Growth hormone therapy in short-stature patients with kyphoscoliosis: a literature review

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- The aim of the study was to conduct a literature review on growth hormone therapy in short-stature patients with kyphoscoliosis.
- The search strategy was performed in which all the relevant papers published in 20 years were included on Pub Med, Central, and Google scholar by using keywords short stature, growth hormones, adverse events of growth hormones in kyphoscoliosis, safety.
- The study investigation supports the idea that giving human growth hormone (HGH) to a diverse population of short-statured children does not enhance the occurrence of scoliosis.
- Patients on HGH therapy for progressing scoliosis had syndromes in which scoliosis was more prevalent in an age-matched group. Short stature attributed to progressive growth failure is prevalent in all mucopolysaccharidosis (MPS) disorders, as per the existing research on growth and growth hormone in MPS.
- MPS should be explored in children who are being tested for short stature since growth failure might be the presenting symptom.

Introduction

In today’s world, medicine is a scientific artwork that assists a physician to choose the right medicine for the right cure of the disease with laboratory investigation for confirmation of disease. Medicine is an art because when justification proves unable to assure then it comes to our beliefs for the availability of better choices (1). People unable to attain adult height suffer from idiopathic short stature (ISS). The patients suffering from mucopolysaccharidosis (MPS) have a distinctive trait of short stature. Short stature is secondary to other abnormalities like structural, metabolic, and endocrine. The skeletal abnormality in MPS as kyphoscoliosis and genu valgum restricts the growth and height of an adult (2).

Growth hormone (GH) – somatotropin is recombinant DNA in origin approved commercially from 1985. It is a substitute for pituitary-derived GH (human) which was withdrawn due to safety issues. At present, GH is approved for conditions like growth hormone deficiency (GHD), ISS, Turner syndrome (TS), Prader–Willi syndrome, chronic renal insufficiency, small for gestational age (SGA), and Noonan’s Syndrome in the US. GH use is still unjustified as far as safety issues. The main concern is regarding the cost–benefit analysis. In clinical trial studies, it has been studied that GH has an anabolic effect and other chronic illnesses.

The potential benefits of GH determine further studies. In the US, approximately 1 in 3500 children has been diagnosed with GH deficiency among which children suffered from organic GHD is 20% which causes central nervous system tumors, radiation, infection, and traumatic brain injury, and the rest of 80% do not have an identifiable cause of GHD and categorized as idiopathic GHD. The duration of therapy is still under investigation. In previous findings, it is prescribed till epiphyseal fusion, while current studies claimed its significance in bone mineralization, lean mass, improvement in resolving cardiac risk factors of decreased visceral adipose tissue, and cardiac profile. In low doses, GH has been approved for the life-long treatment of adults (3). The rationale to conduct a literature review on this topic was to gather the existing data and find the gaps as there are very limited studies have been conducted in this aspect.

Literature review

The search strategy was performed in which all the relevant papers published in 20 years were included on Pub Med, Central, and Google scholar by using keywords short stature, growth hormones, adverse events of growth hormones in kyphoscoliosis, safety. The studies have
shown that 1 in 2500 live female births has TS with either abnormal or missing X-linked chromosome results in short stature and ovarian failure. GH has shown promising results in the growth rate and height of girls with Turner syndrome. Following adverse effects have been reported with the use of GH that includes the effects on glucose metabolism.

Physiologically GH antagonizes the glucose and lipid metabolism by inducing glycogenolysis and lipolysis thus inhibiting glycogenesis and lipogenesis. GH-deficient patients are highly sensitive to insulin, and thus, treatment with recombinant human growth hormone has been reported to cause insulin resistance leading to type 2 diabetes mellitus which is considered as a classical feature observed in the condition of acromegaly. However, the incidence of type 1 diabetes mellitus during recombinant human growth hormone (rhGH) treatment is very much similar to the general population. Similarly, the events of gynecomastia have been reported to the United States Food and Drugs Administration and pharmaceutical companies by the reports of ‘adverse drug experience’.

According to the report among the patients receiving rhGH, 22 cases were reported with prepubertal gynecomastia between ages of 2 and 12. However, estimation of incidence was difficult due to insufficient data on the number of affected children exposed to rhGH in the population that reported the cases. In general, dose adjustment or discontinuation in the context of gynecomastia is not recommended as it is a self-limiting condition and will resolve over time. GH-deficient patients are also highly prone to the development of slipped capital femoral epiphysis (SCFE) that involves either posterior or interior displacement of the proximal femoral epiphysis on the femoral neck. However, treatment with rhGH further increases the chances for the development of SCFE. In the general population, the prevalence of SCFE in GH-deficient patients is reported as 10.8 cases per 100,000 patients per year, while Kabi International Growth Study (KIGS) reports 52 cases from a total of 57,968 patients receiving rhGH treatment presented with SCFE. Cases of SCFE are always resolved via surgical treatment and in situ screw fixation. Mitogenic and anti-apoptotic properties of the GH and insulin-like growth factor-1 (IGF-1) have also been reported by number of studies, and the main issue that concerns the induction of tumor formation during the treatment with GH includes the recurrence of previously treated tumor, development of secondary neoplasm, and appearance of de novo malignancy. However, GHD may also develop as an after effects in the treatment of malignancies.

A study of a Japanese cohort on the treatment of rhGH has raised safety concerns regarding the medication due to the development of 12 cases of hematological malignancies. Despite the high risk of malignancies reported in the Japanese study, results could not be replicated by other cohorts. GH has been reported by number of studies to stimulate the production of neural cell, their proliferation, migration, and survival in animal models. Though there are studies that report GHD in patients with brain lesions, there are no data available in spinal cord injury (SCI) patients. Regarding the efficacy/safety of GH replacement in patients with SCI and suboptimal GH secretion, Guilem Cuatrecasas et al. report GHD as a common feature in traumatic SCI and GH replacement is safe without side effects. Treatment with GH along with physical therapy can improve the quality of life (QoL) of SCI patients and strikingly, the sensory perception below the lesion level.

Growth is influenced by several variables, including genetic, environmental, dietary, and hormonal factors, and any modification in any of these determines growth potential. Short stature is a frequent problem in emerging economies for a variety of reasons. A typical form of short stature does not require hormonal or medical treatment, but chronic disorders can lead to development failure and short stature if they become worse or severe. However, other conditions that need to be addressed for causing short stature include renal, pulmonary and cardiac diseases, malignancy, cystic fibrosis, and celiac disease.

Malnutrition and iatrogenic causes such as intake of steroids, chemotherapy, and radiotherapy and endocrine disorders include hypothyroidism, Cushing’s syndrome, and GHD are other prominent causes for short stature. Turner’s syndrome and skeletal dysplasias are other notable causes, while short stature in kyphoscoliosis condition has also been observed, which is an uncommon deformity causing abnormal posterior convex angulation of a segment of the spin. Therefore, the treatment of such patients with human GH showed progression in the short-statured condition; however, a cohort of 250 patients reported the progression of the condition in six cases out of ten patients on human growth hormone (HGH), among them, five had idiopathic scoliosis, one had acute lymphocytic leukemia, and two with TS were diagnosed with scoliosis prior to treatment, with accelerated growth rate recorded in eight of ten with scoliosis; therefore, children with scoliosis, on treatment with Human Growth Hormone, are more likely to have progression of their scoliosis and an accelerated growth rate compared to those without scoliosis. Whereas, a study by Gregory A Day et al. report no evidence of HGH treatment being responsible for the progression of scoliosis.

Kyphoscoliosis is a musculoskeletal disorder with short stature characteristic of the patients and this secondary abnormality is the combination of structural, metabolic, and endocrine which limit the growth and height of the adult. Other challenges associated with kyphoscoliosis...
comprise pulmonary hypertension, under-ventilation of the lungs, psychological concerns such as anxiety, with trouble accomplishing daily activities. Short stature is prevalent in children with MPS cause of poor growth even if there are no significant abnormalities in spine curvatures or genu valgum; therefore, this does not adequately explain it, but abnormalities of the growth plate include decreased matrix deposition with impaired osteoblast function, hypertrophic chondrocytes, disordered growth plate cellular structure, and glycosaminoglycans accumulation in the growth plate might have some implications (17, 18, 19, 20, 21).

In the feline model of MPS VI, th bone formation has been shown to improve in a dose-dependent manner when treated with enzyme replacement therapy (22); however, there are no data available in humans. According to the literature, previous observation suggests that children with Hurler syndrome (MPS I-H) who were treated with hematopoietic cell transplantation (HCT) had a significant risk of future growth failure, also suggesting that the enzyme was not getting through to the growth plate. Moreover, skeletal and joint abnormalities get to persist and even worsen with time since HCT (23, 24, 25). GH, thyroid hormone, and sex steroids (estrogen and testosterone) are all critical for normal growth and development. Current literature suggests that pituitary dysfunction, hypothyroidism, low IGF-1 and GH, and pubertal disruption may be associated with MPS in some cases and therefore may contribute to the short stature. Clinically, MPS I-H is characterized by short stature, coarse facies, cognitive and gross motor delays, corneal clouding, dysostosis multiplex, cardiac manifestations, and hepatosplenomegaly (26, 27, 28, 29, 30). MPS I-H is typically diagnosed in patients less than 2 years of age. Without treatment, children with MPS I-H typically die by 10 years of age due to cardiac or respiratory complications (28, 30). Currently, most children with MPS I-H are treated with HCT (31, 32, 33, 34, 35). HCT as an intervention, however, compounds the problem of short stature. HCT has been associated with growth suppression, GHD, abnormal gonad), and thyroid function, and function and damage to the epiphyseal growth plate, pituitary gland, and hypothalamus (36, 37, 38, 39, 40, 41, 42, 43, 44), all potential causes of short stature. Early diagnosis and replacement of hormonal deficiencies are critical for optimizing growth and development. While many studies have examined long-term growth for other conditions following HCT (38, 39, 40, 41, 42, 43, 44), there are few growth data specific to patients with MPS I-H children after HCT (23, 34, 35).

According to Polgreen et al., the prevalence of short stature in children with MPS I-H after HCT was found to be 71% at the most recent evaluation. Another study also reported that the prevalence of short stature in children with MPS I-H after HCT was quite high compared to that found in other studies of patients who received HCT for conditions other than MPS I-H (37, 42, 44); 14–31% of patients in these reports had short stature at last follow-up, compared to 71% with short stature in MPS I-H patients. However, the prevalence of short stature increased to 87% (n = 13 of 15) with increase of 10 years of age were associated with the later age at HCT and exposure to TBI whereas with decrease in the mean ± s.d. height, that is −3.2 ± 1.6. Similarly, 46% of children were diagnosed with short stature had a cord blood donor, while 72 and 88% (allied and unallied, respectively) of children received bone marrow. Comparatively, growth in children seems to be improved when treated with cord blood HCT. However, distinctive variation was observed in the length of follow-up, that is, they are shorter in these children compared to those with other donor sources when adjusting for the age as last height evaluation was not demonstrated a statistically significant.

After HCT, Vellodi et al. (35) discovered progressive growth failure in children with MPS I-H. They found out that the average height of children around the age of 8 had plummeted below the normal range. They also examined sitting heights and leg lengths; the majority of the difference was attributable to a decrease in sitting height, according to their findings. Hippocrates aimed to restore the right anatomy utilizing instinctive approaches (45). It was only after the discovery of x-rays by Roentgen, was it finally documented by Duval–Beaupere (46), who gained a better grasp of the natural history of scoliosis during childhood. Psychological well-being (PWB) and Quality of Life (QoL), including ongoing and prospective disability, were plainly evident in the imaginations of pioneers, notably Stagnara (47) who declared that we should treat human beings with deformities to provide them with quality of life by providing them with physical, mental and social capacity (48).

There are pathologic reasons for a subgroup of children with low height. Chronic systemic disorders (renal, pulmonary, cardiac, and inflammatory bowel disease), cancers, endocrine diseases (hypopituitarism, GH deficiency, hypothyroidism, type 1 diabetes mellitus, Cushing syndrome, adrenal insufficiency, rickets), genetic disorders (cystic fibrosis, celiac disease), and chromosomal disorders (chromosome abnormalities) can all cause path (TS) to disorders (renal, pulmonary, cardiac, and inflammatory bowel disorder), cancers, endocrine diseases (hypopituitarism, GH deficiency, hypothyroidism, type 1 diabetes mellitus, Cushing syndrome, adrenal insufficiency, rickets), genetic disorders (cystic fibrosis, celiac disease) and chromosomal disorders (TS).

Short height can be caused by skeletal dysplasia, sexual precocity, malnourishment, and iatrogenic factors such as chemotherapy, radiation, glucocorticoids, and surgery (Table 1). SGA and intrauterine growth retardation are
both associated with growth retardation (49, 50, 51, 52, 53, 54, 55, 56, 57). In addition, toward being an indication of a child’s physical health, small stature can have a detrimental effect on a child's mental health. Children with short stature are more likely, than others, to suffer from psychiatric disorders such as low self-esteem, educational difficulties, and social immaturity (57). Avoidance in society of low stature in youngsters regarding physical and psychological health was to be assessed. Short stature and its underlying reasons are prevalent in different geographic locations, which may be explained by variations in the natural environment and social development (15, 58, 59, 60). It was also concluded by a study that GH is not the only reason for scoliosis (61). However, a study revealed through the radiographic assessment that growth hormone therapy affected the progression of the scoliosis Cobb angle and apical vertebral translation on the coronal plane (62).

According to the majority of research study, normal growth differences are the most prevalent reason for short height in Iran (63, 64). This study was completed on children referred to the Endocrinology Clinic at Zahedan University of Medical Sciences due to the absence of five researches on the etiology of this condition in southeastern Iran. The paucity of unambiguous data on the efficacy of GH treatment in people with idiopathic low stature is especially concerning. Physicians’ recommendations for GH medication vary widely due to differing opinions of its effectiveness, and third-party payer rules for GH coverage are wildly inconsistent (65, 66, 67). Studies with limited numbers of participants, heterogeneity in outcome measures (e.g. short term vs long term and height vs growth velocity), different treatment effects reported, and the absence of organized data synthesis have all made it difficult to interpret the research. Furthermore, randomized, controlled studies of GH have been difficult due to ethical and logistical problems, such as long-term daily placebo injections into youngsters (68, 69, 70).

### Limitations

Leading to the shortage of data, assessing the outcome of growth hormones is challenging. Therefore, the study included the articles from last 2 decades and mentioned as limitations of the study.

### Conclusion

This investigation supports that the idea given regarding human growth hormone to a diverse population of short-statured children does not enhance the occurrence of scoliosis. The results of the only other similar prior study did not show an increased growth rate following HGH therapy in the small number of people with idiopathic scoliosis. Patients on HGH therapy for progressing scoliosis had syndromes in which scoliosis was more prevalent in an age-matched group, according to one study. Short stature attributed to progressive growth failure is prevalent in all MPS disorders, as per the existing research on growth and growth hormone in MPS. The majority of the children with MPS have normal weight and length at birth, but development failure causes short stature by the age of 4–8 years. MPS should be explored in children who are being tested for short stature since growth failure might be the presenting symptom.

### ICMJE Conflict of Interest Statement

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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