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# Evaluation of the Clinical Response to Treatment of Short Stature Using Growth Hormone Injection Versus Arginine Pills

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***ABSTRACT***

**Background**: Growth which is the process of physical maturation resulting in an increase in size of the body and various organ can considered as the final common pathway of many factors, including endocrine, environmental, nutritional, and genetic influences. A normal linear growth pattern is good evidence of overall health and can be considered as a bioassay for the well-being of the whole child.

Short stature is defined as subnormal height relative to other children of the same gender and age, taking family heights into consideration. it can be caused by numerous conditions could be a variation of normal like constitutional and familial short stature or due to endocrine disorders, skeletal dysplasias, lysosomal storage diseases or due to chronic diseases like chronic renal failure

Growth hormone deficiency account for many cases of short stature, growth hormone (GH) is a 191–amino acid protein secreted by the pituitary in a pulsatile fashion, stimulated by hypothalamic GH-releasing hormone, and inhibited by somatotropin release–inhibiting factor or somatostatin. it stimulates growth, cell reproduction, and cell regeneration.

Recombinant human growth hormone injections which contain recombinant human growth hormone are used for treatment of short stature also newly developed pills which contain arginine that stimulates production of the growth hormone in the body are used for treatment of short stature.

**Aim:** To evaluate the efficacy of using arginine pills in the treatment of short stature.

**Patient and method:** A cross-sectional comparative study done on patient with short stature attending the endocrine clinic at Tikrit Teaching Hospital during the period from the first of November 2022 to the last of October 2023.

For each child height in centimeters, and growth rate for height were measured. Height were measured using stadiometer in which standing height was taken with the recommended standard measures like putting off a hat, bare foot, stand straight and looking forward. The previous measures for height for each child were taken from the follow up files of each child that is available at the endocrine clinic.

**Results:** The total number of cases were 63 cases. Male were 25 cases (39.7%) and females were 38 cases (60.3%) . Most of the cases were between 6-12 years 37 cases (58.7%), most of the cases were due to idiopathic short stature, 52 cases (82.54%).

In regard to treatment most of the cases treated with rhGH injections, 49 cases (77.78%), most of them treated for a period equal or less than one year, 52 cases (82.54%).

There is a non-significant relation between the mean increment in height per one month at different ages, genders, causes of short stature, and duration of therapy in regard to type of therapy with rhGH injection versus arginine pills.

Most of the cases have a normal growth rate for height while the relation between the growth rate for height and the age, gender of the child, causes of short stature, duration of therapy, and the type of therapy with rhGH injection versus arginine pills is not significant.

**Conclusion:** The study concludes that there was a non-significant relation between the mean increment in height per one month at different ages, genders, causes of short stature, and duration of therapy in regard to type of therapy with rhGH injection versus arginine pills.

## INTRODUCTION

Growth is the process of physical maturation resulting in an increase in size of the body and various organs. It occurs by multiplication of cells and an increase in intracellular substance. It is a quantitative change of the body which can be measured in Inches/Centimeters/pounds/kilograms. Growth is progressive and measurable phenomenon. [1]

Normal growth is the final common pathway of many factors, including endocrine, environmental, nutritional, and genetic influences. **A** normal linear growth pattern is a good evidence of overall health and can be considered a bioassay for the well-being of the whole child. [2]

Short stature is defined as subnormal height relative to other children of the same gender and age, taking family heights into consideration. it can be caused by numerous conditions could be a variations of normal like constitutional and familial short stature or due to endocrine disorders , skeletal dysplasias, lysosomal storage diseases or due to chronic diseases like chronic renal failure . [2]

The centers for disease control and prevention (CDC) growth charts use the 3rd percentile of the growth curve as the demarcation of the lower limit. [2]

Growth hormone deficiency account for many cases of short stature growth hormone (GH) is a 191–amino acid protein secreted by the pituitary in a pulsatile fashion, stimulated by hypothalamic GH-releasing hormone (GHRH), and inhibited by somatotropin release–inhibiting factor (SRIF) or somatostatin. it stimulates growth, cell reproduction, and cell regeneration [2]

Recombinant human growth hormone (rhGH) injection is licensed for short stature that is associated with growth hormone deficiency (GHD), Turner syndrome (TS),Noonan syndrome (NS) , Prader–Willi syndrome (PWS), chronic renal insufficiency (CRI), short stature homeobox-containing gene deficiency (SHOX-D) and being born small for gestational age (SGA). [3]

Recombinant human growth hormone (rhGH) is given by daily subcutaneous injections and continues until the patient reaches the 50$^{th}$ percentile for midparental height or achieves a final adult height. [3]

Growth Hormone Releaser (GHR) which contains arginine was developed to promote growth of children. GHR stimulates production of the growth hormone in the body. Recommended for short children especially before and during their puberty period. [4]

Arginine can modulate growth hormone release by suppressing its endogenous inhibitory regulator, somatostatin. Arginine also induces the release of the GHRH .so arginine containing pills given orally to enhance growth of children. [4]

## AIM OF THE STUDY

To evaluate the efficacy of using arginine pills in the treatment of short stature.

## PATIENT AND METHOD

Before A cross sectional comparative study done on patient with short stature attending the endocrine clinic at Tikrit teaching hospital during the period from the first of November 2022 to the last of October 2023. Before attending the study written acceptance were taken from the directorate of Tikrit teaching hospital and oral acceptance from the parents of the child before starting the work of the study.

### INCLUSION CRITERIA

Children with short stature who were on treatment regularly and complete the recommendation of the study like

completing the questionnaire and had a previous follow up file at the endocrine clinic.

**EXCLUSION CRITERIA**

1. Children with secondary cause for short stature like hypothyroidism or chronic disease.
2. Children newly diagnosed as short stature or have an irregular treatment or have no previous growth measure.

Each child included in the study were assessed by prepared questionnaire that include age , gender , cause of short stature and type and duration of therapy.(appendix1)

For each child height in centimeters, and growth rate for height were measured. Height were measured using stadiometer in which standing height was taken with the recommended standard measures like putting off a hat , bare foot, stand strait and looking forward.The previous measures for height for each child were taken from the follow up files of each child that is available at the endocrine clinic.The increment in height during the period of therapy was measured by subtracting the previous measure from the new measure. The average increment of height per month for each child was measured by dividing the increment in height during the period of therapy by the period of therapy in months. The height for each child were put on the standard growth charts (CDC growth charts). The growth rate was measured using at least three measures for height with at least one month apart. Each reading were put on the standard growth chart and the growth rate for height for each child was assessed and interpreted as normal or abnormal.[6]

## RESULTS

A The total number of cases were 63 cases . Male were 25 cases (39.7%) and females were 38 cases (60.3%). Figure (1): shows the distribution of study cases according to the age. Most of the cases were between 6-12 years, 37 cases ( 58.7%). Figure (2): shows the distribution of study cases according to the gender. Most of the casas were females , 38 cases (60.3 %) . Figure (3): shows the distribution of study cases according to the cause of short stature were most of the cases were due to idiopathic short stature, 52 cases (82.54%). Figure (4): shows the distribution of study cases according to the type of treatment were most of the cases treated with rhGH injection, 49 cases (77.78%). Figure (5): shows the distribution of study cases according to the duration of therapy. Most of the cases treated for a period equal or less than one year, 52 cases (82.54%).

Table (1) shows the distribution of study cases according to the duration of therapy in regards to gender were most of the female cases treated for a period equal or less than one year, 34 cases (89.47%). The relation between them is not significant. Table (2) shows that there is no significant relation between the mean increment in height per one month at different ages and the duration of therapy.

Table (2): Distribution of study cases according to the mean increment in height per one month at different ages in regards to duration of therapy. Table (3) shows the distribution of study cases according to the mean increment in height per one month at different genders in regards to duration of therapy, and that there is no significant relation between them. Table (5) shows that there is no significant relation between the mean increment in height per one month at different ages and the type of therapy. Table (6) shows that there is no significant relation between the mean increment in height per one month at different genders and the type of therapy. Table (7) shows the distribution of study cases according to the mean increment in height per one month at

different types of therapy in regards to cause of short stature. There is non-significant relation between them. Table (8) shows the distribution of study cases according to the mean increment in height per one month at different types of therapy in regards to duration of therapy and that there is non-significant relation between them. Table (9) shows that there is non-significant relation between the growth rate for height and the age. Table (10) shows the distribution of study cases according to the growth rate for height in regards to gender and that there is non significant relation between them. Table (11) shows the distribution of study cases according to the growth rate for height in regards to cause of short stature and the relation between them is not significant. Table (12) shows the distribution of study cases according to the growth rate for height in regards to type of therapy and the relation between them is not significant. Table (13) shows the distribution of study cases according to the growth rate for height in regards to duration of therapy and the relation between them is not significant.

## DISCUSSION

Most of the cases treated with rhGH injection and a small portion treated with arginine pills this may be due to that the use of rhGH injection was approved by the U.S. Food and Drug Administration (FDA) since 2003 for children with idiopathic short stature with a height of more than 2.25 SDS below the mean height and who are unlikely to attain normal adult height . A consensus statement published by the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Pediatric Endocrinology recommended that children with idiopathic short stature at a height of less than –2 SDS and were also more than 2 SDS below midparental height could be treated with rhGH injection. while arginine pills is a new drug and not well known. [5, 6]

The relation between the type of therapy and gender of the child and the relation between the type of therapy and the cause of short stature is not significant, this may be due to that rhGH injection is widely used in both genders, most of the male and female cases take rhGH injection for treatment of short stature while arginine pill is a new drug and not widely used till now.

Most of the cases treated for a period of time that is equal or less than one year. This may be due to that maximal response to rhGH occurs in the 1st year of treatment, growth velocity during this 1st year is typically above the 95th percentile for age, then with each successive year of treatment, the growth rate tends to decrease.[3]

The relation between the duration of therapy and gender of the child is not significant. This may be due to that there is decrease in response to therapy after one year of treatment in both genders making them stop taking any medication or decrease their compliance to medication after the first year of treatment.

There is a non-significant relation between the mean increment in height per one month at different ages, genders, causes of short stature, and duration of therapy in regards to type of therapy with rhGH injection versus arginine pills. This may be due to that the study needs more time and more number of cases to get a significant relation. RhGH injection is approved by FDA for treatment of short stature in 2003 and there are many studies about its efficacy and safety in children like Ho-Seong Kim et al study in Korea, 2014 their results were that the height velocity significantly increased by 6.36±3.36 cm/year (p-value <0.001) after the use of rhGH injection. Arginine

pill is a new drug there is only one study, Ömer Akcagil et al study in Turkey, 2021, which done to investigate the effect of arginine supplementation on growth velocity in prepubertal boys with idiopathic short stature. In this retrospectively designed study, prepubertal boys over 5 years of age who were diagnosed with idiopathic short stature were randomized into two groups according to their use of multivitamin with arginine (n=24) or multivitamin without arginine (n=34). Both groups were compared statistically according to growth velocity, IGF-1 and IGF-BP3 SDS and bone age maturation rates before and after 1 year of treatment. Basal IGF-1 SDS and basal IGF-BP3 SDS values of the two groups were similar, but after the mean 1-year treatment, IGF-1 and IGFBP3 SDS values of the study group increased significantly compared to the control group. The annual growth velocity of the study group also showed a statistically significant increase compared to the control group. There was no statistical difference between the two groups in terms of bone maturation, so arginine supplementation can be an inexpensive, safe and effective treatment alternative in idiopathic short stature.[7,8]

Most of the cases have a normal growth rate for height while the relation between the growth rate for height and the age, gender of the child, causes of short stature, duration of therapy, and the type of therapy with rhGH injection versus arginine pills is not significant. This may be due to that the study needs more time and more number of cases to get a significant relation between them.

## CONCLUSION

The study concludes that:There is a non-significant relation between the growth rate for height and the age distribution, gender of the child, cause of short stature, duration of therapy, and the type of therapy with rhGH injection versus arginine pills.

## ACKNOWLEDGEMENTS

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Supplemantation in Children with Idiopathic Short Stature. Progress In Nutrition. 2020;Vol. 22 No. (4).

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## TABLES

| Duration of therapy | Male | Female | Total |
|---|---|---|---|
| ≤ year | 18(72%) | 34(89.47%) | 52(82.54%) |
| > year | 7(28%) | 4(10.53%) | 11(17.46%) |
| Total | 25(100%) | 38(100%) | 63(100%) |

*Table 1. Distribution of study cases according to the duration of therapy in regards to gender.*

| Duration of therapy | Mean increment in height per one month in cm/month for children | | | Total mean cm/month |
|---|---|---|---|---|
| | 2_5 year | 6_12 year | >12 year | |
| ≤ year | 0.99 | 0.81 | 0.69 | 0.78 |
| > year | – | 0.37 | 0.62 | 0.51 |
| Total mean cm/month | 0.99 | 0.75 | 0.67 | 0.73 |

*Table 2. Distribution of study cases according to the mean increment in height per one month at different ages in regards to duration of therapy*

| Cause of short stature | Mean increment in height per one month in cm/month for | | Total mean cm/month |
|---|---|---|---|
| | Male | Female | |
| Idiopathic short stature | 0.66 | 0.75 | 0.72 |
| GH deficiency | 0.69 | 0.42 | 0.60 |
| Turner syndrome | – | 1.75 | 1.75 |
| Noonan syndrome | 1.75 | – | 1.75 |
| Total mean cm/month | 0.71 | 0.75 | 0.73 |

*Table 3. Distribution of study cases according to the mean increment in height per one month at different genders in regards to duration of therapy.*

| Cause of short stature | Mean increment in height per one month in cm/month for | | Total mean cm/month |
|---|---|---|---|
| | Male | Female | |
| Idiopathic short stature | 0.66 | 0.75 | 0.72 |
| GH deficiency | 0.69 | 0.42 | 0.60 |
| Turner syndrome | – | 1.75 | 1.75 |
| Noonan syndrome | 1.75 | – | 1.75 |
| Total mean cm/month | 0.71 | 0.75 | 0.73 |

*Table 4. Distribution of study cases according to the mean increment in height per one month at different genders in regards to cause of short stature*

| Type of therapy | Mean increment in height per one month in cm/month for children | | | Total mean cm/month |
|---|---|---|---|---|
| | 2_5 year | 6_12 year | >12 year | |
| HrGH injection | 0.99 | 0.85 | 0.71 | 0.80 |

| | | | | |
|---|---|---|---|---|
| Arginine pills | – | 0.49 | 0.49 | 0.49 |
| Total mean cm/month | 0.99 | 0.75 | 0.67 | 0.73 |

*Table 5. Distribution of study cases according to the mean increment in height per one month at different ages in regards to type of therapy.*

| Type of therapy | Mean increment in height per one month in cm/month for | | Total mean cm/month |
|---|---|---|---|
| | Male | Female | |
| Hr GH injection | 0.77 | 0.83 | 0.80 |
| Arginine pills | 0.42 | 0.51 | 0.49 |
| Total mean cm/month | 0.71 | 0.75 | 0.73 |

*Table 6. Distribution of study cases according to the mean increment in height per one month at different genders in regards to type of therapy*

| Type of therapy | Mean increment in height per one month in cm/month for | | Total mean cm/month |
|---|---|---|---|
| | Male | Female | |
| Hr GH injection | 0.77 | 0.83 | 0.80 |
| Arginine pills | 0.42 | 0.51 | 0.49 |
| Total mean cm/month | 0.71 | 0.75 | 0.73 |

*Table 7. Distribution of study cases according to the mean increment in height per one month at different types of therapy in regards to cause of short stature.*

| Cause of short stature | Mean increment in height per one month in cm/month for | | Total mean cm/month |
|---|---|---|---|
| | HrGH injection user | Arginine pills user | |
| Idiopathic short stature | 0.76 | 0.53 | 0.72 |
| GH deficiency | 0.78 | 0.38 | 0.60 |
| Turner syndrome | 1.75 | – | 1.75 |
| Noonan syndrome | 1.75 | – | 1.75 |
| Total mean cm/month | 0.80 | 0.49 | 0.73 |

*Table 8. Distribution of study cases according to the mean increment in height per one month at different types of therapy in regards to duration of therapy*

| Duration of therapy | Mean increment in height per one month in cm/month for | | Total mean cm/month |
|---|---|---|---|
| | HrGH injection user | Arginine pills user | |
| ≤ year | 0.89 | 0.49 | 0.78 |
| > year | 0.51 | – | 0.51 |
| Total mean cm/month | 0.80 | 0.49 | 0.73 |

*Table 9. Distribution of study cases according to the growth rate for height in regards to age.*

| Age (year) | Growth rate for height | | Total |
|---|---|---|---|
| | Normal | Abnormal | |
| 2_5 | 3(5.88%) | 0 | 3(4.76%) |
| 6_12 | 30(58.82%) | 7(38.33%) | 37(58.73%) |
| >12 | 18(35.29%) | 5(41.67%) | 23(36.51%) |
| Total | 51(100%) | 12(100%) | 63(100%) |

*Table 10. Distribution of study cases according to the growth rate for height in regards to gender.*

| Gender | Growth rate for height | | total |
|---|---|---|---|
| | Normal | Abnormal | |

| | | | |
|---|---|---|---|
| Male | 21(41.18%) | 4(33.33%) | 25(39.68%) |
| Female | 30(58.82%) | 8(66.67%) | 38(60.32%) |
| Total | 51(100%) | 12(100%) | 63(100%) |

*Table 11. Distribution of study cases according to the growth rate for height in regards to cause of short stature.*

| Cause of short stature | Growth rate for height | | total |
|---|---|---|---|
| | Normal | Abnormal | |
| Idiopathic short stature | 42(82.35%) | 10(83.33%) | 52(82.54%) |
| GH deficiency | 7(13.73%) | 2(16.67%) | 9(14.29%) |
| Turner syndrome | 1(1.96%) | 0(0%) | 1(1.59%) |
| Noonan syndrome | 1(1.96%) | 0(0%) | 1(1.59%) |
| Total | 51(100%) | 12(100%) | 63(100%) |

*Table 12. Distribution of study cases according to the growth rate for height in regards to type of therapy*

| Duration of therapy | Growth rate for height | | Total |
|---|---|---|---|
| | Normal | Abnormal | |
| ≤ year | 44(86.27%) | 8(66.67%) | 52(82.54%) |
| > year | 7(13.73%) | 4(33.33%) | 11(17.46%) |
| Total | 51(100%) | 12(100%) | 63(100%) |

*Table 13. Distribution of study cases according to the growth rate for height in regards to duration of therapy*

# FIGURES

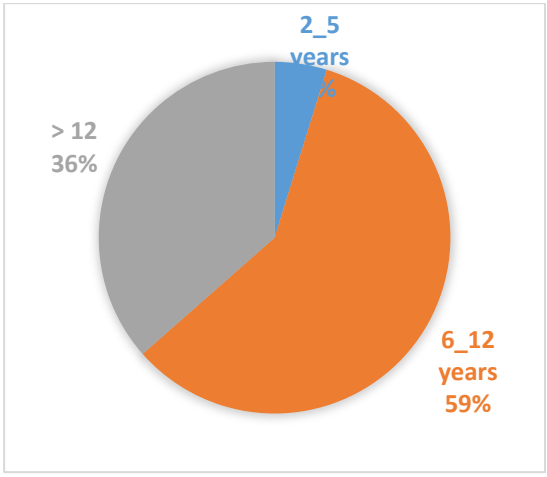


*Figure 1. Distribution of study cases according to the age*

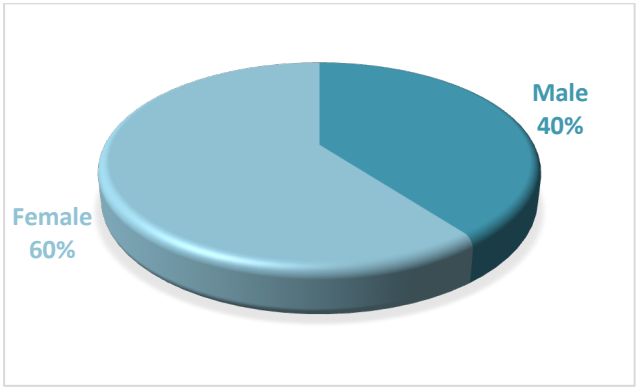


*Figure 2. Distribution of study cases according to gender.*

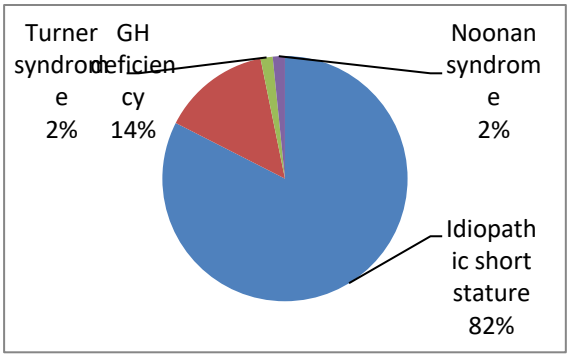


*Figure 3. Distribution of study cases according to the cause of short stature*

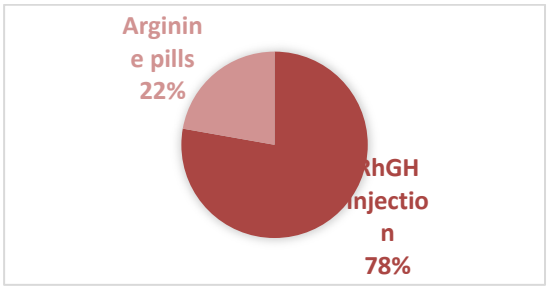


*Figure 4. Distribution of study cases according to the type of treatment*

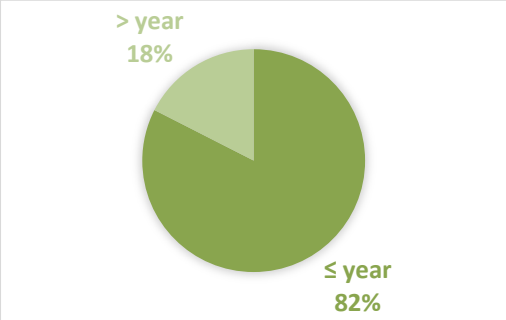


*Figure 5. Distribution of study cases according to the duration of therapy.*