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Research Progress on the Treatment of Idiopathic Short Stature in Children with Traditional Chinese Medicine and Western Medicine

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Abstract

Objective: To summarize all existing studies on the treatment of Idiopathic Short Stature (ISS) with traditional Chinese medicine and Western medicine in the past decade, providing a reference for clinical treatment of ISS. Methods: Articles related to randomized controlled trials on different drug treatments for ankylosing spondylitis published in the last ten years were collected from databases including CNKI, Wan fang Data, PubMed, Cochrane Library, and Web of Science. EndNote software was used to filter the literature. Results: A total of 15 English articles and 9 Chinese articles were collected. Conclusion:(1) The treatment of ISS has always been a concern for every pediatric clinician, and existing medications can only provide limited treatment options.(2) The earlier the cause of ISS is diagnosed, the more decisive it can be for treatment.(3) It is necessary to predict the expected height before treatment, use appropriate drug dosages, and avoid excessive treatment that could affect children's health.(4) Traditional Chinese medicine offers higher safety and lower costs in the treatment of ISS, making it worthy of clinical application.

Keywords

Short stature; Growth hormone; Diagnosis; Treatment; Genetic testing.

1. Introduction

Idiopathic Short Stature (ISS) is defined as individuals who are two standard deviations (−2SD below the mean height of the normal population, or below the third percentile (−1.88SD), in the same race, gender, and age which is partially a normal physiological variant [1]. It is generally a multifactor disease regulated by genetic, epigenetic, and environmental factors, and is a cause of modern pediatric visits. There are many causes of short stature, and the existing studies have shown that the lack of growth hormone, genetic factors, hypothyism, and sex hormones, endocrine and other reasons can lead to short stature [2]. ISS patients have a normal bone age, corresponding to the age delay of the patient's actual age, usually 2SD [3]. If no cause is found in children born small for gestational age, the descriptive small for gestational age (SGA) is usually used to describe these children. Patients with pathological causes of short stature have a severe delay in bone ageusually more than 2SD) and the bone age delay worsens with the progression of the disease [4].

Epidemiological studies have shown that prevalence of diagnosed short stature ranges from 2.5% to 8.8%. There is a correlation between short stature and poorer performance on language among 3- to 11-year-old children in a sample of 12,536 British children. It is a significant predictor of language development [5]. Short stature, as an isolated physical characteristic, is associated with psychosocial disorders; treatment can increase height and improve psychosocial. The results of studies on psychiatric disorders associated with growth hormone treatment have not been conclusive [6]. Research has shown that the prevalence of autism is highest when least one parent is short [7]. Previous related reviews have shown a

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positive understanding and treatment effect of Traditional Chinese Medicine on short stature [8]. However the related treatment mechanisms of combined Chinese and Western medicine in the treatment of ISS have not been systematically discussed. This article systematically discusses the treatment research progress of ISS in the Chinese and Western medicine. And the advantages and disadvantages of existing research are proposed to provide theoretical basis for the further treatment of ISS by combined Chinese and Western medicine.

2. Growth Hormone Deficiency

Growth hormone (GH) has been considered the main regulator of growth, composed of 191 amino acids, and is capable of promoting growth of the bones, muscle tissues, and the body as a whole, regulating the synthesis and of proteins and fat-mineral. The most common genetic causes of growth hormone deficiency (GHD) are GH1 and GHRHR defects, with mutations inHSR, RNPC3, and IFT172 also being described. There are also effects of NF-κB signaling, STAT3, and I2. Heterozygous IGF1R deletion is a relatively common cause of prenatal and postnatal growth retardation. TRHA result in syndromic forms of short stature with increased T3/T4 ratio. Various paracrine factors FGF, BMP, WNT, PRP/IHH, and CNP/NPR2 signaling disorders or genetic defects affecting the extracellular matrix of chondrocytes usually cause disproport short stature. Heterozygous NPR2 or SHOX defects can be found in about 3% of ISS.

Growth hormone insensitivityGHI) as a broad disease. Mutations in the GH receptor gene are the first mechanism leading to GHI, and another numerically large and highly variable population of with regard to etiology is represented by those with SGA and persistent short stature. In comparing the clinical features and the response to GH treatment in children with S. It was found that children with SGA syndrome were shorter when treated with growth hormone. And were started GH treatment earlier, received higher doses of GH, but were as adults [9]. Therefore, to better understand the causes of short stature, it is not possible to focus only on GH [10]. Path causes of ISS involve systemic diseases and treatment, GHD, and a range of genetic syndromes. Early reasonable diagnosis, treatment helps improve clinical outcomes [11. In sum; GH deficiency, GHI and SGA all can result in short stature in children, and the mutation of genes can result in GH deficiency,HI and SGA, thus genetic testing is of great significance in the diagnosis of ISS. Early diagnosis of the main cause of short stature is the main measure to the disease.

3. Growth Hormone Deficiency

GH is one of several substances produced by a gland called the pituitary gland which is located near the base of the brain. It triggers the release of a hormone called insulin-like growth factor 1 (IGF-1). Ex production of growth hormone in adults leads to a condition called acromegaly. Children with typical GHD have increased subcutaneous fat, immature facial development, a skull, underdeveloped nasal bridge, and delayed dental eruption. Impairment of growth velocity correlates positively with the severity of GHD. The specificity IGF-1 for the diagnosis of GHD is 100%, and the sensitivity is about 70% to 90%. The IGF-1 serum carrier, IGFBP-3, is growth hormone-dependent, and IGFBP-3 may be more meaningful in children under 3 of age.

GH can be synthesized artificially and used in children with GHD, called hormone replacement therapy. For children with growth hormone deficiency, hormone replacement allows them grow normally. Taller people are thought to be more successful, but there are certain risks associated with the inappropriate use of growth hormone. Long-term risks of stroke been observed in children treated with growth hormone for short stature [12]. When compared to the general population, those who received GH in childhood had a increased risk of stroke. Growth hormone treatment should be done with reasonable indications and ensure that its benefits outweigh the risks [13]。

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The use of GH treatment can help short children reach their adult target height [14]. GH treatment brings short children closer to average without pushing them above average. This is a normalizing intervention and not a tool for self-customization or consumer choice [15]. Children with SGA poor growth in the first years of life and may remain short in childhood and as adults, and GH treatment can effectively improve SGA. The growth effect can be estimated the SGA model [16]. The consensus statement from the International Society of Pediatric Endocrinology and the Growth Hormone Research Society proposes that actual and height should be considered together when deciding on GH treatment: children with a height of less than -2.5 SDS at 2 years or less than - SDS at 4 years should meet the criteria for GH treatment [17]. Thus, the addition of IGF-1 to the diagnosis of ISS is significant importance, and earlier application of GH is better, and the earlier use of GH treatment has more benefits than risks. Children with a dose within the recommended range have better effect.

4. Vitamin D

Vitamin D can promote the absorption of calcium ions and plays a vital role in the growth and of bones. Vitamin D deficiency is a prevalent disease in developing countries, with a prevalence rate of 30-90% depending on the critical value used in specific region, irrespective of latitude [18]. Older age, female, higher latitude, winter, darker skin pigmentation, less sunlight exposure, and dietary are the main factors for lower levels of vitamin D [19]. Vitamin D has a correlation with GH and IGF-1, and deficiency in vitamin D is improved after treatment with GH [20]. Vitamin D physiologically stimulates the intestine to absorb calcium and phosphate and the kidney to reabsorb calcium inhibits parathyroid hormone. Both GH and IGF-1 promote renal cell production of vitamin D, and IGF-1 stimulates placental synthesis vitamin D. IGF-1 stimulates the kidney to produce active vitamin D to increase the absorption of calcium and phosphate in the body and inhibits the secret of parathyroid hormone [21]. These actions may be related to the bone status of active acromegaly, which is characterized by a significant elevation serum vitamin D, increased plasma calcium, phosphate, and urinary calcium excretion [22]. Good vitamin D status helps to achieve normal IGF1 levels in GHD patients [23]. Vitamin D is to promote the absorption of calcium ions, which in turn promotes the normal growth of bones. In Chinese medicine, ISS is summarized as TCM diseases such as fetal weakness, fetal fright, consumptive disease, five delays, five softness, andism, and the symptoms are similar to those of vitamin D deficiency.

5. Oxandrolone

Short-term treatment of boys with delayed puberty and adolescents with testosterone is effective in the of secondary sex characteristics and growth acceleration. The addition of oxandrolone to GH can promote height. Treatment with GnRH analogs is a therapy for centralocious puberty and may be considered in children with SGA or SHOX deficiency who are still short at the start of puberty despite a short birth. The main treatment options for short stature are GH, but the use of sex steroids will also affect growth.

To reduce the masculinizing effects of testosterone testosterone-like compound oxandrolone (OX) was synthesized. This compound does not aromatize and does not suppress the production of endogenous testosterone. At present time, OX is available only in the United States. In prepubertal children, OX at a dose of 1.25-50 mg can increase the velocity of height and bone maturity. OX is not very effective in the treatment of ISS. Side effects of OX include deepening of voice, a transient delay in breast development, a decrease in high-density lipoprotein cholesterol, but these side effects are mild if the dose is less than0.06 mg/kg/d. OX ancillary therapy can be considered starting at 8-10 years of age in severely underaged girls a dose of 0.03 to 0.05 mg/kg/d; in addition to its effect on growth, OX may also affect arithmetic

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memory. The mechanism of action of OX on growth is unclear, but OX may increase the activity of the GH–IGF-1 axis and may also an effect on estrogen receptors.

6. Estrogen

Since the impact of estrogen on bone maturation is greater than on growth, clinicians tend delay estrogen replacement therapy in girls, but a later initiation of estrogen replacement may have negative impacts on psychosocial development, life quality and bone health. Therefore estrogen should be initiated no later than 12 years of age. Children with ISS can be intervened by delaying pubertal status, reducing the biological of estrogen, delaying the speed of epiphyseal closure and the advancement of bone age, which can play a role in prolonging the growth period ultimately achieve the effect of improving adult height. Common approaches include sex steroid hormones, gonadotropin-releasing hormone analogs (GnRHa and aromatase inhibitors (AI). The use of sex steroid treatment for individuals with constitutional delay of growth and puberty in ISS can accelerate linear and the onset of pubertal changes, but it does not help with the final adult height.

GnRHa as the first-line treatment for central precious puberty (CPP), the use of GnRHa in children with pubertal ISS is considered to improve adult height. It is generally believed thatnRHa can delay the advancement of bone age by inhibiting the hypothalamic-pituitary-gonadal axis and reducing the level of sex hormones in blood. However, during GnRHa treatment, children may experience a decrease in the speed of height growth. Some children may achieve the predicted adult height during the course treatment [20]. During GnRHa treatment, children may experience a decrease in bone mineral density, and the bone mass of the children will return to normal stopping the medication. The use of GnRHa to postpone puberty also needs to be alert to the adverse effects that may be caused by the cess and regression of sexual development, such as psychosocial adverse effects. For children with early-onset or moderate development pubertal ISS, treatment can achieve more, and the specific effects need to be further studied and verified [24].

7. Combined gonadotropin and growth hormone treatment

In children with GHD, the addition of GnR to GH treatment can improve the ISS. Addition of GnRHa at the start or already ongoing puberty and continued for at least 2 years has been to be effective in increasing height by an average of about 6–9 cm. The possible association between GnRHa treatment and polycystic ovary syndrome (OS) has not been proven by present studies to be specifically linked.

In SGA patients treated with GH, an increase in GnRHa increases height, this requires further studies for confirmation. In conclusion; combined treatment enables: (1) an average height increase of 5 cm, which may have a positive impact onosocial conditions; (2) the negative impact on bone mineral density is temporary and will be neutralized after the end of puberty. The negative effects include (1) delay of puberty which may have a negative impact on psychosocial conditions; (2) medicalization; (3) risk of sterile abs formation, polycystic ovary syndrome (PCOS) and decreased bone mineral density; (4) high cost; (5) GH is not registered for this.

For children with severe CPP, treatment with GnRHa before the age of 6 years can effectively block pubertal development and increase height by about10 cm. In milder CPP (onset of puberty at 6–8 years of age), the effect on height ranges from 3 9 cm. If the growth velocity during GnRHa treatment is very low, the addition of GH or OX may increase height. In children with GH deficiency to CPP or low height SDS at the start of puberty, the addition of GnRHa is effective in increasing height. In children with peripheral precious puberty of rare causes, such as aromatase excess syndrome, testotoxicosis, AI may be effective. For boys with CDGP, course

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of 3–6 months. Testosterone is usually effective for secondary sexual characteristics and growth acceleration, but not for AH; there are no sufficient data to experimental treatment schedules such as AI or OX. In children with ISS, all of the above-investigated treatments are experimental.

8. The role of AI therapy

AI therapy is considered experimental in all growth disorders and its use should ideally be restricted to well-controlled studies If a clinician still considers AI therapy in a child with short stature, anastrozole seems to be more effective, possibly because of incomplete aromataseition. However. Thorough monitoring for possible side effects is mandatory, especially for vertebral deformities. Other potential safety issues include increased low-density lipoprote cholesterol and triglycerides, insulin resistance, and an effect on spermatogenesis, cognitive function, vascular wall function, and prostate growth.

9. Traditional Chinese medicine treatment

Professor Xiao believes that the main pathological locations of idiopathic short stature in are the kidney and spleen, and it is related to the heart. The main pathogenesis is the deficiency of the spleen and kidney and the deficiency of heart, which leads to the deficiency of primordial qi due to the failure of the heart to store the spirit. The Peiyuan Zhushang prescription was used treatment [25]. The concept of treating the disease before it occurs in traditional Chinese medicine is also reflected in the treatment of ISS [26]. Zushang decoction is safe and effective in the treatment of ISS (spleen and kidney deficiency syndrome), and the clinical efficacy is obvious. Professor Li J believes that the pathogenesis of this disease can include spleen and kidney deficiency, lung spleen qi deficiency, and liver depression spleen deficiency, and most children ISS caused by spleen and kidney deficiency are seen clinically. The treatment method is to invigorate the spleen and nourish the kidney, and the "Zushang decoction" is used as the clinical drug [27]. After treatment with the spleen and kidney double tonifying prescription, the concentration of I-1 in the serum of children increased, suggesting that the mechanism of the growth-promoting effect of the spleen and kidney double tonifying prescription may be related the up-regulation of the serum IGF-1 level [28]. Cang Hu Zhushang decoction and spleen and kidney double ton prescription can improve the height and height growth of children with ISS. However, in terms of improving the growth rate in half a year, the spleen and kidney doubleifying prescription can improve the level of IGF-1 in the serum of children with ISS, and the efficacy is comparable to GH. The spleen and kidney doubleifying prescription can reduce the traditional Chinese medicine syndrome score of children with ISS, and compared with GH, the advantages of the spleen and kidney double tonifying prescription are prominent. The spleen and kidney double tonifying prescription is safe for the treatment of ISS, and there is no obvious difference with GH. The cost of treatment with spleen and kidney double tonifying prescription is lower, and it is obviously more economical than GH.

10. Early diagnosis of ISS

Early diagnosis is crucial for individuals with ISS as each patient requires a unique treatment plan, and prognosis risk of relapse also differ. Incorporating genetic screening for ISS into newborn screening programs allows for rapid and early diagnosis. Prenatally, ISS can be suspected on polyhydramnios, abnormal lymphatic system, and cardiac or renal abnormalities. Maternal blood alpha-fetoprotein, human chionic gonadotropin, and unconjugated estriol may also be indicative of ISS. Diagnosis can also be confirmed through fetal and echocardiography techniques, and further confirmed through prenatal or postnatal molecular testing. Postnatally,

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suspicion can be raised based on facial features bleeding or cardiac abnormalities. Scoring systems have also been proposed to aid in the clinical diagnosis of ISS. Genetic testing methodologies can include the use of multig panels, sequence-based single-gene tests, and more comprehensive genomic tests with copy number analysis. Multigene panels are the preferred tests.

The concept of treating the disease in its early stage in traditional Chinese medicine also reflects the importance of early diagnosis and intervention. The selection of children with below the mean value of the same age and gender normal population by -1SD or the 10th percentile as the target population for intervention, and the of comprehensive management measures for treating the disease in its early stage combined with the theory of constitution differentiation can provide a set of simple, low-cost and effective prevention and plans for children with short stature [26].

11. The impact of GH on bone

Children with delayed bone age may show accelerated maturation during GH treatment [29]. The increase in growth has a greater impact in younger SDS. GH will affect body composition but specific tests such as DEXA scans are needed to demonstrate this change and to evaluate the changes in children with GHD undergoing growth hormone therapy to ensure long-term health maintenance. Greater height difference between the child and their parents and greater bone age delay are factors for a better response to GH in ISS patients.

12. Safety of growth hormone treatment

Regarding the safety of GH in ISS patients, as referenced by the Oxford population-based registry, who received GH treatment during childhood had a significantly higher risk of stroke. The additional risk of stroke was mostly due to a highly significant increase in the risk of hemoragic stroke, especially subarachnoid hemorrhage [12]. Thus, GHD is considered an effective predictor of stroke in adults [30]. Short-term complications include insulin resistance, pseudotumor cerebri, and slipped capital femoral epiphysis. There may be an association cancer risk and IGF-1 levels, but the data are controversial. Adults who have received GH treatment have an increased risk of death compared with the general population The long-term safety of GH treatment is still unclear.

For individuals with cardiomyopathy and ISS who require GH treatment, periodic echocardiography should be performed. Severe cardomyopathy patients should not be treated with GH. Because of the increased risk of cancer in multiple sclerosis patients, all clinically diagnosed multiple sclerosis patients who require GH need to be considered for further risk. Doctors should communicate with patients and their families in all aspects. It is recommended that brain MRI screening, molecular testing to identify path variants should be performed before the start of growth hormone treatment. For patients with gene variants associated with a high risk of bone marrow proliferative diseases, the decision growth hormone treatment should be carefully discussed with parents, either postponed until after the age of 5 or started with appropriate monitoring before the age of 5.

The of traditional Chinese medicine treatment for ISS is relatively good, and no obvious adverse events were found. It was concluded through statistical analysis that 6 months of RhGH treatment promote the increase of PLT in children with ISS, some of which can exceed the normal range, which may lead to hypercoagulable state of the blood increase the risk of thrombosis, and the change of platelet count is of great significance for monitoring the safety of recombinant human growth hormone. It speculated that the mechanism of RhGH treatment causing an increase in platelet production in children with ISS might be related to the regulation

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of carbohydrate and lipid metabolism RhGH treatment, but the exact mechanism needs to be further studied.

13. IGF-1

The growth decline in adolescence, and low-dose estradiol may be appropriate [31]. The probability of a GH stimulation test (positive) is extremely low in ISS. Most children diagnosed with GHD are short in stature due non-pituitary causes and are incorrectly thought to be GHD [32]. Recombinant human IGF-1 has been approved for treatment children with “severe primary IGF-1 deficiency” with a height SD score of ≦-3.0 and normal or elevated growth hormone levels. This be due to lower IGFBP-3, which reduces the delivery of IGF-1 to certain target tissues; lack of GH-induced chondrocy proliferation in the growth plate; lack of GH-induced local production of IGF-1 in the growth plate [33]. Common adverse reactions include lymphoid hyperplasia, and accumulation of body fat. Intracranial hypertension and gynecomastia may be more common than growth hormone therapy. Circulating I-1 is associated with the pathogenesis of cancer [34].

Massage therapy of "Regulating Transport Hub" based on the theory of meridians acupoints in combination with recombinant human growth hormone in the treatment of ISS found; the growth rate significantly increased, IGF-1 were all increased and IGFBP-3 levels were all increased [35]. The Shang fu Zhu Sheng Tang can promote the growth of height and weight in with ISS of spleen deficiency and liver hyperactivity, improve clinical symptoms, reduce the traditional Chinese medicine syndrome score, improve the concentration of serum IGF-1, this prescription is safe, without adverse reactions. Through key targets such as IGF1R, IGFBP3, and through signaling pathways such as insulin resistance, plays a role in the treatment of ISS [36].

The GH-IGF-1 axis is one of the numerous regulatory systems that control chondrogenesis in the growth plate, the biological that drives height increase. Normal growth in children depends not only on GH and IGF-1 but also on multiple hormones, paracrine factors, extracellular molecules, and intracellular proteins that regulate the activity of chondrocytes in the growth plate [37]. Mutations in the genes encoding these proteins lead to short or tall stature. The normal variation in height appears to be largely due to the influence of genes other than the GH-IGF-1 on growth plate growth through multiple mechanisms [38]. These findings provide a new conceptual framework for understanding the different heights [39]. Interventional treatment traditional Chinese medicine Jianpi Yishen prescription Shangguan Zhuliang Granule can also increase bone mass and promote the growth and development of bone[40].

14. Treatment goals and costs

A major issue in the determination of treatment for ISS children is the inability to accurately predict adult height based on patient's current bone age. The target height of the patient's family is also a factor that influences GH treatment. The predicted percentile of adult height completed on the skeletal results, gender, and whether the bone is more than 1 year later than the chronological age. The adult height of ISS children may beimated, more so in boys than in girls. There is a correlation between the predicted adult height and the actual height, although there may be considerable individual variability.

incremental cost-effectiveness ratio of GH treatment is $52,634 per 2.54 cm, an increase of 4.8 cm height over 5 years, and an incremental cost of $9,995.90 per child. More than 585,000 children qualify for GH treatment, with potential costs exceeding $11 billion. Treatment requires injections continuously for several years until growth approaches completion and frequent medical checks and laboratory tests monitor treatment. Traditional Chinese medicine treatment starts from the spleen and kidney, considering the physiological characteristics of children as "lack of spleen and kidney" and "ans are not fully developed, fully developed but not

yet strong," and treatment is mainly given to nourish the spleen and kidney, with overall analysis, and treatment has the advantages of low cost, safety, effectiveness, and few side effects.

15. Conclusion

(1) The treatment of ISS has always been a concern for every pediatric clinician, the existing drugs can only provide limited treatment. (2) The earlier the cause of ISS is diagnosed, the more decisive it can be to the treatment. (3 It is necessary to predict the height of treatment before treatment, and use the drug dosage reasonably to avoid excessive treatment affecting the health of children. (4) Traditional Chinese has a higher safety and less cost in the treatment of ISS, which is worth clinical application.

The existing combined treatment methods traditional Chinese and Western medicine for ISS have achieved certain results to some extent, but there are still shortcomings. For example, (1) there is often a lack of-by-step and systematic research on the existing treatment options for ISS. In addition, some patients and their families may have concerns about the traditional Chinese or Western medicine they receive, and fail to make full use of the unique advantages of traditional Chinese and Western medicine. (2) There is less research on the specific mechanism of growth children, which fails to fully and completely explain the specific genes and endocrine, external environment and other many influencing factors of ISS. (3) There is a of sufficient basic and clinical research in the clinical application of traditional Chinese medicine theory combined with modern medicine in a step-by-step and systematic way.

In the, we need to strengthen basic research and explore the mechanism of action of GH, genetic factors and traditional Chinese medicine, so as to provide stronger theoretical support. In addition promoting multidisciplinary cooperation and integrating knowledge from nutrition, psychology and other fields will provide comprehensive intervention programs for patients. According to the standards and guidelines of ACMG the causal relationship of genetic variants can also be proved by other methods. The segregation of genetic variants in families of short children is an important factor. The prediction using N as much as possible and early intervention will achieve better results in the treatment of short stature. At the same time, further genomic analysis and the generalization of these to children diagnosed with GHD. In addition, using artificial intelligence and big data analysis to develop personalized treatment plans will be able to better meet the needs of different patients

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References

[1] Pu Fang. Research on the Correlation between the Influencing Factors and Traditional Chinese Medicine Syndrome Types of Short St in Children [D]. Yunnan University of Traditional Chinese Medicine, 2023.

[2] Liu Feng, Yang Wenx, Liu Qiansheng, et al. Research Progress in Traditional Chinese Medicine Treatment of Short Stature Children [J]. Chinese Journal of Integrated Traditional and Western Medicine Pediatrics, 2020, 12(02): 128-131.

[3] Tekın A, Cesur Aydın K. Comparative determination of skeletal maturity by hand-wrist radiograph, cephalometric radiograph and cone beam computed tomography. Oral Radiol. 2020 Oct;36(4):327-336.

[4] Basu S. Health Care Transition: Need of the Hour. Indian J Pediatr. 2020 Jun;87(6):411-412.

[5] Freer J, Orr J, Morris JK, et al. Short stature and language development in the United Kingdom: a longitudinal analysis of children from the Millennium Cohort Study. BMC Med. 2022 Dec 5;20(1):468.

[6] Gardner M, Boshart ML, Yeguez CE, et al. Coming Up Short: Risks of Bias in Assessing Psychological Outcomes in Growth Hormone Therapy for Short Stature. J Clin Endocrinol Metab. 2016 Jan;101(1):23-30.

[7] Stavber L, Gaia MJ, Hovnik T, Jenko Bizjan B, et al. Heterozygous NPR2 Variants in Idiopathic Short Stature. Genes (Basel). 2022 Jun 15;13(6):1065.

[8] Li Lingyun, Zhao Linghui. Recent Advances in the Treatment of Short Stature in Children with Chinese and Western MedicineJ]. Chinese Medical Journal, 2020, 33(04): 194-197.

[9] Plachy L, Amaratunga SA, Dusatkova P, et al. Isolated growth hormone deficiency in children with vertically transmitted short stature: What do the genes tell us? Front Endocrinol (Lausanne). 2023 Jan 13;13:1102968.

[10] Plachy L, Deodati A, Tornese G. Editorial: Short stature: beyond growth hormone. Front Endocrinol (Lausanne). 2024 Mar 28;15:1403112.

[11] Stoupa A, Franca MM, Abdulhadi-Atwan M, et al. Severe neurodevelopmental phenotype, diagnostic, and treatment challenges in patients with SECISBP2 deficiency. Genet Med. 2024 Dec;26(12):101280.

[12] Plachy L, Deodati A, Tornese G. Editorial: Short stature: beyond growth hormone. Front Endocrinol (Lausanne). 2024 Mar 28;15:1403112.

[13] van Iersel L, Li Z, Srivastava DK, et al. Hypothalamic-Pituitary Disorders in Childhood Cancer Survivors: Prevalence, Risk Factors and Long-Term Health Outcomes. J Clin Endocrinol Metab. 2019 Dec 1;104(12):6101-6115.

[14] Kaplan W, Al Amiri E, Attia N, et al. Assessment and referral of patients with short stature by primary care physicians in the Arabian gulf region: Current perspectives from a regional survey. Front Pediatr. 2022 Nov 25;10:988614.

[15] Witt S, Bloemeke J, Bullinger M, et al. Growth hormone treatment in children with short stature: impact of the diagnosis on parents. J Pediatr Endocrinol Metab. 2024 Mar 1;37(4):326-335.

[16] Upners EN, Raket LL, Petersen JH, et al. Timing of Puberty, Pubertal Growth, and Adult Height in Short Children Born Small for Gestational Age Treated With Growth Hormone. J Clin Endocrinol Metab. 2022 Jul 14;107(8):2286-2295.

[17] Clayton PE, Cianfarani S, Czernichow P, et al. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endocrinol Metab. 2007 Mar;92(3):804-10.

[18] Arabi A, El Rassi R, El-Hajj Fuleihan G. Hypovitaminosis D in developing countries-prevalence, risk factors and outcomes. Nat Rev Endocrinol. 2010 Oct;6(10):550-61.

[19] Harvey NC, Ward KA, Agnusdei D, et al. International Osteoporosis Foundation Vitamin D Working Group. Optimisation of vitamin D status in global populations. Osteoporos Int. 2024 Aug;35(8):1313-1322.

[20] Alkan F, Ersoy B, Kızılay DO, et al. Cardiac functions in children with growth hormone deficiency: Effects of one year of GH replacement therapy. Growth Horm IGF Res. 2021 Oct-Dec;60-61:101432.

[21] Giustina A, Mazziotti G, Canalis E. Growth hormone, insulin-like growth factors, and the skeleton. Endocr Rev. 2008 Aug;29(5):535-59.

[22] Parkinson C, Kassem M, Heickendorff L, et al. Pegvisomant-induced serum insulin-like growth factor-I normalization in patients with acromegaly returns elevated markers of bone turnover to normal. J Clin Endocrinol Metab. 2003 Dec;88(12):5650-5.

[23] Li W, Yu T. Relationship between 25-hydroxyvitamin D and IGF1: a cross-sectional study of the Third National Health and Nutrition Examination Survey participants. J Health Popul Nutr. 2023 Apr 18;42(1):35.

[24] Zhang Xu. Clinical study of anastrozole combined with recombinant human growth hormone in the treatment of pubertal idiopathic stature boys [D]. Anhui Medical University, 2023.

[25] Yang Bingbin, Guo Kai, Wang Hongjuan, et al. Treatment of idiopathic short stature in children based on the of solid foundation and nourishing origin [J]. Journal of Guangxi University of Chinese Medicine, 2023, 26(02 22-25.

[26] Ju Wei, Wang Suting, Gong Zhixia. Application of TCM preventative treatment in the prevention and treatment of dwarf [J]. Journal of Traditional Chinese Medicine Research, 2014, 27(12): 9-10.

[27] Lin Ke Xin. Clinical efficacy observation of soup therapy for children with idiopathic short stature [D]. Changchun University of Chinese Medicine, 2022.

[28] Liang Yueping. Meta-analysis of Traditional Chinese Medicine Treatment of Idiopathic Short Stature and Clinical Research on Spleen and Kid Dual-tonifying Prescription for Children with Deficiency of Spleen and Kidney in Idiopathic Short Stature [D]. Tianjin University Traditional Chinese Medicine, 2022.

[29] Wu H, Li Y, Li H. Brachydactyly Type A3 Is More Commonly Seen in Children With Short Stature But Does Not Affect Their Height Improvement by Growth Hormone Therapy. Front Endocrinol (Lausanne). 2022 Feb 3;13:824315.

[30] Virú-Loza MA, Chávez-Nomberto RE. Letter to the Editor From Virú-Loza and Chávez-Nomberto: "Safety and Efficacy of Pediatric Growth Hormone Therapy: Results From the Full KIGS Cohort". J Clin Endocrinol Metab. 2023 May 17;108(6):e354-e355.

[31] Ferruzzi A, Vrech M, Pietrobelli A, et al. The influence of growth hormone on pediatric body composition: A systematic review. Front Endocrinol (Lausanne). 2023 Feb 9;14:1093691.

[32] Zhou E, Hauser BR, Jee YH. Genetic evaluation in children with short stature. Curr Opin Pediatr. 2021 Aug 1;33(4):458-463.

[33] Muthuvel G, Dauber A, Alexandrou E, et al. Five-Year Therapy with Recombinant Human Insulin-Like Growth Factor-1 in a Patient with PAPP-A2 Deficiency. Horm Res Paediatr. 2023;96(5):449-457.

[34] Bang P, Polak M, Bossowski A, et al. Frequency and Predictive Factors of Hypoglycemia in Patients Treated With rhIGF-1: Data From the Eu-IGFD Registry. J Clin Endocrinol Metab. 2023 Dec 21;109(1):46-56.

[35] Xiang Hong, Sun Xiangjuan, Chang Ke, et al. The effect of massage at transport hub combined with recombinant human growth on the growth and development of children with dwarfism [J]. Shaanxi Journal of Traditional Chinese Medicine, 2020, 41(6): 766-769.

[36] Zhang Qingling. Clinical Observation and Exploration of the Mechanism of Tianma Guben Decoction in the Treatment of Children Constitutional Short Stature of Spleen Deficiency and Liver Hyperactivity Syndrome [D]. Heilongjiang University of Chinese Medicine, 2023.

[37] Fan Xin, Peng Yan, Li Chuan, et al. Classification and Diagnostic and Therapeutic Progress of Metaphyseal Dplasia [J]. Chinese Journal of Practical Pediatrics, 2022, 37(08): 583-58.

[38] Xu Jinliang, Zeng Yan, Shen Wenxia. Research progress on the correlation between growth plate genes and short stature [J. Chinese Journal of Human Genetics and Genetic Engineering, 2022, 30(04): 706-710.

[39] Baron J, Sävendahl L, De Luca F, et al. Short and tall stature: a new paradigm emerges. Nat Rev Endocrinol. 2015 Dec;11(12):735-46.

[40] Zhou Ying. Research on the Mechanism of Osteo-metabolism of Zhenwu Zugan Granule and Recomant Human Growth Hormone in SGA Rats [D]. Nanjing University of Traditional Chinese Medicine, 2015.