

**Short Stature in children: Review Article**

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**Abstract**

**Background:** Humans' final adult height is influenced by a variety of factors. A common paediatric endocrine issue, short stature has a variety of reasons, but normal variations account for the majority of cases. Certain situations may be helped by the early identification of low stature causes. There is a list of pertinent findings from the medical history, physical exam, and certain investigations based on clinical suspicion. A lab screen and an X-ray of the hand/wrist are often done in the absence of any aberrant clinical signs. Although there is a dearth of scientific data supporting the various aspects of laboratory screening, collected experience and theoretical considerations have produced a list of investigations that may be taken into account in the interim.

**Objective:** The review article highlights the short stature causes, evaluation and treatment.

**Conclusion:** There are normal and abnormal forms of short stature (proportionate and disproportionate short stature causes). The growth hormone provocation test is still crucial for identifying GHD. The course of action depends on the ailment. A specific dose of human growth hormone may be required for some short stature conditions in order to improve length.

**Keywords:** Normal growth; Short stature; Growth hormone provocation tests; Bone age; Human growth hormone.

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## Introduction

Although there is a strong hereditary component to height, the genetic code that controls this regulation is not entirely understood. Negative feedback processes control the growth of the skeleton as a whole as well as the growth of particular organs, which cause growth to decelerate and eventually stop as the organs and the body reach their final sizes (Kliegman et al., 2017).

The various hereditary forms of short stature and skeletal dysplasias are produced by more significant differences in individual genes, whereas the ultimate height and growth pattern are altered by minor abnormalities in vast numbers of many gene (Richmond et al., 2020).

When the head is held in the Frankfurt horizontal plane, stature is defined as the height of a person measured from the ground to the vertex (Warrier et al., 2021).

Shortness is described as having a height that is two standard deviations (SD) or less below the average height for one's age, sex, and population (Wit et al., 2008). El Shafie et al. (2020), revealed that 17 percent of the youngsters in their big cross-sectional survey from 2020, which included sample 33150 from a stratified listing of Egyptian primary school students aged 6 to 11 years, reported being low in stature. Farahata et al. (2017) discovered that 13.32 percent of 1225 children under the age of 5 in the Qalyoubia Governorate who participated in another cross-sectional survey from 2015 to 2016 had short height. Short stature was found to be prevalent in 2.86 percent of school-aged children in South India,

according to a study by Velayutham et al. (2017) that involved 15644 youngsters. The prevalence of low stature in Saudi Arabia was found to be 11.3 percent in children and 1.8 percent in teenagers, according to Zayed et al. (2016) Short stature was also shown to be more common in men.

## Classification of short stature

### A) Normal variants short stature:

#### 1) Familial short stature

Familial short height is the most common type of short stature. It is characterised by slower growth rates than average throughout life and stable bone size during growth, which helps distinguish familial short stature children from those who have constitutional growth delays in children (Rogol, 2008).

#### 2) Constitutional growth delay

The constitutional growth delay addresses the rate of growth. These people's growth rates could be modest or typical. Some kids mature later than others, or their bone age is delayed. They enter puberty later than others and are petite for their age. They typically catch up as adults, having a small stature as children but a height that is generally normal as adults (Pérez-Ríos et al., 2019).

#### 3) Idiopathic short stature

When the height is less than 2 SDs of the age mean and there are no endocrine, metabolic, or other diagnoses, the condition is known as ISS. ISS kids were distinguished by normal growth rates, findings from biochemical testing, and outcomes from endocrine screening exams, including those for GH insufficient (Cohen et al., 2007). A heterozygous deletion or mutation of SHOX,

which has been reported in roughly 2.5 percent of ISS children, should be examined for in the kids (**Rappold et al., 2002**). Growth hormone binding protein (GHBP) levels in some ISS children have been discovered to be low, which may indicate diminished GHR function (**Carlsson, 1996**). These patients typically have higher endogenous GH secretion but lower IGF-I levels, suggesting partial GH insensitivity (**Attie et al., 1995**).

## B) Pathological variants of short stature

### 1) Proportionate short stature causes

PSS is diagnosed when the individual has the usual proportion in the limbs and trunk height (**Rani et al, 2022**).

#### ❖ Endocrinal disorders

- **Growth Hormone deficiency:**

GHD can be isolated or present in conjunction with other pituitary hormone abnormalities. It can be inherited or acquired. Congenital GHD has a hereditary component to it. It is known that combined pituitary hormone insufficiency has a number of hereditary origins. Lack of TSH, LH, FSH, GH, and PRL is the outcome of inactivating mutations in the Prop-1 gene (**Wuet al., 1998**). Patients with GH, PRL, and TSH deficiency have Pit-1 gene mutations (**Tatsumi et al., 1992**). Inactivating mutations in the GH-1 and GHRH-R genes have been implicated in the development of isolated GH deficiency. Patients with deficient GHRH showed solitary GH deficit and pituitary hypoplasia (**Maheshwari et al., 1998**). Severe GH shortage is typically caused by deletions of the GH-1 gene's

6.7, 7.0, and 7.6 kb as well as various nonsense and frameshift mutations (type IA). A milder form of GH deficiency (type IB), in which some aberrant GH is produced, is brought on by less crippling mutations of the GH-1 gene. In a unique circumstance, biologically inactive GH is created (**Takahashi et al., 1997**). Splice-site mutations in one allele that enable exon 3 to be skipped are what lead to dominantly inherited GH-1 gene mutations (type II), which have a deleterious impact on the normal GH protein produced by the intact allele. In a patient with dwarfism, a mutant GH functions as an antagonist at the level of the GHR (**Takahashi et al., 1996**).

- **Hypothyroidism**

Juvenile hypothyroidism is characterised by short stature in children because thyroid hormone regulates growth and development of the skeleton through direct impacts and growth hormone-permissive effects. Lowered spontaneous GH production and muted responses to GH provocative tests are symptoms of hypothyroidism (**Ranke et al., 1998**).

- **Diabetes mellitus**

Gender, age at diagnosis, puberty status, duration of the disease, glycemic management, genetics, and growth hormone levels are among the variables influencing growth in diabetes patients (**Virmani, 2015**). Although the exact reason why children with Type 1 diabetes mellitus experience impaired linear development is still unknown, numerous studies have shown that

patients' metabolic control is a significant factor in determining their eventual adult height (Marcovecchio et al. 2014) (Elamin et al., 2006).

- **Diabetis insipitus.**

Anterior pituitary hypofunction in patients with central diabetes insipidus may be worsened by GHD alone or multiple pituitary hormone deficiencies, resulting in anomalies in the anterior pituitary hormone axis that impact growth and development (Liu et al., 2019).

- **Cushing's syndrome:**

The characteristics of Cushing's syndrome in growing children and adolescents are weight gain, growth failure, and pubertal arrest, which reduces eventual adult height. Children who have hypercortisolism also have lower peak bone mass (Abadet al., 2001).

- **Hypogonadism.**

Both female and male bone structures are impacted later in life by oestrogen and androgen deficiencies, which can impair periosteal and endosteal apposition, lower bone growth, and affect cortical and trabecular thickness (Fintini et al., 2009).

- **Hypopituitarism:**

Due to deficits of various pituitary hormones, including growth hormone, hypopituitarism may potentially be a factor in bone loss (Bolanowskiet al, 2015). Low bone mineral density is common in patients with numerous pituitary deficit (Holmer et al., 2007) (Colao et al., 1999). Additionally, it was discovered that GHD caused

osteopenia in hypopituitary patients (Holmer et al., 2007) (Colao et al., 1999) (Wusteret al., 2001).

- ❖ **Genetic disorders:**

- **Turner syndrome:**

A neurogenetic condition called Turner syndrome is characterised by partial or total monosomy-X. It is linked to specific characteristics like low levels of oestrogen, small stature, heart issues, and a higher chance of developing a number of diseases (Kesler, 2007).

- **Noonan's syndrome :**

Congenital heart disease, small height, a broad and webbed neck, sternal deformity, varying degrees of cryptorchidism, an increased tendency to haemorrhage, developmental delay, and features of the face are all symptoms of Noonan's syndrome, a common genetic illness. In most situations, molecular genetic testing can confirm the diagnosis, which is crucial for genetic counselling and management (Romano et al., 2010).

- **Down syndrome:**

The musculoskeletal, neurological, and cardiovascular systems are most affected by the symptoms of the Down syndrome phenotype, which affects many different body systems. Short stature, muscular hypotonia, atlantoaxial instability, reduced neuronal density, cerebellar hypoplasia, intellectual disability, and congenital heart problems, notably atrioventricular septal defects, are all common in people with Down syndrome. Additionally, individuals are more prone to experience the onset of

early-onset Alzheimer's disease as well as hypothyroidism, autoimmune illnesses, obstructive sleep apnea, epilepsy, hearing and vision issues, haematological disorders (including leukaemia), recurrent infections, and anxiety disorders (Hasle et al., 2000).

- **Russel silver syndrome:**

Associated with growth hormone insufficiency, Russell Silver Syndrome is a rare hereditary cause of short stature that is characterised by prenatal and postnatal growth retardation as well as relative macrocephaly, a triangular face, bilateral clinodactyly, congenital body asymmetry, and feeding issues (Mascarenhas et al., 2012). The postnatal growth and birth weight are at least two SD below the mean. Growing slowly over the first three years of life, it then stays parallel to the curve but below the third percentile from this point on (Beserra et al., 2010).

- **Seckel's syndrome:**

It is a rare genetic condition with autosomal recessive inheritance that causes intrauterine growth retardation, which causes low birth weight, and postnatal development delays, which cause short stature (Seckel, 1960).

- ❖ **Systemic disorders:**

Malnutrition, chronic kidney illness, gastrointestinal issues, chronic anaemia, chronic asthma, congenital heart diseases, and chronic infections are just a few of the systemic conditions that can cause low stature in children.

- **Malnutrition:**

One factor affecting the rate of growth and bone development is malnutrition, which can

exacerbate short stature in a person who is genetically susceptible to it (Pérez-Ríos et al., 2019). Infants born underweight due to malnutrition during pregnancy develop delayed growth during childhood (Ranke, 1996).

- **Chronic kidney diseases:**

In children with CKD, growth failure is a clinically serious problem that is linked to high morbidity and mortality rates. These children's stunted growth is brought on by malnutrition, acidosis, renal bone disease, and anomalies in the (GH)-(IGF-I) axis (Mahan and Warady 2006).

- **Gastrointestinal disorders:**

Contrary to people with endocrine diseases, who are frequently overweight-for-height, the failure of growth caused by gastrointestinal disease is marked by a more considerable deficiency in weight than height (Kasirer et al., 2017). Inflammatory disease processes, reduced food intake, malabsorption, and high-dose glucocorticoids, if used as treatment, are all intimately associated to growth failure. Additionally, celiac disease can cause growth failure, particularly in young infants (Rogol, 2008).

## 2) Disproportionate short stature:

When the proportion in the limbs and trunk height is absent and the individual shows a great difference in his sitting and standing height, this is called DSS (Raniet al, 2022).

- **Skeletal dysplasias:**  
A crucial step for longitudinal growth, endochondral ossification at the growth plate is controlled by hormonal and local stimuli, including C-type natriuretic peptide and its receptor, natriuretic peptide receptor B. Acromesomelic dysplasia, Maroteaux type (AMDM), a skeletal abnormality marked by very low stature and asymmetrical shortening of limbs, is brought on by biallelic loss of function mutations in the NPR2 gene, which codes for this receptor (Jacob et al., 2018).
- **Rickets:**  
Children and adolescents who have rickets are at risk for poor health, stunted growth, and developmental problems. It is the outcome of growth plate cartilage anomalies, which primarily impact longer bones and cause impaired bone development, improper mineralization, and skeletal malformations (Jagtap et al., 2012). Therefore, it causes small stature.

### Evaluation and diagnosis of short stature

To eliminate out conditions such growth hormone insufficiency, chronic illnesses, Turner syndrome, ISS hypothyroidism, familial short stature, and/or constitutionally delayed growth and puberty, evaluation is necessary (Kappy, 2013).

- ❖ **Anthropometric Measurement:**  
The Z score should be calculated along with the examination of height, weight, and anthropometric assessment (Fryar et al, 2012) (World Health, O., WHO child growth standards

(2006), Additionally, the ratio of the upper to lower body segments is evaluated, as well as the arm breadth and mid parental height (MPH) (Turan et al., 2005) (ESPE, 2016).

- ❖ **Screening investigations:**  
Potential endocrine (thyroid, for example), renal (electrolytes, creatinine), inflammatory/immune (ESR, tissue transglutaminase antibodies), and hematologic (CBC) problems are the focus of screening laboratory examinations. Physical findings or merely a development pattern and height projection that differs significantly from the family may suggest genetic testing for particular syndromes (Allen and Cuttler, 2013).
- ❖ **Growth hormone provocation tests:**  
Growth hormone secretion fluctuates throughout the day, with peaks occurring during slow-wave electroencephalographic rhythm. Many peptides and neurotransmitters, particularly GHRH and somatostatin, control growth hormone secretion (Richmond and Rogol 2008).
- ❖ **Serum IGF-I level:**  
The GH-IGF axis is evaluated using blood levels of IGF-1. However, data must be interpreted in respect to skeletal age rather than chronological age because levels expand significantly during puberty (Narayanan et al., 2013).
- ❖ **Bone age:**  
X-ray on the left wrist for bone age (Ratib and Gilsanz (2005).

**Table 1: Growth hormone provocation tests**

References	Provocation test	Dose	GH Peak	Side effects
<b>Bozzola et al., 2016</b>	Insulin tolerance test	IV at a dose of 0.1 unit/kg in children over 4 years and 0.05 unit/kg in younger children	After the glucose nadir, between 15 and 30 minutes later.	Hypoglycemia may be a consequence in children with GHD.
<b>Lemamy et al., 2016</b>	Argininetest	IV Arginine HCl at a dose of 0.5 g/kg to a maximum of 40 g)	After arginine administration by one hour	Nausea and vomiting
	Clonidinetest	0.15 mg/m <sup>2</sup>	After clonidine administration by one hour	Children's blood pressure may drop, and they may feel sleepy for many hours.
<b>Bozzola et al., 2016</b>	Glucagon test	IM or SC at a dose of 0.03 mg/kg to a maximum of 1 mg	2 hours after glucagon injection	nausea and vomiting
<b>Ahmid et al., 2018</b>	L-Dopa test	10 mg/kg (Max 500 mg)	30-120 minutes after administration	Nausea & vomiting, vertigo, fatigue and headache

**Table 2: Growth hormone therapy in short stature types**

References	Type of short stature	Dose
Human growth hormone (somatropin) (2010)	GHD	0.7 – 1 mg/m <sup>2</sup> /day
Kim et al., (2018)	ISS	0.37 mg/kg/week
Bondy (2007)	Turner syndrome	0.375 mg/kg/week
Cotterill et al., (1996) Choi et al., (2012)	Noonan's syndrome	0.045 mg/kg/day Or 0.066 mg/kg/day
Clayton et al., (2007)	Russell silver syndrome	35–70 µg/kg/day
Mahan et al., (2006) Molony et al., (2011) Haffner et al., (2001)	Chronic renal diseases	0.05 mg/kg/day Or 0.35 mg/kg/week

mg/kg/week (the standard dose approved by the FDA) (Kimet al., 2018).

Recombinant hGH therapy for Turner syndrome is often started at the recommended dose of 0.375 mg/kg/week given as daily injections (Bondy, 2027). In girls with TS, treatment with growth hormone at greater doses (0.630 mg/kg/week) promotes growth even more, although this results in unusually high IGF-I levels (Sas et al., 1999a) (Bannink et al., 2006a) (Park and Cohen, 2004) (Ranke and Lindberg 2007) .

Recombinant hGH therapy, the majority of patients with Noonan's syndrome who received GH (0.045 mg/kg/day) for a year experienced significant increase in mean height SDS (-3.01 to -2.36) and height velocity (4.9 to 8.1 cm/yr) (Cotterill et al., 1996). According to another study, after receiving GH medication for a year (0.066 mg/kg/day), the mean height SDS increased from -2.8 to -2.0 and the growth rate from 5.0 to 8.9 cm/year (Choi et al., 2012).

For children born with SGA, including those with russell silver syndrome and who had severe growth retardation (height SDS 2.5), the early therapy with GH at a dose of 35–70 g/kg/day is recommended (Clayton et

#### ❖ Pituitary MRI:

The best way to diagnose children with pituitary short stature brought on by GHD is through magnetic resonance imaging (MRI), which can clearly identify the pituitary, the pituitary stalk, and the nearby structures of the saddle area (Wolfsdorf et al., 1996).

#### Management of short stature

Human growth hormone (hGH) therapy:

Among GHD patients, there is a wide range of responses to GH therapy, which is most likely a result of patient compliance concerns, variation in the severity of GHD, and the tissue responsiveness of the patient to GH. The range of GH's licenced dose for GHD is 0.7-1.0 mg/m<sup>2</sup>/day (Human growth hormone (somatropin) (2010)).

GH therapy for ISS caused a significant increase in height velocity (10.68 1.95 cm/year) after six months, and the height increase was 10.17 1.95 cm/year during the

first year, when it was administered to Korean children with ISS at a dose of 0.37



**AMDM:** acromesomelic dysplasia, Maroteaux Type.

**BMI:** body mass index.

**CBC:** Complete blood count.

**CDGP:** Constitutional delay in growth and puberty.

**CKD:** Chronic kidney diseases.

**Cm:** centimeter.

**DSS:** Disproportionate short stature.

**ESR:** Erythrocyte sedimentation rate.

**FDA:** Food and drug administration.

**FSH:** follicle-stimulating hormone.

**FSS:** Familial short stature.

**GH:** Growth hormone.

**GHBP:** Growth hormone binding protein.

**GHR:** Growth hormone receptor.

**GHRH:** Growth hormone releasing.

**GHRH-R:** Growth hormone releasing hormone receptor.

**hGH:** human growth hormone.

**IGF-I:** Insulin like growth factor 1.

**IM:** Intramuscular.

**ISS:** Idoipathic short stature.

**IU:** International unit.

**IV:** Intravenous.

**Kg:** kilo gram.

**LH:** Luteinizing hormone.

**al., 2007).** In patients with chronic renal diseases, the dose is (0.05 mg/kg/day or 0.35 mg/kg/week), and treatment effectiveness is attained to target adult height with an average height gain of about 4 cm/year (**Mahan and Warady, 2006**)(**Molony and Stephens, 2011**) (**Haffner and Shaefer, 2001**).

Fluid retention, headaches, scoliosis, and pseudotumor cerebri are typical GH side effects. Insulin resistance and GH-neutralizing antibodies may both develop sporadically (**Horne et al., 2018**).

Over short peri-pubertal males, non-hGH growth-promoting drugs include low-dose androgen therapy with either injectable testosterone or oral oxandrolone (1.25–2.5 mg/day), both of which boost growth rate by 3–5 cm/year for a period of one to three years(**Schroor et al, 1995**) (**Keenan et al., 1993**).

When skeletal age is greater than 11 years, oxandrolone is preferable to testosterone for slowing down estrogen-mediated epiphyseal growth (**Lee et al., 2006**).

## Conclusion

The process of growth is intricate and is impacted by a variety of variables, including genetic, endocrinological, environmental, and other factors. But there are also other common reasons for short stature, like inherited short stature and a genetic delay in puberty and growth. In order to evaluate, a thorough history and examination are required. The correct diagnosis and the underlying cause must be considered when treating low stature.

## ABBREVIATION

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**Mg:** milli gram.

**MPH:** Mid parental height.

**MRI:** Magnetic resonance imaging.

**PRL:** Prolactin.

**PSS:** proportionate short stature.

**PWS:** Prader-Willi syndrome.

**RSS:** Russell Silver Syndrome.

**SD:** Standard deviations.

**SGA:** Small gestational age.

**SHOX:** Short stature homeobox.

**TSH:** Thyroid stimulating hormone.

**WHO:** World Health Organization.

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