Review Paper

Growth and Related Treatment Factors in Mucopolysaccharidoses Type I and II: A Systematic Review

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Citation Tabatabayipoor SE, Rostampour N, Hovsepian S, Raispour H, Hashemipour R, Khachikian A, et al. Growth and Related Treatment Factors in Mucopolysaccharidoses Type I and II: A Systematic Review. Journal of Pediatrics Review. 2023; 11(4):301-314. http://dx.doi.org/10.32598/jpr.11.4.512.4

http://dx.doi.org/10.32598/jpr.11.4.512.4

Article info:
Received: 29 Apr 2023
First Revision: 07 May 2023
Accepted: 09 Sep 2023
Published: 01 Oct 2023

Key Words:
Mucopolysaccharidoses, Growth, Treatment, Height

ABSTRACT

Background: There is an association between treatment options and growth in patients with mucopolysaccharidoses (MPS). The appropriate management of MPS is an essential factor for the growth of the patients.

Objectives: This study aims to review systematically the available data on the growth status and related treatment factors in patients with MPS type I and MPS type II.

Methods: A systematic literature search was performed in PubMed, Scopus, and the Web of Science using related keywords by March 2023. In this systematic review, the primary outcome was determining the growth status (mainly height z-score) of patients with MPSI and MPSII from reviewed studies and its association with different treatment options. The author's name, year of publication, country, type of MPS, growth status, treatment options, and any associations between growth status, disease, and treatment variables in the article were extracted.

Results: From the initially retrieved 743 references, 100 were removed due to being duplicates, 31 articles were evaluated by reading the full text, and finally 20 were included in the systematic review. Based on the analyses, treatment options improved growth in the MPS patients. Certain variables regarding the treatment were key factors, such as the age of treatment initiation, combination therapy, and human growth hormone therapy. Some factors related to the characteristics of the patients, including genotype (type of mutation) and disease severity, are also key factors. Patients with MPSI and MPSII had normal growth and height during the first years of life, but after 2-5 years, their growth rate decreases progressively.

Conclusions: The findings of this review indicated that growth impairment is common in patients with MPSI and MPSII. Treatment improved the growth development in these patients but not as much as expected. Some patients' characteristics, such as disease severity and type of mutations, affect treatment efficacy and height gain. From treatment-related factors, the most important factor is the age of treatment initiation. Regarding other factors such as donor type, human growth hormone administration, and combination therapies, current findings are inconclusive, and more studies are needed.

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Introduction

Mucopolysaccharidoses (MPS) are a group of inborn errors of metabolism. These lysosomal storage disorders result from the dysfunction of specific enzymes responsible for the degradation of glycosaminoglycans (GAGs) or mucopolysaccharides [1, 2]. MPS is a group of heterogeneous disorders with different types and manifestations due to impaired dysfunction of 11 enzymes related to GAGs catabolism [1, 2].

Impaired catabolism of GAGs and their accumulation in different cells and tissues leads to severe multisystem dysfunction such as cardiac defects, facial feature abnormalities, hepatosplenomegaly, corneal clouding, hearing impairment, respiratory disease, skeletal deformities, hydrocephalus, central nervous system dysfunction, spinal cord compression, growth and developmental delay, and short stature [3, 4].

Different types of MPS exhibit various clinical manifestations, age of onset, and rate of progression [3]. The most common and key manifestation of all types of MPS is growth impairment and short stature. The underlying mechanisms responsible for this manifestation are still unclear. It is suggested that deposition of GAGs in the growth plate, bone, and cartilage, osteoblast dysfunction, reduced matrix deposition, and hypertrophic chondrocytes contribute to the growth abnormalities [4, 5].

The main and well-tolerated treatments that have been used currently are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). These treatments could improve or slow the progression of the disease without significant adverse effects [6].

Growth measurements are essential for monitoring disease progression and treatment efficacy [5]. Some therapeutic options, including substrate reduction therapy, gene therapy, and pharmacological chaperone therapy, have also been introduced, but their efficacy has not been confirmed yet [4, 7].

There is also evidence for the use of recombinant human growth hormone (hGH) as a supportive treatment for growth impairment in this group of patients. Still, the findings of the studies regarding its efficacy are inconclusive [8].

Considering the association between treatment options and growth in patients with MPS and the importance of appropriate management of these disorders, this study aims to review the available data on growth status and related treatment factors in patients with MPS type I and MPS type II systematically.

Methods

Data sources

This study was designed as a systematic review and conducted based on the 2020 PRISMA (the preferred reporting items for systematic reviews and meta-analyses) guidelines. The main outcome of this study was to determine the growth status (mainly height z-score) of patients with MPSI and MPSII from reviewed studies and its association with different treatment options.

A systematic literature search was performed through PubMed, Scopus, and the Web of Science based on the keywords and the following search strategy: ((("Mucopolysaccharidosis I" [Title/Abstract]) OR ("mucopolysaccharidosis II" [Title/Abstract]) OR (hunter syndrome [Title/Abstract]) OR (sulfoiduronate sulfatase deficiency [Title/Abstract]) OR (iduronate 2-sulfatase deficiency [Title/Abstract]) OR (lipochondrodystrophy [Title/Abstract]) OR (hurler syndrome [Title/Abstract]) OR (mucopolysaccharidosis type Ih [Title/Abstract]) OR (pfaundler-hurler syndrome [Title/Abstract]) OR (scheie syndrome [Title/Abstract]) OR (alpha l iduronidase deficiency [Title/Abstract]) OR (Hurler-Scheie syndrome [Title/Abstract]) AND ((growth [Title/Abstract])OR (weight [Title/Abstract]) OR (height [Title/Abstract]) OR (growth [MeSH Terms])) AND (stem cell transplantation, hematopoietic, [Title/Abstract]) OR (enzyme therapies [Title/Abstract]) OR (genetic therapies [Title/Abstract])))). Two independent reviewers (Seyed Ebrahim Tabatabayipoor, Homyra Raispour) did the literature search through the studies published until March 2023.

Study selection

Inclusion and exclusion criteria

All studies in English or Persian that have reported the growth status of patients with MPSI and MPSII were explored. Studies before 1990 were excluded. Letters, editorial articles, non-relevant ones, duplicates, reviews, conference abstracts, and studies in other languages were excluded. Using EndNote citation manager software, version X9 all duplicates were removed. The remaining articles were assessed using the title and the

abstract. Non-related studies and reviews were excluded. The full text of the remaining articles was read, and non-related ones were excluded. Study selection was done by two independent reviewers (Seyed Ebrahim Tabatabayipoor, Silva Hovsepian). References of the final articles were also reviewed to find the references that cannot be found through the search.

Quality assessment

The STROBE (strengthening the reporting of observational studies in epidemiology) statement, a checklist of items that should be included in reports of observational studies, was used for quality assessment. Two reviewers independently did quality assessment (Seyed Ebrahim Tabatabayipoor, and Silva Hovsepian), and expert opinion was considered (Noushin Rostampour and Silva Hovsepian)) in the case of controversies.

Data extraction

The author's name, year of publication, country, type of MPS, growth status, treatment options, and any associations regarding growth status and diseases and treatment variables in the article were extracted by two independent reviewers (Seyed Ebrahim Tabatabayipoor, Silva Hovsepian).

Results

From the initially retrieved 743 references, 100 were removed due to being duplicates, 31 articles were evaluated by reading the full text, and 20 were included in the systematic review [9-28] (Figure 1). The list of these studies and the extracted data regarding the growth of patients with MPSI and MPSII are summarized in Table 1. Growth status was evaluated in 11 studies on patients with MPSI and 12 on patients with MPSII.

MPSI and growth

The samples in studies that evaluated growth in MPSI patients ranged from 5 to 670 participants [9-12, 15, 17, 21, 24-28]. Two studies with a larger sample size (670 and 295) included patients from the USA, the UK, Canada, Argentina, and France [24, 27]. The first study that evaluated growth in MPSI patients included 5 patients [9]. Treatment options in the studied population were ERT (3 studies) [9, 21, 27] and HSCT (6 studies) [10-12, 15, 17, 26]. Some studies compared ERT and HSCT treatments with those without treatment [27, 26]. Three studies evaluated the outcomes of the supplementary use of hGH treatment on the growth of patients with MPSI [11, 15, 17].

Height, growth, and growth velocity

The most significant impairment in growth was seen for height. The height SDS (standard deviation score) was <-2 in most studies. Almost all studies indicated delayed growth with lower SDS for patients with MPSI. Based on the evaluated research findings, patients with MPSI had normal growth during the first years of life (0-24 months), and the delay was initiated later in their lives. The reported time of growth delay was different in evaluated studies and between males and females. The age when the delay was initiated was lower in those not receiving treatment, or the age of treatment was later. Growth velocity also had a similar pattern.

Sex differences

The mean z-score of height in boys was lower than in girls [12]. One study reported that though growth impairment continued till 18 years of age in both sexes, the decreasing rate appeared earlier in boys than girls [24].

One study indicated that the height z-score decline over time was less significant in females than males [27].

Treatments

In most studies, the treatment choice was HSCT. In two studies [10, 26], the findings indicated significant improvement in the growth of the patients under treatment with HSCT. One study compared ERT with no treatment and reported significant growth improvement compared to non-treated patients [27].

Two studies showed that having a history of total body irradiation (TBI) during treatment could significantly slow growth development [10, 11]. In one study, there was no significant association between the use of TBI, number of transplants, genotype, donor source, post-transplant enzyme levels, and height SDS [12].

In one study, the height z-score for normal, impaired, and low enzyme levels were -2.6 (1.8), -4.2 (2.1), and -4.4 (3.2), respectively [10].

One study demonstrated no difference in various treatment options, including HSCT, ERT+HSCT, and TBI+HSCT [17].

Table 1. Characteristics of finally reviewed articles

	MPSI	Number of patients/mean age	Treatment/ Age at Treatment	Findings	Association
1	Sifuentes et al. 2006, USA [9]	5/8-17 years old	ERT (laronidase)	In three patients height and weight were within the normal range for their chronological age. In two patients height and weight for their chronological age were <5th percentile.	
2	Polgreen et al. 2008, USA [10]	48 (20 females)/ 8.2 (range: 1.6–18.39)	HSCT/1.7 years (range: 0.5–3.7)	- Both male and female patients had growth retardation compared with CDC standards - HSCT improves the expected adult height - Mean height SDS for normal, impaired, and low enzyme levels were -2.6(1.8), -4.2(2.1) and -4.4(3.2), respectively.	- Patients who had no TBI exposure, and were younger at the time of HSCT, had a better height prediction. - Short stature was higher in patients who had BM donor recipients than those with a cord blood donor (88% vs 46%).
3	Polgreen et al. 2008, USA [10]	8 /5.8 years (range: 6-13)	HSCT and growth hormone /9.6 (2.3) years [time since HSCT was 7.5 (1.5) years]	- Baseline growth velocity was 3.5 (1.5) cm/yr [-2.6 (1.9) SDS] and increased to 5.2 (3.0) cm/yr [-0.1 (3.6) SDS) after 1 year of treatment. - One patient discontinued GH because of slipped capital femoral epiphysis (SCFE). - One year of GH treatment could modestly improve growth velocity.	- Having a history of TBI was associated lower increase in growth velocity in all patients (treated or untreated patients with MPSI) - Adding GH therapy increased the growth velocity regardless of TBI using history.
4	Gardner et al. 2011, UK [12]	22/ 12.2 (range 6.3–21.6)	HSCT/1.3 years (range 0.6–3.2)	- Final height SDS was <-2SD in all patients. - Final height SDS were -4.3 and -3.4 in boys and girls respectively. - BMI SDS decreased from +2.2 to -0.04 from two years after transplant to ten years after transplant.	The number of transplants, use of TBI, genotype, degree of chimerism, donor source, and post-transplant enzyme levels did not influence height SDS.
5	Polgreen et al. 2012, USA [15]	10 (5 treated; 1 GHD)	HSCT	- Growth velocity was higher in those treated with hGH than those not treated [4.5(1.0) vs. 2.4(2.7)]. - On average, growth velocity was 2.1 cm/yr higher in treated than non-treated patients. - There were no significant adverse effects in the children treated with hGH.	
6	Polgreen et al. 2014, USA [17]	13/ 9.8 (3.1)	HSCT ERT+HSCT TBI+HSCT HSCT+hGH(6) 2 of them had GHD	- Growth velocity and height SDS was not different between patients with different treatment options as well as hGH therapy - Annual growth velocity was significantly higher in MPSI patients with GHD treated with hGH than those without GHD [6.5 (1.9) vs 3.5 (2.1)]	- There was no association between having a history of TBI, peritransplant ERT, or age at HSCT and annual change in height (cm) or height SDS between patients with and without hGH treatment
7	Zuber et al. 2015, Poland [21]	16/2,2 (0.5 to 21 years)	ERT	- Until the 24th month of life, the growth pattern was similar and the average z-score values for body height were greater than the reference charts (range: 0.02 to 1.71 for all groups). - The body height below the 3rd percentile was reached after the 24th month of life - The mean z-score values ranged from -0.6 to -7.8 - The tendency of growth until the 2nd year of life, this tendency was not statistically significant (P=0.34). Afterward, the negative direction became statistically significant (P=0.01).	

	MPSI	Number of patients/mean age	Treatment/ Age at Treatment	Findings	Association
8	Viskochil et al. 2019. USA, Canada, Argentina, and France [24]	670 (463 severe and 207 attenuated form)		In severe form; - Median body length was slightly higher than the reference median in the 1st year. - Growth patterns were similar in both sexes and tend to follow the reference curves between 12 and 24 months. Increased length relative to the reference is observed for both untreated males and untreated females between 6 and 12 months of age. - By 4 years of age, the estimated median height drops below the 3rd percentile and remains below the reference curves. In attenuated form; - The estimated median height for untreated individuals falls below the CDC 3rd percentile by 9 years old, although divergence in height from the standard median growth curve is apparent beginning at 2 years of age. - Growth in both untreated males and females continues through age 18 but appears to slow in males at an earlier age than females. - Median head circumference in both sexes rises above the CDC median from 5 months through 3 years of age.	
9	Lin et al. 2019, Taiwan [25]	49/age range (0.7 to 19.5 years)		- The mean z scores for the 1st recorded values of height, weight, and body mass index in the patients 'medical records were -4.25, -1.04, and 0.41, respectively.	- Both z scores for height and weight were negatively correlated with increasing age ($p < 0.01$). -The height and weight of the MPS patients younger than 2–5 years of age were higher than those of healthy individuals, however, their growth significantly decelerated after that time.
10	Cattoni et al. 2021, Italy [26]	15 (4 male)/15.6±5.4	HSCT No treatment	- Median height SDS in our population of transplanted patients showed a progressive and significant increase (-0.39 SDS to +1.35 SDS from t0 to t60, P<0.001) - The greatest increase being recorded after 24 months [-0.84 (1.79) SDS at t24 vs -2.49 (2.24) SDS at t0, P=0.049]. - Based on WHO growth charts, height SDS showed a progressive decrease from t0 to t9yrs in 11 patients and 3 showed either a stable or an increased height SDS at t9yrs. - Mean height SDS was lower at t9 years than t0 [- 2.35 (1.43) vs - 1.28 (1.55)], though the difference was not statistically significant (P=0.069). - Six out of the 7 patients who attained final height presented with short stature (height <-2 SDS). The only patient with a normal final height was a male, 170.1 cm tall (- 0.85 SDS, WHO charts), remarkably below his MPH (Δ MPH-H SDS=2.14 SDS). - The adult patients mean final height SDS was - 3.81 (1.60), that was significantly lower than their MPH [Δ MPH-H SDS=3.61 (1.33) SDS] and their recorded height SDS at t9yrs (P=0.048) and at t0 (P=0.01).	HSCT positively affects growth and provides transplanted patients with a remarkable height gain compared to untreated gender- and age-matched individuals

	MPSI	Number of patients/mean age	Treatment/ Age at Treatment	Findings	Association
11	Polgreen et al. 2022, USA, UK, Argentina, Canada, France [27]	295 (142male, 154female)/ 7.5 (4.4)	No treatment and ERT with laronidase	- In patients treated with ERT, the rate of score decline is significantly slower than those not treated for both sexes. - The height z-score decline over time was less pronounced in females than in males. -In the early diagnosis and treatment group (3-4 years old) the estimated ages at which short stature (i.e. z-score ≤ 2.0) occurred in the ERT-treated group was >15 years for males and > 8 years for females. In no treatment group, this age was <6 years of age for both. - For females, median height during the natural history period was similar to the CDC 3rd percentile for height from age 8 through 12 years of age. During the ERT-treated period, median height remained above the CDC 3rd percentile until 12 years of age. - Median heights at 13 years of age during the natural history and ERT periods were between 135 and 140 cm. - In males, median height for the natural history period fell below the CDC 3rd percentile at approximately 9 years of age. During the ERT-treated period, the age at which median growth fell below the CDC 3rd percentile was between 14 and 15 years. - Median heights at 18 years of age during the natural history and ERT periods were between 145 and 155 cm.	- Later age at 1st treatment was associated with worse growth in both sexes.
12	Różdżyńska-Świątkowska et al. 2022, Poland [28]	18/3 months to 18 years		- The average z-scores for height were greater than the reference charts until the 24th month of life. - Height below the 3rd percentile was noted from the 24th month of life - The tendency of growth before the 3rd year of life was negative but not statistically significant (P=0.13),and for after the 3rd year of life was negative and statistically significant (P=0.01)	
	MPSII				
1	Schulze-Frenking et al. 2011, Mainz, Germany, and Manchester, UK [13]	18/6-19 years old	ERT/ two groups; aged<10 years and aged >=10 years old at ERT treatment initiation	- Height was 108–154 cm (median, 126.5 cm) - Ten of the patients (55.5%) had short stature - In the group 1; The mean increase in height over the 3-year period of ERT was 14.6 (5.5) cm. The growth curves during ERT show that the height of eight of these patients was still within the normal range based on CDC growth charts - In group 2; all nine patients were considered to be of short stature (height range, 121–154 cm; median 130 cm). During 3 years of ERT, the mean increase in height was 8.1 (1.6) cm. The increase in height was 1.5 cm (Z score=-0.8) in the year before ERT compared with 3.9 cm (Z score=-0.17), 3.6 cm (Z score=0.23), and 1.3 cm (Z score=-0.06) for the 1st, 2nd and 3rd years of ERT respectively.	
2	Marucha et al. 2011, Poland [14]	29/11.5 years (ranging from 2 to 29 years)	ERT	The mean z score of height for all patients was -4.58 (-3.24 for those with mild MPSII and -5.06 for severe form)	A medium correlation was observed between the z-score of patients' height and passive shoulder flexion and abduction (R=0.697, P<0.001 and R=0.63, P<0.001, respectively).

	MPSI	Number of patients/mean age	Treatment/ Age at Treatment	Findings	Association
3	Polgreen et al. 2012, USA [15]	6 (3 treated; 2 GHD)		- No difference in age between treated and untreated patients [11.6 (3.0) vs 10.9 (1.3) years (P=0.7)]. - Growth velocity in treated and untreated patients were 7.3 (1.6) and 5.7 (0.3) cm/yr, respectively (P=0.2). - Growth velocity in patients treated with hGH was on average 2.1 cm/yr and 1.6 cm/yr higher than those not treated; - There were no significant adverse effects in the patients treated with hGH.	
4	Jones et al. 2013, UK, Italy, Brazil, USA [16]	133/ 8-15 years old [14.7 (2.8)]	ERT with idursulfase/ Two groups; 8-11 years and 12-15 years old	- Height remained within the normal range expected based on age and gender until 8–9 years of age. - In the total population, the slope of the regression was significantly improved after treatment compared with that before treatment (difference in z-score, 0.038; P=0.004). - Patients aged 8–15 years were shorter on average than their peers. -The height deficit was most pronounced in patients aged 12–15 years of age at the start of treatment, as indicated by a lower z-score relative to patients aged 8–11 years at the start of treatment (difference in z-score at the start of ERT, -1.63; p b 0.001)	- There was a significant association between growth and mutation (P=0.002) and age of treatment (P =0.0001). - There were no differences between groups when stratified according to puberty at the start of ERT, cognitive impairment, or functional classification by clinical impression - There was a significant influence of mutation type (height deficit in terms of z-scores more pronounced in patients with deletions/ larger rearrangements/ nonsense mutations than in patients with other mutations, age at the start of ERT
5	Cho et al. 2014, Korea [18]	32/3-23 years old	ERT/ Three groups; <6 years old 6-10 years old 10-20 years old	In group 1(<6 years old); the heights of the patients at the initiation of ERT ranged from 78 to 119.4 cm (median, 106.3 cm). None of the boys were of short stature (<-2 SDS) at the start of the ERT, and the mean height SDS of the patients in group 1 was 0.48 (1.71). The mean increase in height over the 2-yr period of ERT was 11.5 (5.8) cm. The growth curves during the ERT show that the height of 12 of these patients was still within the normal range based on normative data from Korean references. In group 2 (6-10 years old); the patients' heights at the initiation of ERT ranged from 98 to 122.5 cm (median, 116.2 cm). Six patients were considered to be of short stature at the start of ERT, and the mean height SDS of the patients in group 2 was -2.6 (1.79). During 3 yr of ERT, the mean increase in height was 9.4 ± 6.1 cm. In group 3 (10-20 years old); the heights of the patients at the initiation of ERT ranged from 116.7 to 142.4 cm (median, 127.7 cm). Five patients were considered to be of short stature at the start of ERT, and the mean height SDS of the patients in group 3 was -5.12 (3.79). During 3 yr. of ERT, the mean increase in the height of the patients was 9.5 (7.6) cm.	- The height deficit was more pronounced in patients without cognitive impairment (difference in zscore at the start of ERT, 1.549; P=0.337) - There was no significant difference regarding z-scores between the two groups according to the type of mutation - Patients with Hunter syndrome aged 6-20 yr were shorter on average when compared to their peers. The height deficit was more pronounced in patients aged 10-20 yr of age at the start of treatment (difference in z-score at the start of ERT, 2.89; P=0.095) - Age at the start of ERT (6-10 vs 10-20 yr) had a significant impact on growth.

	MPSI	Number of patients/mean age	Treatment/ Age at Treatment	Findings	Association
6	Patel et al. 2014, Japan [19]	44/	ERT (26) HSCT (12) Both (6)/ ERT[4.49(2.35)] HSCT[4.68(1.63)]	- ERT and HSCT-treated patient heights were not significantly different from untreated patient heights for children younger than 8 years of age - Heights of treated or untreated patients were similar to normal controls for patients younger than 6 years of age. - Both treatments showed a similar effect in improving growth curves for MPS II - BMI of untreated patients was significantly higher than that of controls. - BMI was significantly lower in ERT-treated patients in the 10-year age group and HSCT-treated patients in the 16-year age group compared to age-matched untreated patients but were not significantly different in other age-groups - Patients younger than 8 years old appeared to be heavier than age-matched controls, with or without ERT- or HSCT treatment. - Weight gain in ERT- or HSCT-treated patients younger than 10 years of age was not significantly different from that in untreated patients. After the age of 10, weight gain slows in untreated patients and weight is significantly lower in 12-year-old patients compared to the age-matched treated patients	HSCT can be a recommended option at an early stage in MPS II considering its effectiveness towards brain or heart involvement.
7	Polgreen tal.2014. USA(17)	13/12.0 (2.7)	ERT ERT+hGH(4) 2 of them had GHD	There was no difference in growth velocity and height SDS for participants with Hunter syndrome treated versus those not treated with hGH.	
8	Zuber et al. 2014, Poland [20]	63/	ERT before 6 years of age (n=13) No ERT(n=50)	For patients in group 1, the Mean±SD height increase was 14.6(5.5) cm during 3 years of ERT. Patients in group 2 (no ERT) had a Mean±SD height increase of 8.1 (1.7) cm after 3 years of ERT Dursulfase did not appear to alter the growth patterns.	
9	Różdżyńska-Świątkowska et al. 2015, Poland [21]	60/7.9 (0.5-21 years)	ERT	- Until the 24th month of life, the growth pattern was similar and the average z-score values for body height were greater than the reference charts (range: 0.02 to 1.71 for all groups). - For patients with severe MPS II between the 6th and 7th year of life, and for patients with attenuated MPS II between the 8th and 9th year. - The mean z-score values ranged from -2.1 to -8.6 for the severe form of MPS II, and from -2.3 to -9.3 for the attenuated form of MPS II. - In boys with MPS II severe form, the tendency was statistically significant (P=0.04). There was an upward tendency until the 3rd year of life. Afterward, a statistically significant negative tendency was observed (P<0.01). In boys with MPS II attenuated form, the tendency until the 3rd year of life could not be analyzed because of the lack of data. After the 3rd year, the straight-the line regression model showed a statistically significant negative tendency of growth (P<0.01).	

	MPSI	Number of patients/mean age	Treatment/ Age at Treatment	Findings	Association
10	Parini et al. 2016, UK, USA, Italy, Brazil [22]	676/ 8.3 (4.5; 14.1)	No treatment	- Short stature diagnosed after approximately 8 years of age. - Large head circumference was reported at all ages. - Increased body weight and BMI reported during early childhood. - Height z score (median) ; 2–4 years; 0.5 , >4–8 years; −0.9 , >8-12 years; −3.1 , >12-16 years; −4.2 , >16-20 years; −4.5 - Weight z score (median); 2–4 years; 1.7, >4–8 years; 0.7 , >8-12 years; −1.0, >12-16 years; −2.8,>16-20 years; −3.7, - BMI z score; 2–4 years; 2.0 , >4–8 years; 1.6 , >8-12 years; 1.0 , >12-16 years; 0.1, >16-20 years; 0.4,	- Cognitive involvement was associated with increased BMI, increased weight, and head circumference. - There was no association between the presence of cognitive involvement and impaired linear growth
11	Bodamer et al. 2017, UK, USA, Italy, Brazil, Germany, Switzerland [23]	609/<at birth		Z score of weight at birth; -0.03 (1.28)	The mean birth weight of these patients was similar to that of the general population.
12	Lin et al. 2019, Taiwan [25]	49/age range: 0.7-19.5 years)		- The mean z scores for the 1st recorded of height, weight, and body mass index were -2.31, 0.19, and 0.84. - The mean height z scores were -2.67 and -2.01 and the mean weight z scores were -0.11 and 0.42 for the mild/intermediate and severe forms of MPS II, respectively.	The height and weight of the MPS patients younger than 2–5 years of age were higher than those of healthy individuals, however, their growth significantly decelerated in subsequent years. - Both z scores for height and weight were negatively correlated with increasing age (P<0.01). - The BMI z scores of the patients with MPS II were negatively correlated with increasing age (P<0.01).
13	Różdżyńska-Świątkowska et al. 2022, Poland [28]	47/3 months to 18 years		- The mean z-scores that until the 24th month of life, the growth pattern for all patients was similar, and the average z-scores for body height were greater than the reference charts. - Height below the 3rd percentile for patients with severe MPS II was noted between the 6th and 7th year of life and for patients with attenuated MPS II was noted between the 8th and 9th year. - The tendency of growth before the 3rd year of life was positive but not statistically significant (P=0.14),and for after the 3rd year of life was negative and statistically significant (P=0.01)	

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Abbreviations: HSCT: Haematopoietic stem cell transplantation; ERT: Enzyme replacement therapy; hGH: Human growth hormone.

Age at treatment initiation

In two studies for ERT [27] and HSCT [10], findings indicated that treatment initiation at younger age was associated with better growth in both sexes.

Type of donor

Short stature was higher in patients with bone marrow (BM) donor recipients than those with a cord blood donor (88% vs 46%) [10]. In another study, there was no such association [12].

Growth hormone treatment

From 3 studies that evaluated the efficacy of hGH therapy for growth impairment, 2 studies reported improved growth velocity and increased height z-score in patients treated with hGH [11, 15]. They reported 1.7-2.1 cm/y

higher growth velocity in the group that received hGH. In another study, the results failed to show a significant difference in growth velocity and height SDS of patients with and without hGH treatment. They indicated that in a patient with growth hormone deficiency (GHD) who received hGH, the growth velocity was significantly higher than those who received hGH but had no GHD [17]. All of the studies did not report serious adverse effects due to hGH therapy in MPSI patients [11, 15, 17].

MPSII and growth

The studied population in studies that evaluated growth in MPSII patients ranged from 6 to 676 participants [13-23, 25, 28]. The two studies with a larger sample size (679 and 609) included patients from the UK, the USA, Italy, Brazil, Germany, and Switzerland [22, 23]. Treatment options in the studied population were ERT (8 studies) [13, 14, 16-18, 19-21] and HSCT (1 study) [19]. Two studies evaluated the outcomes of the additional use of hGH treatment on the growth of patients with MPSII [14, 15].

Height, growth, and growth velocity

The most significant impairment in growth was seen for height. The height SDS was <-2 in most studies. Almost all studies indicated delayed growth with lower SDS for patients with MPSII. Based on the evaluated research findings, patients with MPSII had normal growth during the first years of life (2-5 years, median 3 years of life), and the delay was initiated later in their lives. The reported time of delay in growth was different in evaluated studies based on the severity of MPSII and in males and females. The age when the delay was initiated was lower in those not receiving treatment, or the age of therapy was later. The growth delay initiation was also lower in the severe form than in a mild form of MPSII. Growth velocity also followed a similar pattern.

In the reviewed studies, 3 studies compared MPSII growth based on the treatment initiation age [13, 16, 18]. Their classification was different (<10 and >10 years old, 8-11 and 12-15 years old, and <6, 6-10, 10-20 years old). Comparing the findings of the studies, it is suggested that the best growth improvement was seen with the age of treatment initiation of <6 years old.

Treatments

In most studies, the treatment was ERT, and most reported growth improvement in patients under treatment with ERT. However, it seems that the age of treatment initiation is the most important factor [16, 18].

In 2 studies [10, 25], the findings indicated significant improvement in the growth of the patients under treatment with HSCT. One study's comparison of ERT with no treatment group indicated significant growth improvement compared to non-treated patients [26].

In a study that compared the effectiveness of different treatment options on patients' growth, the findings indicated that HSCT could be a recommended option at an early stage in MPSII patients, considering its effectiveness on the brain or heart involvement [19].

Growth hormone treatment

From 3 studies that evaluated the efficacy of hGH therapy for growth impairment, 2 studies reported improved growth velocity and increased height z-score in patients treated with hGH [15, 17]. One study did not show a significant difference in growth velocity and height SDS of patients with and without hGH treatment [17]. One study indicated that those treated with hGH had greater growth velocity [15].

Cognitive involvement

In 3 studies, the association between cognitive involvement and the patient's growth has been evaluated [16, 18, 22], but the findings were not similar. In one study, patients without cognitive involvement had more pronounced height deficits than those with cognitive involvement [18]. In two studies, there was no significant difference in linear growth of the patients with and without cognitive involvement [16, 22]. One study indicated that patients with cognitive involvement had increased weight, body mass index, and head circumference [22].

Type of mutation

In 2 studies, the association between height z-score and mutations has been investigated. One study did not find any association between the type of mutation and height z-score [18]. One study demonstrated that in patients with deletions or larger nonsense mutations, the growth impairment, especially height, was more prominent than in those with other types of mutations [16].

Discussion

This study systematically reviewed studies that evaluated growth patterns, especially height SDS, in patients with MPSI and MPSII. Our findings indicated that treatment would improve growth in the MPS patients. Some variables regarding the treatment are important, such as the age of treatment initiation, combination therapy, and hGH therapy. Some factors related to the characteristics of the patients, including genotype (type of mutation) and disease severity, are also key factors in this field. Patients with MPSI and MPSII had normal growth and height during the first years of life, but after 2-5 years, their growth rate decreases progressively.

In healthy children, growth tracking is used to evaluate their health status. Still, in children with a rare disease such as MPS, height monitoring is considered a critical variable for assessing disease severity and progression, as well as the efficacy of treatment.

Based on reviewed papers, we concluded that the growth impairment was initiated later in patients with MPSII than in MPSI.

During the first years of life, the growth parameters for both types of MPS are similar to those of the healthy population. Further, in MPSII, the patients have better growth patterns than the healthy population. However, the disease's severity or the treatment initiation age could have an important role in this field.

In this study, we evaluated the growth pattern of MPSI and MPSII because the accumulated GAGs in both types are dermatan sulfate (DS) and heparan sulfate (HS). It is suggested that the differences in height and growth patterns of the patients with MPSI and MPSII could be explained by the difference in the levels of DS accumulation. Evidence indicated that in MPSI patients, the accumulation of DS is higher, and in MPSII, the accumulation of HS is higher. In MPSI patients, DS accumulation is higher at birth than in MPSII. It is suggested that this accumulation affects the growth of patients with MPSI. In patients with MPSII, the accumulation of DS is more gradual, which could result in the later onset of growth impairment [29, 30].

The age of treatment initiation is one of the most important and well-documented factors. Most of the studies [10, 13, 16, 18, 27] show a significant association between the age of treatment initiation and the height of SDS, and it is suggested that it is one of the main factors in this field. In studies among MPSII patients, different age groups have been evaluated. Treatment initiation before 6 years of life seems more appropriate for improving height SDS [6].

Few studies reported the differences between male and female patients in MPSI, and the reports indicated that the height of SDS in boys was lower than in girls [12]. Some of them indicated that the rate of height SDS decline over time was less significant in female patients, and the time of height decline onset is earlier in males than females [27, 24]. The exact mechanism for the reported sex differences is not clear yet. Recently, Polgreen et al. attributed this difference to the later initiation of ERT in females than males [27]. They reported that though the age at diagnosis was similar in both sexes, the ERT was initiated later in females than males, especially in some geographic regions.

In MPSI patients, the association between donor type and height SDS has been investigated in 2 studies [10, 12]. The results were not similar. One study did not find an association [12], and another one reported that short stature was higher in patients who had bone marrow (BM) donor recipients than those with a cord blood donor (88% vs 46%) [10].

Previous research indicated that using cord blood (CB) is considered an appropriate donor source due to its better chimerism, leading to better therapeutic effects [31]. In addition, recent evidence indicates that the CB cell has a capacity for differentiation, regeneration, and cellular repair. Many studies have supported the hypothesis that due to the characteristics of CB cells, including being a rich source of progenitor and non-hematopoietic cells and capacity for transdifferentiation, they could induce an earlier clinical response [32, 33].

In reviewed studies among patients with MPSII, there was controversy regarding the type of mutation and height z-score. Cho et al. in Korea did not report such an association [18]. Whereas, Jones et al., in a study from different countries with larger sample sizes, classified the severity of MPSII based on the type of mutation and found a significant association between the type of mutations representative for disease severity (large deletion, recombination, deletion or nonsense mutation) and height z-score. They demonstrated that height deficit in patients with mutations related to severe forms of the disease was more significant than those with less severe mutations, including insertion, splicing, missense mutation, or insertion/deletion [16]. Thus, it is suggested that the growth impairment would be more

pronounced in patients with severe mutations and consequently severe phenotype.

In reviewed studies, we did not find a study that evaluated the association between cognitive involvement and growth in patients with MPSI. In MPSII patients, the findings were controversial. Two studies did not report any significant association [16, 22], and one reported better growth in those with cognitive involvement [18].

Parini et al., in a multi-national study among a large sample size of patients from different countries, found no association between cognitive involvement and linear growth. Based on their suggestion in MPSII patients, DS is related to growth, and HS is mainly related to intellectual development [22]. Some studies demonstrated no association between CNS involvement in MPS and growth development [14, 16]. Given that the HS accumulation is higher than DS in MPSII patients, it could explain the findings. Another explanation is that MPSII patients with cognitive involvement exhibit a severe form of the disease and mostly die at a younger age and may miss the adult height. However, the ethnic and genetic background of the patients also could have a role in this issue [5].

In some studies, among patients with MPSI and MPSII, the efficacy of hHG therapy on the growth tendency and growth velocity has been evaluated. Polgreen et al. conducted some studies [11, 15, 17], but the findings were not similar. However, more studies in this field are needed, with larger sample sizes and wider genetic backgrounds. One of the critical findings that could be used in clinical practice was that the efficacy of hGH was more significant in patients with growth hormone deficiency than those without it. So, the effectiveness of hGH in this group of patients is supported. Another important finding was that the rate of adverse effects related to hGH was not high, and the reported adverse effects were not serious.

In the reviewed studies, we did not find studies regarding the effectiveness of gene therapy on the height of MPSI and MPSII patients, and available studies were mainly conducted in animal studies [34-36].

The main limitation of this review was the heterogeneity of the studies that evaluated growth, especially height, among MPSI and MPSII patients. In some fields, such as the association of type of donor, the effectiveness of hGH therapy, and cognitive involvement, few studies are available, and the findings are controversial.

Conclusion

The findings of this review indicated that growth impairment is common in patients with MPSI and MPSII. Treatment improved the growth development in this group of patients, but it would not normalize. Some patients' characteristics, such as disease severity and type of mutations, impact the treatment efficacy and height gain. From treatment-related factors, the most important factor is the age of treatment initiation. Regarding reminder factors such as type of donor, hGH administration, and combination therapies, current findings are inconclusive, and more studies are needed.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This study was funded by the Vice Chancellor of Research, Isfahan University of Medical Sciences (No.: 340243).

Authors contributions

All authors equally contribute to preparing all parts of the research.

Conflicts of interest

The authors declared no competing interests. The authors confirmed no concerns of financial involvement with organizations, entities, or individuals with an interest in the subject matter or materials discussed in the manuscript and no conflict of interest.

Acknowledgements

The authors acknowledge resources and support from the Vice Chancellor of Research, Isfahan University of Medical Sciences.

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