

The Physiology of Childhood Growth: Hormonal Regulation

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Growth · Growth and puberty · Growth factor · Growth hormone · Growth hormone physiology · Growth in children · Hormones · Normal growth/auxology · Nutrition

Abstract

The growth patterns of a child changes from uterine life until the end of puberty. Height velocity is highest in utero and declines after birth until puberty when it rises again. Important hormonal regulators of childhood growth are growth hormone, insulin-like growth factor 1, sex steroids, and thyroid hormone. This review gives an overview of these hormonal regulators of growth and their interplay with nutrition and other key players such as inflammatory cytokines.

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Introduction

A child's growth is affected by numerous factors where for example impaired nutritional status, a poor psychosocial situation, and a variety of chronic diseases may impair the growth rate, and if not treated appropriately these conditions may cause short adult height. Normal growth is therefore an excellent indicator of the general health of

a child [1]. The growth rate of a child varies being highest during fetal life and infancy, slowing down during childhood, accelerating during puberty, and then ultimately ending when adult height has been reached by the end of the adolescent period [2]. These different phases of growth are illustrated in Figure 1. In this review, we first give a brief overview of the regulation of normal growth in children and adolescents, which is followed by a more detailed description of important hormones regulating human growth and how these interact with each other. Lastly, we discuss the impact of nutrition and inflammation on human growth.

Phases of Normal Growth

Karlberg [3] introduced the infancy-childhood-puberty growth model where postnatal growth is divided into three different stages. These stages reflect different hormonal phases of the growth process.

Prenatal/Fetal Growth

The size of a newborn child depends on many different factors including genetics, gestational age, and maternal factors such as body size, uterine growth potential, nutrition, diabetes, blood pressure, and smoking [3, 4]. The fastest growth occurs in utero and especially between gestational weeks 20 and 24 when the growth rate is 2.5 cm per week [5].

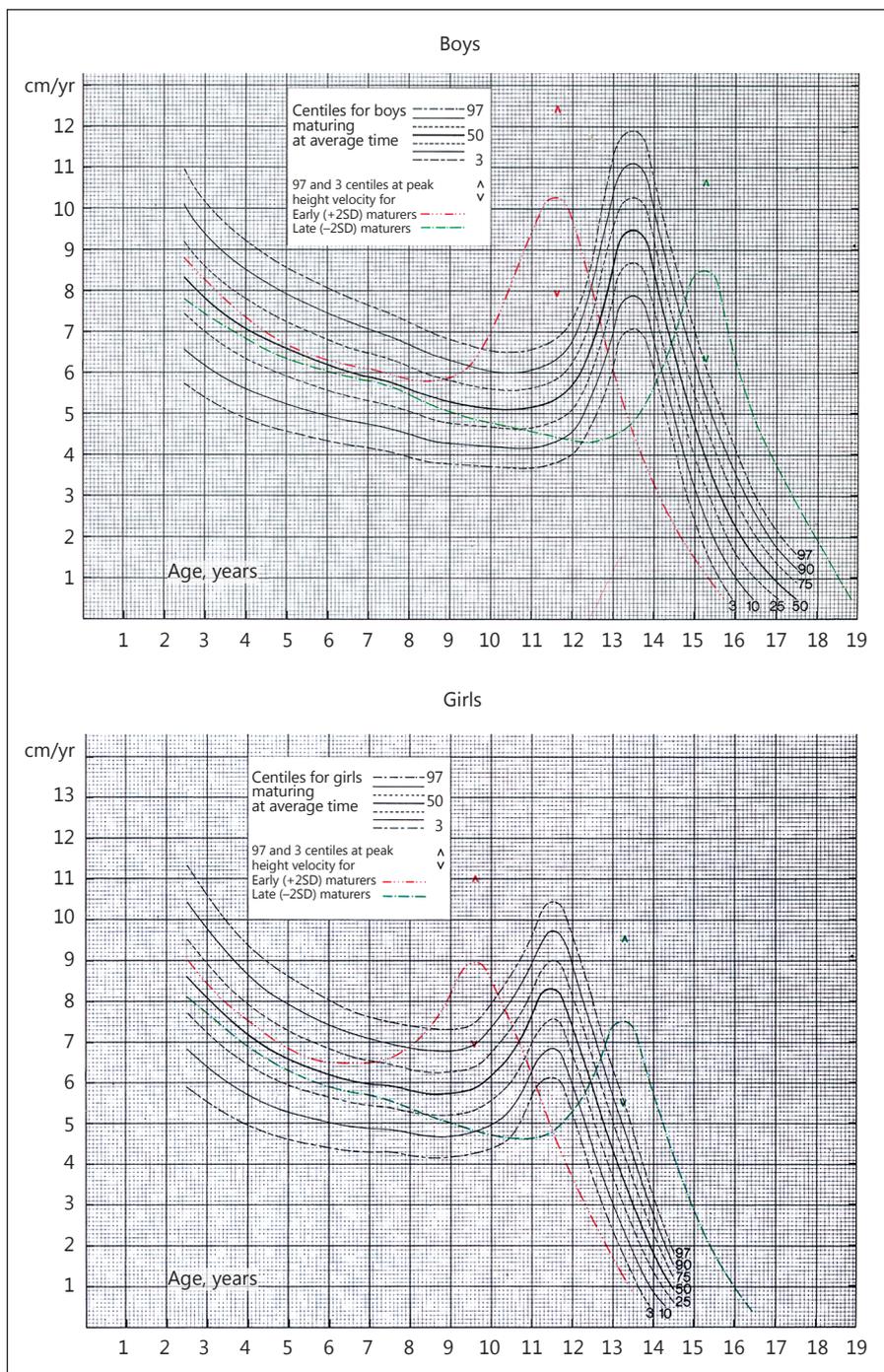


Fig. 1. Different phases of growth. Adapted from Tanner and Davies [2], with permission from Elsevier.

Growth during Infancy

During the first year of life, growth rate is still high averaging 25 cm per year. Thereafter, growth rate slows down to about half in the second year. The nutritional status largely influences infancy growth, and nutritional causes may explain why the height curve often crosses percentile lines during the first 24 months of life.

Growth during Childhood

At 2 years of age, the children have usually found a more steady growth rate where they do not cross height centiles and then follow this path until puberty with similar growth patterns in boys and girls [6]. Contrary to the growth during infancy, nutrition has less influence on growth during this period whereas hormonal regulators

are more important [7]. The height velocity is usually 6–8 cm per year from 2 to 6 years, after which it slows down somewhat. Between 6 and 8 years, adrenarche occurs. There is an increase in anabolic hormones released by the adrenal glands leading to a small transient growth spurt.

Growth during Puberty

During puberty, a growth spurt occurs when girls and boys increase their heights by 20–25 and 25–30 cm, respectively. In boys, signs of puberty appear somewhat before this growth spurt begins whereas in girls it starts in parallel. The growth starts distally in the extremities with hands and feet. Then arms and legs will grow and lastly the spine. The maximum growth rate, the so-called peak height velocity (PHV), occurs during later stages of puberty at around 12 years in girls and 14 years in boys [8]. After PHV, there is a steep decline. Typically menarche occurs in girls after PHV, and they grow for approximately 2 more years. However, there is a large individual as well as ethnic variation in the timing and tempo of pubertal development and growth patterns [9].

Attainment of Adult Height

By the end of puberty, the growth plates become narrower and eventually close. This process is stimulated by increased levels of circulating sex steroids as normally found during puberty. When all growth plates have been closed, no further growth can take place and adult height has then been achieved.

The Growth Plate

Long bones are formed through a process called endochondral ossification. It involves mesenchymal stem cell condensation and the development of a hyaline cartilage model. In the shaft of this model, a primary ossification center forms and gets vascularized, and thereafter secondary centers of ossification form in both ends of the long bones, the so-called epiphyses. After birth, further longitudinal bone growth takes place in a thin remnant of cartilage localized between the primary and secondary ossification centers called the growth plate or epiphyseal plate. It has different structural and functional zones as seen in Figure 2. The resting zone is made up of stem-like cells, waiting to be recruited to the proliferative zone under the influence of the growth hormone (GH) where they undergo mitosis and get stacked in columns. They then reach the hypertrophic zone where they undergo hypertrophy and secrete extracellular matrix proteins and undergo apoptosis giving rise to lacunae which are invaded by bone-forming cells. This process causes the

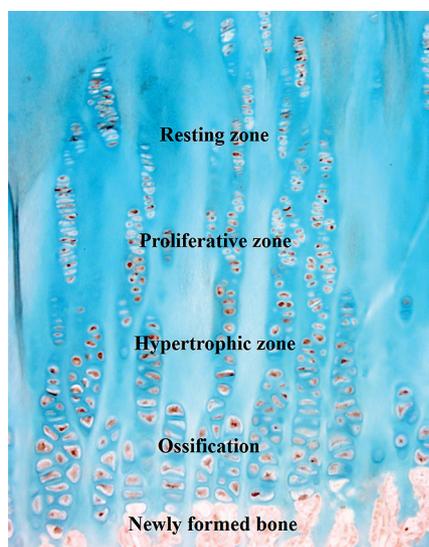


Fig. 2. Growth plate zones. Illustration of the different zones in a sectioned human growth plate.

elongation of the diaphysis of the bone [10]. The growth plates fuse at the end of puberty and leave an epiphyseal line which for a period of time is visible on X-ray.

Hormonal Regulation of Growth

The hormonal regulation of longitudinal bone growth is complex and involves both local and systemic pathways [11, 12]. An overview of these regulatory pathways is shown in Table 1 and some of the most important ones are detailed below. Growth factors that act only locally in the growth plate are described in a different paper.

GH-Insulin-Like Growth Factor 1 Axis and Insulin

GH is a single polypeptide chain made up of 191 amino acids produced by the pituitary gland. Two GH genes on chromosome 17 have been discovered [13]. GH is mainly regulated by two peptides secreted by the hypothalamus, GH-releasing hormone and the inhibitory hormone somatostatin. It is also stimulated by ghrelin produced in the stomach, and insulin-like growth factor 1 (IGF-1) exerts negative feedback control [14]. GH exerts its action by binding to the GH receptor (GHR) which is abundantly expressed in most tissues. The GHR is a transmembrane receptor belonging to the cytokine receptor family. GH stimulates longitudinal bone growth both via direct stimulation of the growth plate and indirectly via

Table 1. Overview of hormones and growth factors regulating growth

Type of hormone/ growth factor	Main effects on growth
GH	Affects mainly postnatal growth Stimulates hepatic IGF-1 production and chondrogenesis in the growth plate [18]
IGF-1	Affects both prenatal and postnatal growth Stimulates uptake of amino acids from the circulation and chondrogenesis in the growth plate (proliferation, hypertrophy, and ossification) [15, 16]
Insulin	Binds to the IGF-1 receptor and increases growth velocity Increases free IGF-1 in the circulation [22]
Thyroid hormones	Regulate bone turnover and bone mineral density Stimulate clonal expansion of chondrocyte progenitor cells, inhibit subsequent cell proliferation, and promote hypertrophic chondrocyte differentiation and cell volume expansion [25]
Sex steroids	Regulate the secretion and effects of GH Affect chondrogenesis and growth plate fusion (ER α) [14, 41]
Leptin	Regulates GH secretion and stimulates chondrogenesis locally in the growth plate [50, 51]

GH, growth hormone; IGF-1, insulin-like growth factor 1; ER, estrogen receptor.

IGF-1. Serum concentrations of GH and IGF-1 may be increased more than 3-fold during puberty (Fig. 3).

IGF-1 is a polypeptide encoded by the *IGF1* gene on chromosome 12 [13]. It is structurally homologous with proinsulin. Circulating IGF-1 is mainly produced in the liver but IGF-1 is also ubiquitously expressed in many other tissues such as fat and muscle. IGF-1 is also produced in the growth plate, thereby acting in a paracrine/autocrine fashion under the influence of GH [15]. In the circulation, IGF-1 is bound to IGF-binding proteins (IGFBPs), mainly IGFBP-3, and the acid-labile subunit forming a ternary complex. IGF-1 is believed to stimulate linear growth, both systemically as well as locally in the growth plate [16]. It has earlier been suggested that local effects of IGF-1 in the growth plate are more important

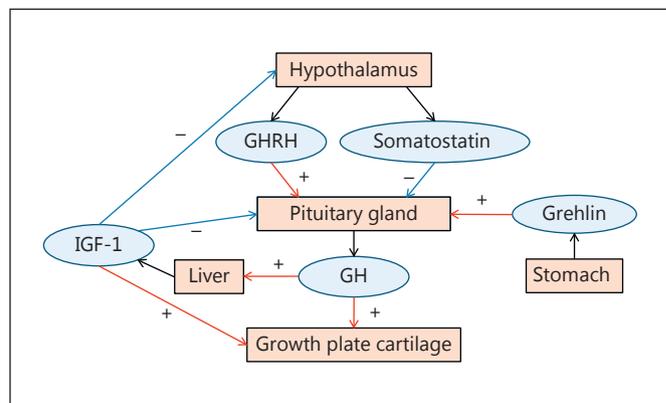


Fig. 3. The growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis. Basic overview of the GH/IGF-1 axis with focus on bone growth regulation. GHRH, GH-releasing hormone.

than its endocrine effects for stimulating longitudinal bone growth [17]. However, a recent knockout study in mice lacking the IGF-1 receptor exclusively in the growth plate showed that GH can stimulate chondrogenesis and longitudinal bone growth even when local IGF-1 and IGF-2 action is inactivated [18]. Within the growth plate, IGF-1 stimulates proliferation and hypertrophy of the chondrocytes as well as ossification by affecting the osteoblasts.

Conditions affecting the GH/IGF-1 axis can lead to abnormal growth in children. GH deficiency appears to mainly affect postnatal growth whereas IGF-1 deficiency affects both prenatal and postnatal growth [19]. IGF-2 is another polypeptide in the same family that also affects pre- and, to a lesser extent, postnatal growth. IGF-1 is however the predominant regulator of postnatal growth [20]. Primary IGF deficiency is associated with short stature, and these patients have low serum IGF-1 but normal or increased GH concentrations [21]. An example is GH insensitivity (Laron syndrome) where the GHR gene is affected. Secondary IGF deficiency, on the other hand, is caused by abnormalities of the hypothalamus or pituitary gland and leads to insufficient secretion of GH. As a result these children will also have low serum IGF-1 concentrations and exhibit short stature. Excessive secretion of GH in childhood by contrast can lead to gigantism which is a rare condition typically caused by a pituitary tumor (pituitary gigantism).

Mouse studies have shown that inactivation of the insulin receptor in the growth plate initiates a compensatory upregulation of IGFs and their receptors to regulate

the proliferation and hypertrophy of chondrocytes [22]. Insulin is important for both fetal and childhood growth. Insulin and IGF-1 are both strongly connected to nutrition. A high intake of protein and minerals has been found to lead to a 25% increase in serum IGF-1 concentration [23]. IGF-1 is an anabolic hormone-stimulating protein synthesis through the uptake of amino acids from the circulation. It also increases bone mineral density and muscle mass and causes lipolysis [19].

Thyroid Hormones

Thyroid hormones are important for postnatal growth. Thyroxine is converted into triiodothyronine in peripheral tissue, and the latter is usually considered to be the physiologically active hormone. Expression of thyroid hormone receptor $\alpha 1$ (TR $\alpha 1$) and TR $\beta 1$ has been shown in the resting and proliferative zones of the growth plate [24]. Local regulation involves chondrocyte maturation, cartilage matrix synthesis, mineralization, and degradation. Hypothyroidism during childhood and adolescence causes a delay in skeletal maturation and growth arrest. Thyrotoxicosis, on the other hand, advances skeletal maturation and causes growth acceleration but due to early fusion of the growth plates, the outcome will be a decreased final height [25].

Sex Steroids

Sex steroids including estrogen and testosterone are mainly produced by the gonads. Estrogens play an important role for growth in both girls and boys. In girls estrogens are mainly produced by the ovaries. There is also estrogen production in the testes although the main production in boys occurs in peripheral tissues by aromatizing androgens. This is mediated by the converting enzyme CYP450arom, which can be found in many different tissues including gonads, brain, fat, placenta as well as the growth plates where estrogen appears to be synthesized locally [26–28]. The three major endogenous estrogens are estrone, estradiol, and estriol [29]. Except for pregnancy when estriol is the primary estrogen, estradiol is the most abundant estrogen in women until menopause after which estrone dominates.

Puberty is characterized by an activation of the hypothalamic-pituitary-gonadal axes [30]. Gonadotropin-releasing hormone pulses trigger the release of luteinizing hormone and follicle-stimulating hormone from the pituitary which stimulates sex hormone release from the gonads. An increase in GH pulse amplitude before pubertal onset in girls and somewhat later in boys has been shown [31]. It was recently reported that also IGF-1 levels

during puberty correlate closely with PHV [32]. Estrogens affect growth by regulating the effect of GH, and its secretion by reducing IGF-1-mediated negative feedback [14]. Estradiol and GH have been shown to regulate pubertal growth in both girls and boys, and in boys testosterone has been found to lead to a stimulatory effect of GH on IGF-1 secretion [33]. Androgen receptors are present in the human growth plates as well as in those of rodents, but no local direct effects on longitudinal growth by androgens were found in fetal metatarsals from rats [34]. Estrogens, although stimulating growth during puberty, is the factor that finally leads to growth plate fusion at the end of puberty in both females and males [35].

Estrogens act by binding different nuclear receptors in the growth plate, estrogen receptor (ER) α and ER β , and a more recently discovered G protein-coupled estrogen receptor 1 (GPER1) which is membrane-bound and was previously called GPR30 [36, 37]. ER α and ER β are both expressed throughout the growth plate [38]. The abundance of both receptors increases as the cells differentiate [39]. Estrogens stimulate osteoblasts and inhibit osteoclasts but the exact mechanisms through which they promote bone growth are not yet fully understood [40]. The two receptors have been studied in knockout mice. Inactivation of ER β but not ER α stopped growth plate fusion [41]. ER α inactivation has been shown to decrease bone growth in female mice [41, 42]. ER β inactivation affected growth in some studies but not in others, and differences between male and female mice in the effects of ER α and ER β inactivation on bone growth have been observed [41, 43, 44]. Simm et al. [39] concluded that ER α stimulates different steps of chondrogenesis whereas ER β inhibits skeletal growth in mice. The receptor GPER1 is highly expressed in the hypertrophic zone especially before puberty when it starts a gradual decrease, suggesting a role in longitudinal bone growth regulation [37].

There are important differences between mice and humans to consider when interpreting mouse data. For example, a pubertal growth spurt is lacking in mice, and their growth plates do not fuse after sexual maturation as they do in humans. Observations suggest that ER β is important for growth plate fusion in mice. However, open growth plates at 28 years of age were observed in a male patient (the so-called “hERKO man”) who had an ER α -inactivating mutation [45]. He was 204 cm tall and had reduced bone mineral density. More recently, an ER α mutation was also described in an 18-year-old woman who appeared to have complete estrogen insensitivity with a lack of breast development and elevated serum levels of estrogens [46]. Patients with aromatase deficiency

exhibit a similar phenotype including a lack of pubertal growth spurt and growth plates which remain open into adulthood leading to tall stature. A patient with aromatase deficiency will respond to estrogen treatment whereas such therapies will have no effect on bone mineral density and bone maturation in an ER α -mutated patient [47].

Leptin

Leptin is a hormone secreted mainly by white adipose cells but is also produced in other tissues such as skeletal muscle, placenta, and the pituitary gland. It is involved in body weight regulation and is often referred to as the “satiety hormone.” Studies have also shown that it is involved in the regulation of GH secretion and thereby affects growth. Leptin appears to stimulate GH secretion by acting on the hypothalamic level [48, 49]. It has also been shown to have a local effect in the growth plate by stimulating chondrocyte proliferation and cell differentiation [50, 51].

Interplay between Hormones

An overview of hormones and growth factors is shown in Table 1.

Inflammation and Linear Growth

Children with chronic inflammatory diseases, such as juvenile idiopathic arthritis or inflammatory bowel disease, often display growth retardation. Several factors related to the disease itself including malnutrition, hypercortisolism, and proinflammatory cytokines as well as glucocorticoid (GC) treatment may contribute to the abnormal growth (Fig. 4).

Malnutrition is common in children with chronic inflammatory diseases and is suggested to account for approximately 60% of the growth retardation in these children [52]. The inflammatory processes include elevated serum levels of proinflammatory cytokines and endogenous cortisol, which both have been shown to negatively affect growth [53].

Endogenous GCs are part of the body’s inflammatory response. They have been shown to act systemically by inhibiting GH secretion, downregulating GH receptors in the liver and thereby inhibiting IGF activity [54, 55]. Locally in the growth plate they inhibit chondrocyte differentiation and increase apoptosis [56]. Commonly in children with chronic inflammatory diseases, exogenous GCs such as prednisolone or dexamethasone are used to suppress the inflammation. Long-term treatment however has a further negative impact on growth in these patients [57, 58]. It has been shown to suppress chondrocyte dif-

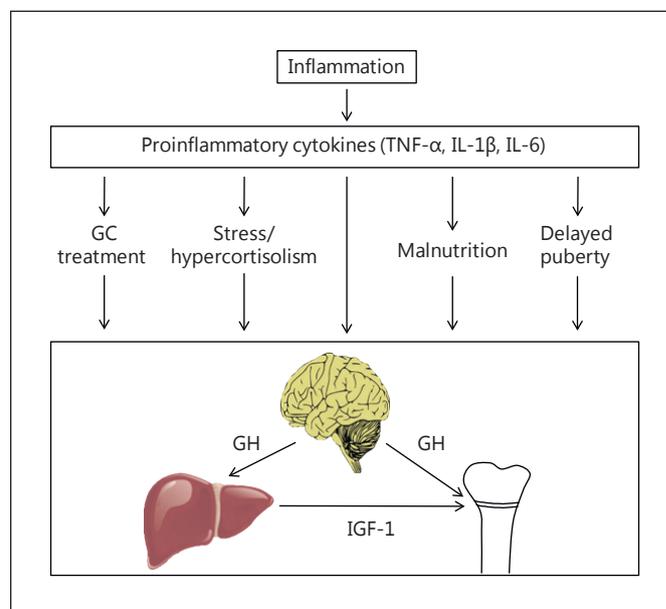


Fig. 4. Overview of mechanisms behind growth failure caused by chronic inflammation. GH, growth hormone; IGF-1, insulin-like growth factor 1; TNF- α , tumor necrosis factor- α ; IL, interleukin.

ferentiation as well as inducing apoptosis locally in the growth plate [59, 60]. Partial catch-up growth is possible but depends on the dosage and duration of the GC treatment [52, 61].

Cytokines affect growth by acting both locally in the growth plate as well as systemically by suppressing IGF-1 and sex steroid levels [53, 62, 63]. The most extensively studied cytokines with regard to growth impairment are tumor necrosis factor- α , interleukin (IL)-1 β , and IL-6. Local effects in the growth plate have been demonstrated of both tumor necrosis factor- α and IL-1 β which act synergistically by decreasing chondrocyte proliferation and hypertrophy as well as increasing apoptosis [53].

Nutrition and Linear Growth

The nutritional status has a major impact on children’s growth, an effect which is most obvious during the first 2 years of life. Protein or energy deficiency leads to growth failure [64]. It has been demonstrated that IGF-1 levels are decreased in children suffering from malnutrition [65].

In the growth plates of food-restricted mice decreased IGF-1 levels and lower GHR expression have been found [66]. Insulin and leptin are two other known mediators of nutritional effects on growth [22, 49]. Fibroblast growth factor 21 (FGF21) is another possible mediator. During

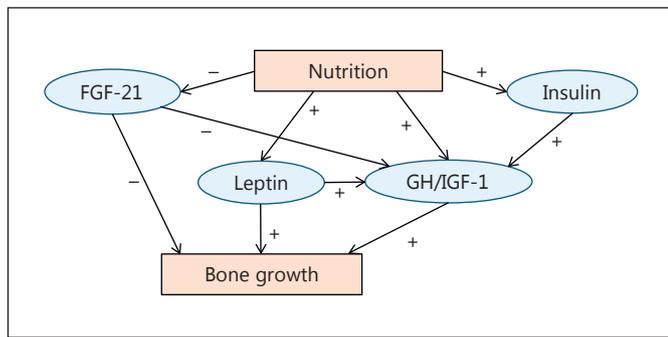


Fig. 5. Schematic overview of mediators of nutritional effects on growth. GH, growth hormone; IGF-1, insulin-like growth factor 1; FGF21, fibroblast growth factor 21.

fasting or food restriction, the expression of FGF21 increases, and studies have shown that it causes GH insensitivity and suppresses chondrogenesis directly at the growth plate level [67].

Normal calcium, phosphate, and vitamin D levels are important for growth plate physiology, and human studies have shown an association between calcium and vitamin D deficiency and stunting [68]. In rickets caused by vitamin D deficiency due to malnutrition, supplementation with vitamin D and calcium saves bone growth [69]. Furthermore, a positive effect of supplementation with vitamin A and zinc has been demonstrated in stunted children [70].

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Conclusion

Hormonal regulation of growth is a complex interplay between many different factors where GH and IGF-1 are key components. GH is produced in the pituitary gland and stimulates hepatic secretion of IGF-1 which stimulates endochondral ossification in long bones leading to growth. Furthermore, GH has local effects in the growth plate. Growth is however also regulated by many other hormones such as insulin, thyroid hormones, estrogen, and leptin. The influence of these different factors varies during fetal life, childhood, and adolescence. During fetal growth, IGF-1, IGF-2, and insulin are the main regulators. During infancy insulin and IGF-1 still play a role although nutrition is becoming a more important factor driving growth. During childhood, hormonal regulators such as GH, IGF-1, and thyroid hormone are important factors driving growth. In conditions of chronic inflammation, growth impairment is frequently seen and has been linked to malnutrition, increased levels of pro-inflammatory cytokines, and GCs. Nutrition evidently has a significant role in regulating growth. Key mediators of this interplay between nutrition and growth are insulin, IGF-1, leptin, and FGF21 (Fig. 5).

Disclosure Statement

The authors have no conflicts of interest to disclose.

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