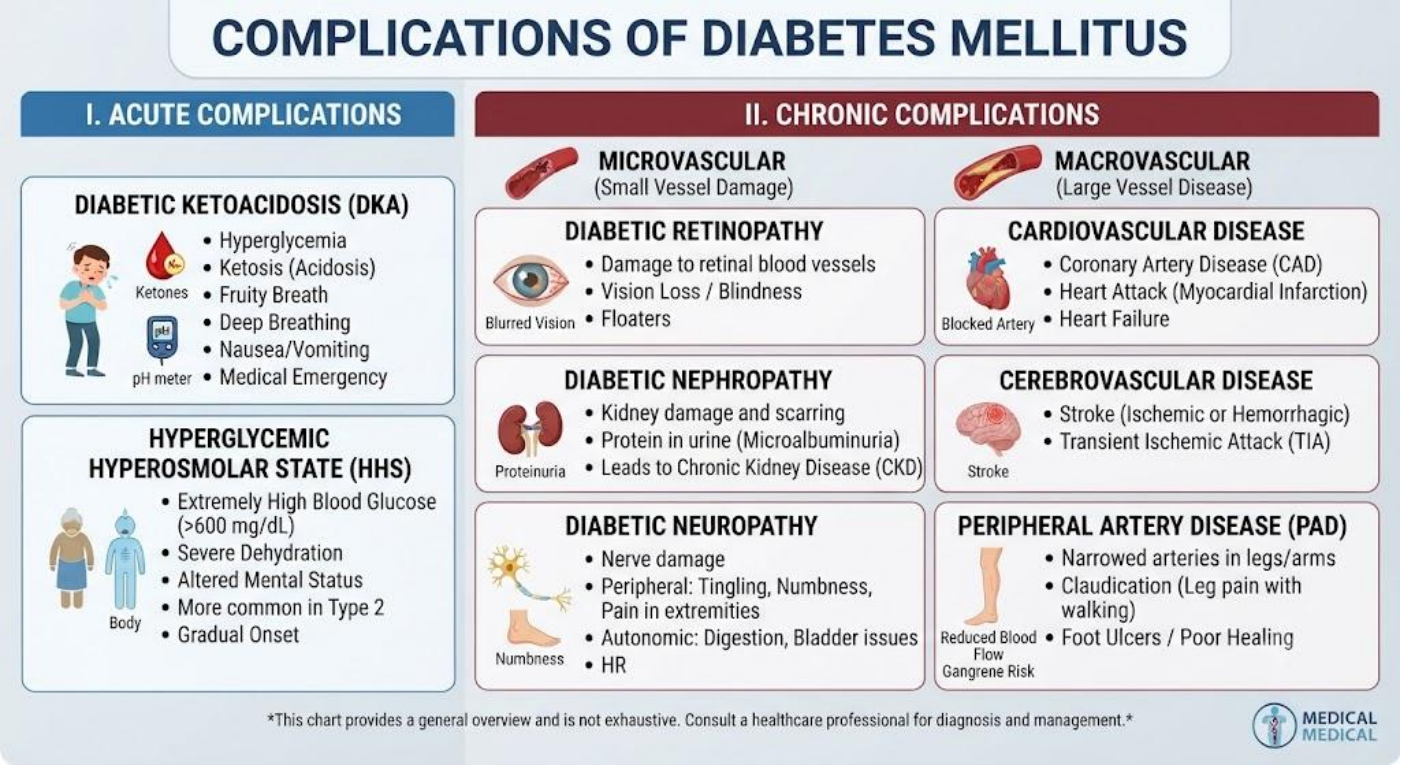


Figure 5.3: Acute versus chronic complications of diabetes mellitus.

Pilot questions 5.3

1. Describe the clinical features of mild and severe hypoglycaemia. (Linked to SLO 5.6)
2. Describe the emergency treatment of severe hypoglycaemia. (Linked to SLO 5.6)
3. List the three classic microvascular complications of diabetes mellitus. (Linked to SLO 5.6)
4. Explain why children with type 1 diabetes are screened for autoimmune thyroid disease and coeliac disease. (Linked to SLO 5.6)
5. Describe the psychosocial complications relevant to children and adolescents with diabetes. (Linked to SLO 5.6)

5.4 Monitoring of Patients with Diabetes

5.4.1 glycaemic monitoring

Different tools answer different questions about control

Self-monitoring of blood glucose, using a capillary blood glucose meter, remains a cornerstone of day-to-day diabetes management, allowing the child and family to make real-time decisions about insulin dosing, food intake, and activity, typically performed **several times daily** in

children on multiple daily insulin injections or pump therapy, with frequency and timing individualised to the child's specific regimen and circumstances.

Continuous glucose monitoring, using a sensor that measures interstitial glucose at frequent intervals throughout the day and night, provides considerably more detailed information about **glucose trends and patterns**, including detection of asymptomatic hypoglycaemia, particularly overnight, and is increasingly recommended where available, since this additional information can meaningfully improve overall glycaemic control and reduce the burden of frequent fingerstick testing.

Fill in the blank: Continuous glucose monitoring measures _____ glucose at frequent intervals throughout the day and night.

5.4.2 periodic monitoring and complication screening

HbA1c should be measured periodically, typically every **three months**, to assess average glycaemic control over the preceding two to three months, complementing the day-to-day information from self-monitoring or continuous glucose monitoring, and providing a key metric used both to guide treatment adjustments and to assess longer-term risk of complications.

Regular **screening for chronic complications** should begin once a child has had diabetes for an appropriate duration, generally after some years of disease or from a certain age depending on local protocols, and includes periodic **retinal screening**, **urine testing for microalbuminuria** as an early marker of diabetic nephropathy, **blood pressure measurement**, and **lipid profile**, alongside the autoimmune condition screening for thyroid disease and coeliac disease discussed in the previous Part.

Fill in the blank: HbA1c should typically be measured every _____ months to assess average glycaemic control.

5.4.3 education and psychosocial support in ongoing monitoring

Effective, sustained diabetes monitoring depends heavily on ongoing **structured education**, covering insulin administration, glucose monitoring technique and interpretation, recognition and management of hypoglycaemia and intercurrent illness, or **sick day rules**, and dietary carbohydrate counting, delivered progressively as the child matures and takes on increasing responsibility for their own self-management with appropriate ongoing support from family and the diabetes care team.

Psychosocial support, including access to **psychology services** and structured **peer support**, is an essential, integral part of comprehensive diabetes care rather than an optional addition, since

the relentless daily demands of diabetes self-management can meaningfully affect mental health and, in turn, glycaemic control itself, meaning attention to psychosocial wellbeing directly supports, rather than merely accompanies, good physical health outcomes for the child.

Fill in the blank: Guidance for managing insulin and glucose during intercurrent illness is commonly referred to as _____ day rules.

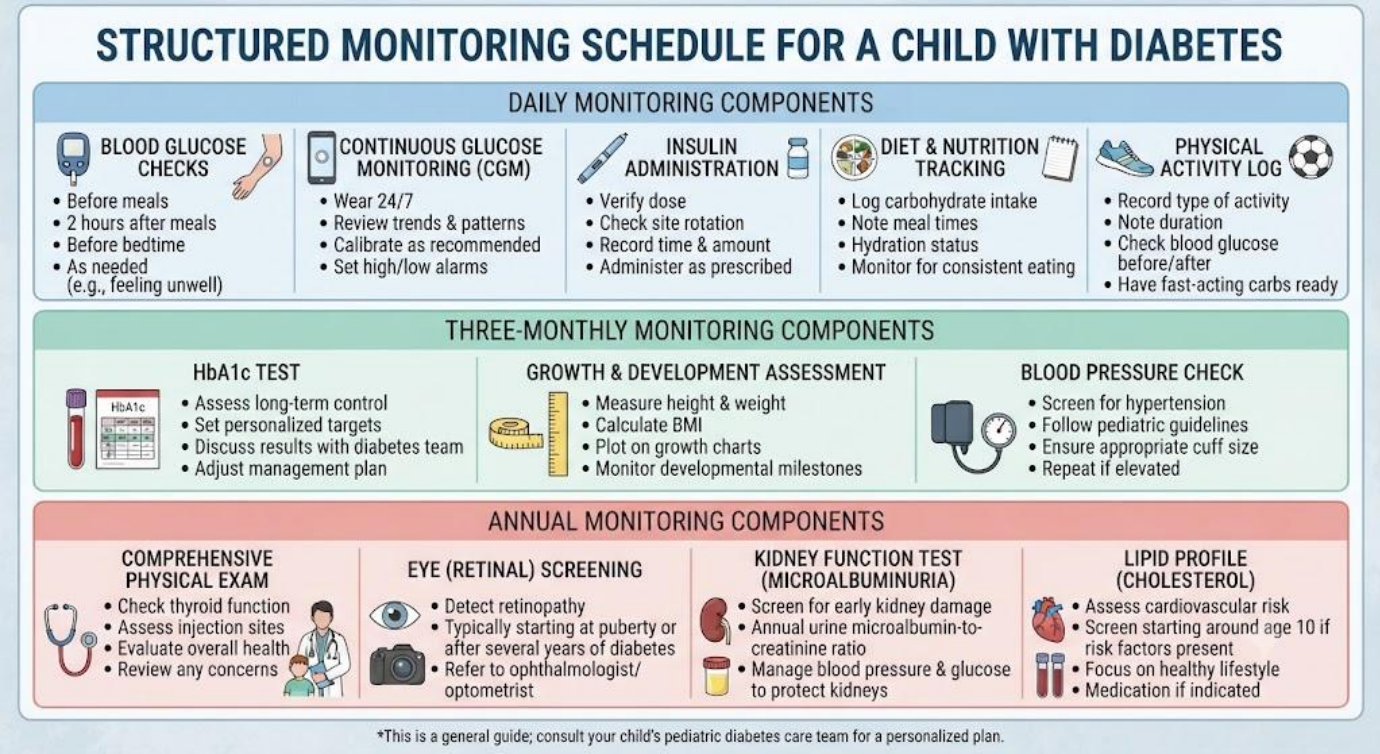


Figure 5.4: A structured schedule for ongoing monitoring of a child with diabetes.

Pilot questions 5.4

1. Describe the role of self-monitoring of blood glucose in day-to-day diabetes management. (Linked to SLO 5.7)
2. Describe the advantage of continuous glucose monitoring over intermittent fingerstick testing. (Linked to SLO 5.7)
3. How frequently should HbA1c typically be measured, and what does it assess? (Linked to SLO 5.7)
4. List two components of chronic complication screening in a child with diabetes. (Linked to SLO 5.7)
5. Explain why psychosocial support is considered an integral part of comprehensive diabetes care. (Linked to SLO 5.8)

Series Summary

This Series examined **diabetic ketoacidosis**, beginning with its definition, pathophysiology, and diagnosis, before turning to its **laboratory investigation and treatment**, including the careful, gradual approach required to minimise the risk of cerebral oedema.

We then examined the **acute and chronic complications** of diabetes mellitus, before concluding with the **plan for ongoing monitoring** of a child with diabetes, including glycaemic monitoring, complication screening, and the essential role of education and psychosocial support. Having worked through this Series, and indeed this course, you should now be equipped with a systematic approach to the evaluation and management of the common endocrine and metabolic conditions encountered in paediatric practice.

Glossary of Terms

1. **Diabetic ketoacidosis:** a life-threatening acute complication of diabetes defined by hyperglycaemia, ketosis, and metabolic acidosis.
2. **Ketone bodies:** products of fat breakdown that accumulate in the blood and cause metabolic acidosis in DKA.
3. **Osmotic diuresis:** increased urine output driven by high blood glucose, contributing to dehydration in DKA.
4. **Cerebral oedema:** a rare but potentially devastating complication of DKA treatment, more common in children than adults.
5. **Hypoglycaemia:** a low blood glucose level, the most common acute complication of day-to-day diabetes management.
6. **Hyperglycaemic hyperosmolar state:** an acute complication of severe hyperglycaemia and dehydration without significant ketosis, seen mainly in type 2 diabetes.
7. **Diabetic retinopathy:** a microvascular complication of diabetes affecting the blood vessels of the retina.
8. **Diabetic nephropathy:** a microvascular complication of diabetes causing progressive kidney damage.
9. **Microalbuminuria:** a small amount of urinary albumin used as an early marker of diabetic nephropathy.
10. **Continuous glucose monitoring:** a sensor-based method of measuring interstitial glucose frequently throughout the day and night.

11. **HbA1c:** glycated haemoglobin, measured periodically to assess average glycaemic control over the preceding two to three months.
12. **Sick day rules:** guidance for managing insulin and glucose monitoring during intercurrent illness.

Concept Check Questions [Series 5]

Objective questions

- Insulin deficiency drives lipolysis, releasing free fatty acids converted in the liver to _____ bodies.
- DKA severity is graded as mild, moderate, or severe based primarily on the degree of _____.
- Insulin therapy in DKA is generally given as a continuous intravenous _____ rather than a bolus.
- Diabetic retinopathy, nephropathy, and neuropathy are collectively termed _____ complications.
- HbA1c should typically be measured every _____ months to assess average glycaemic control.

Short-answer questions

1. Describe the clinical features of diabetic ketoacidosis.
2. Explain why total body potassium is depleted in DKA despite a normal or elevated serum level.
3. Describe cerebral oedema as a complication of DKA treatment.
4. List the three classic microvascular complications of diabetes mellitus.
5. Describe the advantage of continuous glucose monitoring over intermittent fingerstick testing.

Long-answer questions

6. Discuss the pathophysiology and diagnosis of diabetic ketoacidosis. (Linked to SLO 5.1, SLO 5.2)
7. Discuss the laboratory investigation and treatment of diabetic ketoacidosis. (Linked to SLO 5.3, SLO 5.4)
8. Discuss the potential complications of diabetic ketoacidosis and its treatment. (Linked to SLO 5.5)
9. Discuss the acute and chronic complications of diabetes mellitus. (Linked to SLO 5.6)

10. Discuss the plan for monitoring a child with diabetes, including the role of education and psychosocial support. (Linked to SLO 5.7, SLO 5.8)

Answers to Concept Check Questions [Series 5]

Objective questions

11. Ketone.
12. Acidosis.
13. Infusion.
14. Microvascular.
15. Three.

Short-answer questions

16. Polyuria, polydipsia, vomiting, abdominal pain, dehydration, Kussmaul breathing, and a fruity breath odour.
17. Acidosis causes potassium to shift out of cells, masking significant total body depletion despite a normal or elevated serum level.
18. Cerebral oedema presents with headache, altered consciousness, or focal neurological signs, typically within the first several hours of treatment.
19. Diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy.
20. It provides more detailed information on glucose trends and detects asymptomatic hypoglycaemia, particularly overnight.

Long-answer questions

21. **Basic response:** DKA results from insulin deficiency causing lipolysis and ketone body accumulation, diagnosed by the triad of hyperglycaemia, ketosis, and acidosis, with severity graded by degree of acidosis.

Value-added response: Common precipitants include new-onset diabetes or missed insulin doses during intercurrent illness, and clinical features include Kussmaul breathing and a fruity breath odour.

22. **Basic response:** Investigation includes glucose, venous blood gas, ketones, and electrolytes, and treatment involves gradual fluid resuscitation followed by continuous insulin infusion with careful potassium replacement.

Value-added response: Overly rapid fluid or osmolality correction risks cerebral oedema, so treatment protocols emphasise gradual correction over 24 to 48 hours with close monitoring.

23. **Basic response:** Cerebral oedema is a rare but serious complication of DKA treatment, presenting with headache, altered consciousness, or focal signs, more common in children than adults.

Value-added response: Risk is reduced by adhering to gradual fluid correction protocols and maintaining close clinical monitoring, particularly in the first several hours of treatment.

24. **Basic response:** Acute complications include hypoglycaemia and DKA, while chronic complications include microvascular disease affecting the eyes, kidneys, and nerves, and macrovascular cardiovascular disease.

Value-added response: Children with type 1 diabetes also have increased risk of autoimmune thyroid disease and coeliac disease, alongside psychosocial complications such as anxiety and disordered eating.

25. **Basic response:** Monitoring includes daily self-monitoring or continuous glucose monitoring, three-monthly HbA1c, and periodic screening for microvascular complications and associated autoimmune conditions.

Value-added response: Structured education and psychosocial support are essential, integral components of care, since the demands of self-management can affect mental health and, in turn, glycaemic control.

Answers to Pilot Questions [Series 5]

Part 5.1

1. DKA is defined by the triad of hyperglycaemia, ketosis, and metabolic acidosis.
2. Insulin deficiency drives lipolysis, releasing free fatty acids that are converted to ketone bodies causing acidosis.
3. New-onset undiagnosed diabetes and missed insulin doses during intercurrent illness are common precipitants.
4. Polyuria, polydipsia, vomiting, abdominal pain, dehydration, and Kussmaul breathing.
5. Hyperglycaemia, ketosis, and acidosis, defined by pH below 7.3 or bicarbonate below 15 mmol/L.

Part 5.2

6. Blood glucose, venous blood gas, ketones, electrolytes, urea, and creatinine are key investigations.
7. Acidosis shifts potassium out of cells, masking significant total body depletion.
8. Fluid resuscitation with isotonic crystalloid, correcting the deficit gradually over 24 to 48 hours.
9. Insulin can precipitate a dangerous fall in potassium or osmolality if given before adequate fluid replacement.
10. Cerebral oedema presents with headache, altered consciousness, or focal signs, typically in the first several hours of treatment.

Part 5.3

11. Mild hypoglycaemia causes shakiness and sweating; severe hypoglycaemia causes confusion, seizures, or loss of consciousness.
12. Fast-acting oral glucose for mild episodes, or glucagon or intravenous glucose for severe episodes.
13. Diabetic retinopathy, nephropathy, and neuropathy are the three classic microvascular complications.
14. These conditions are more common in children with type 1 diabetes than in the general population.
15. Increased risk of anxiety, depression, and disordered eating behaviour related to diabetes self-management burden.

Part 5.4

1. It allows real-time decisions on insulin dosing, food intake, and activity based on current glucose levels.
2. It provides detailed glucose trend information and can detect asymptomatic hypoglycaemia, particularly overnight.
3. HbA1c is typically measured every three months to assess average glycaemic control over the preceding two to three months.
4. Retinal screening and urine testing for microalbuminuria are components of complication screening.
5. Self-management demands can affect mental health, which in turn affects glycaemic control, making psychosocial support essential.

References and Attributions [Series 5]

1. Kliegman, R. M., St Geme, J. W., Blum, N. J., Shah, S. S., Tasker, R. C. and Wilson, K. M. (2020). Nelson Textbook of Pediatrics (21st ed.). Elsevier.
2. Wolfsdorf, J. I. et al. (2018). ISPAD Clinical Practice Consensus Guidelines: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatric Diabetes, 19(Supplement 27), 155 to 177.
3. International Society for Pediatric and Adolescent Diabetes (2022). ISPAD Clinical Practice Consensus Guidelines.
4. American Diabetes Association (2023). Standards of Care in Diabetes. Diabetes Care, 46(Supplement 1).

Figures, Plates, Tables, and Boxes

1. Table 5.1: Classification of diabetic ketoacidosis severity. AI-generated using the prompt: "Create a clean reference table titled Classification of Diabetic Ketoacidosis Severity, listing severity, venous pH, and serum bicarbonate. Simple clinical reference table style with outside border."
2. Box 5.2: Key principles in the treatment of diabetic ketoacidosis. AI-generated using the prompt: "Create a simple single-column reference box titled Key Principles of DKA Treatment. Clean clinical reference box style."
3. Figure 5.3: Acute versus chronic complications of diabetes mellitus. AI-generated using the prompt: "Create a professional educational chart titled Complications of Diabetes Mellitus, organising acute and chronic (microvascular and macrovascular) complications with examples. Clean clinical educational diagram style."
4. Figure 5.4: A structured schedule for ongoing monitoring of a child with diabetes. AI-generated using the prompt: "Create a professional educational timeline titled Structured Monitoring Schedule for a Child with Diabetes, showing daily, three-monthly, and annual monitoring components. Clean clinical educational diagram style."