GEORGIAN MEDICAL NEWS

ISSN 1512-0112

N0 10 (331) Октябрь 2022

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

GEORGIAN MEDICAL NEWS
No 10 (331) 2022

Содержание:

GEORGIAN MEDICAL NEWS
No 10 (331) 2022

COMPARISON OF BONE MATURATION RESPONSE TO TREATMENT WITH SHORT AND LONG-TERM GROWTH HORMONE THERAPY IN SHORT-STATURE PEDIATRIC PATIENTS

Bashar Sh. Mustafa[1], Ali A. Shareef[1], Mohammed D. Mahmood[2]*.

[1]*College of Medicine, Ninevah University, Mosul, Iraq.*

[2]*College of Pharmacy, University of Mosul, Mosul, Iraq.*

Abstract.

Growth hormone deficiency is one of the major causes of short stature in children. It has been noted that hormonal treatment can be vindicated in short-stature children unless there are contraindications. This study aimed to investigate the impact of rhGH therapy duration on the increase of subjects' height at the end of therapy. Materials and methods: A retrospective longitudinal study of children diagnosed with short stature was followed. Participants aged between 5 and 15 years old who had their GH stimulation test done were included in the study. Collected data were patients' age, gender, rhGH therapy duration and height (cm) at presentation and the end of therapy. GH stimulation test readings and bone age were also gathered. Results: 129 children aged between 5-15 years of both gender were included in the study. They were grouped into three groups according to the duration of the received GH therapy: an 8-month group (n=25), a 14-month group (n=59) and 22-month group (n=45). No significant difference between males and females in regards to bone age, but the readings significantly increased with the increase in therapy duration ($p < 0.05$). Growth hormone assay results were conversely reduced with the increase in GH therapy duration, with no significant difference between the two genders. Interestingly, an increase in the participant's height in the three treatment groups both males and females were reported. Overall, the increase in height was 7.08 cm, 12.58 cm and 20.84 cm in 8, 14 and 22-month groups (± 1.6, 3.3 and 4.3), respectively, a significant statistical difference between the three groups (p-value < 0.05). This study provides evidence of the effect of long-term 22-month rhGH therapy on bone age and body height both in male and female children. Further prospective studies are required to assess the effect of the GH stimulation test on GH therapy.

Key words. Growth hormone, short stature, GH stimulation test, bone age, height.

Introduction.

Since growth is a vital parameter of individuals' growth, one of the common cases frequently presented to physicians is short stature. Besides sufficient nutrition, important hormones involved in growth are growth hormone (GH), sex steroids, insulin-like growth factor-1 and others [1]. Short stature is diagnosed, after considering the individual's age, gender, and genetic background, when the individual height is less than two standard deviations below the median appropriate height for a population. Using a growth chart, short stature can be considered when the patient is presented with a height below the 3rd percentile on the chart [2,3]. Somatotropin or human growth hormone (hGH) secreted from the anterior pituitary gland is in charge of the growth of almost all body tissues and bones.

Maximum linear growth is achieved in infancy age then drops gradually to 25 cm in the first year of age. In the following two years, the body grows by 10 cm per annum and then 6-7 cm per annum. During puberty, growth increases in a sigmoidal manner of 10 cm per annum where GH level is the utmost level [1].

Short stature is multifactorial and can be caused due to many reasons. However, familial short stature and constitutional growth delay are the main causes of short stature yonder the first two years of life [4]. Deficiency of GH is a rare condition with an approximated incidence of 1:4,000 to 1:10,000 live births [5].

Clinical examination of children presented to the endocrine clinics includes child history and physical examination. Bone age is another parameter that is considered during examining short-stature children. Bone age represents skeletal maturity and can be applied to many medical and nonmedical situations [6]. Hand and wrist radiography is best used for bone age estimation. Short stature that is established secondary to other systemic anomalies can only be reversed following treatment of the underlying causes. However, short stature due to GH deficiency can benefit from GH therapy. Since its discovery, recombinant human growth hormone therapy (rhGH) has gained a good reputation for use in a variety of growth conditions where child growth is retarded. Studies also reported a beneficial effect of GH therapy in improving the final height in different subgroups [7,8]. This study aimed to investigate the effect of rhGH administered at different periods in children of both genders.

Materials and methods.

A retrospective longitudinal study of children diagnosed with short stature was followed. The study included the files of those patients who regularly visit and adhere to clinical follow-up over 2.5 years (starting from 2020-to 2022). After a thorough explanation of the study, a consent agreement was taken from the parents of the studied population. The study was approved by the ethical and scientific committee in the department. Subjects with syndromic short stature and systemic illnesses such as renal failure were excluded. Participants aged between 5 and 15 years old who had their GH stimulation test done were included in the study. Collected data were patients' age, gender, rGH therapy duration, and height (cm) at presentation and the end of therapy. The bone age of each participant was measured by means of an imaging study (x-ray of wrist joint) calibrated according to ossification of the carpal bone diagnosed by a specialist radiologist (Figure 1). The given dose of growth hormone (Norditropin Nordilet, Novo Nordisk, Denmark) is 0.035mg/kg/day [every day with Fridays-off-therapy] subcutaneously.

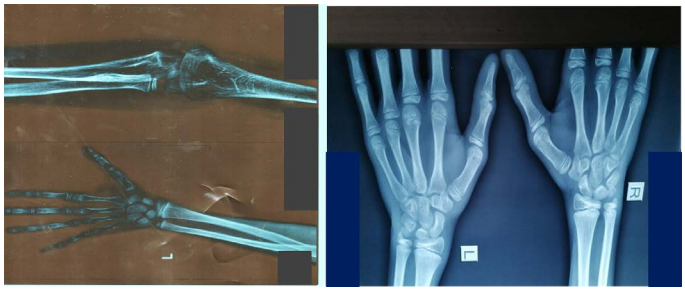

Figure.1. *Representative images of a sample of carpal bone ossification used as a diagnostic tool for growth stature identification.*

Height below the third centile on the growth chart and delayed bone age was used as a tool to classify the patient group.

The GH assay was assessed by laboratory measurement of GH baseline and after stimulation using Cobas e 411 analyzers (Roche Diagnostics, Germany) using a kit supplied by Elecsys hGH (#cat no. 05390125500V8.0).

Data were collected and tabulated using excel sheets. Clear-cut variables were presented as percentages and numerical variables were presented as mean and standard deviation (SD) using Microsoft excel. One-way ANOVA (GraphPad Prism v 3.1) was used to assess the difference among the different treatment groups and statistical significance was set at a p-value of < 0.05.

Results.

The study involved 129 children aged between 5-15 years of both genders. They were grouped into three according to the duration of receiving rGH therapy; 8-month group of 25 participants where 10 were males and 15 were females (age, 8.56 ± 2.28), 14-month group of 59 participants (26 males and 33 females, age 9.01 ± 2.29) and 22-month group of 45 children 15 males and 30 females (age,10.43 ± 2.65).

Regarding bone age, no significant differences were encountered between male and female participants in all three treatment periods (8, 14 and 22 months). However, A significant increase was monitored over the treatment periods starting with 1.56 ± 0.45 and 1.75 ± 0.48 for females and males, respectively in the 8-month treatment group (Figure 2), followed by 2.98 ± 0.59 and 3.07 ± 0.52 for females and males, respectively in the 14-month treatment group. Maximum bone age values were recorded at the GH long-term therapy of 22 months (3.8 ± 0.86 and 3.7 ± 0.82 for females and males, respectively).

Regarding GH stimulation assay, although no differences were found between the two genders, groups treated for the longer period showed a declined level of GH assay. Participants treated for 8 months demonstrated the highest level of 5.03 and 5.16 for females and males, respectively while GH assay levels of participants exposed to the extended treatment of 14 months decreased to 3.5 for female children and 3.26 for their male counterparts. Treatment GH therapy for 22-month caused the GH assay to drop to the lowest level in comparison to the other groups (2.7 and 2.6 for female and male participants, respectively). Statistical analysis revealed a significant difference between 8 and 22-month periods of the female gender, however, the overall trend is of a decline with treatment duration (Figure 3).

Children's height (cm) was measured at clinical presentation (i.e., diagnosis) and the end of therapy. Results showed that there is an increase in the participant's height in the three treatment groups and both males and females (Figure 4). Overall, the increase in height was 7.08 cm, 12.58 cm and 20.84 cm in 8, 14 and 22-month groups (± 1.6, 3.3 and 4.3), respectively. Using one-way ANOVA, a significant difference (p-value < 0.05) was found between 8-month and 14-month groups; between 14-month and 22-month groups (p-value < 0.01) and between 8 and 22-month groups (p-value < 0.001) with an increasing trend with the increase of treatment duration (Figure 5).

Discussion.

Treatment of short-stature children using GH is idiosyncratic and depends on many variables such as GH stimulation test results. It has been noted that hormonal treatment can

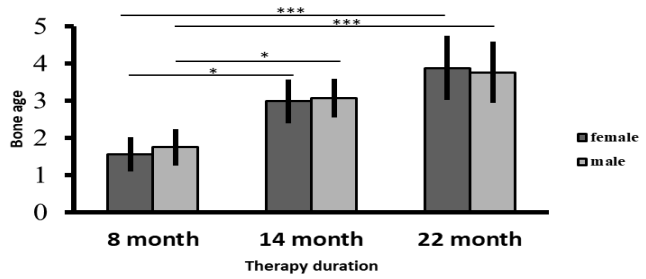

Figure. 2. *Mean bone age of the three treatment periods. * p-value < 0.05; *** p-value < 0.001 using Dunnett's one-way ANOVA.*

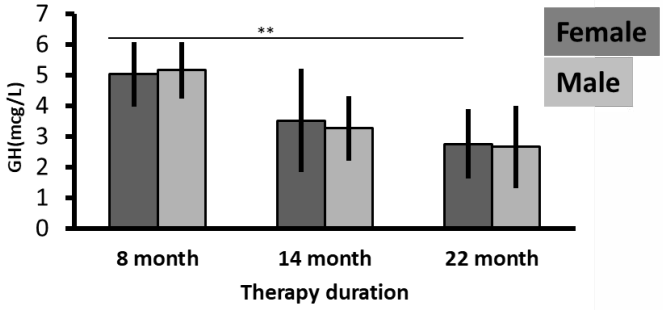

Figure. 3. *Average GH assay readings were collected during the three treatment periods. ** p-value < 0.01 using Dunnett's one-way ANOVA.*

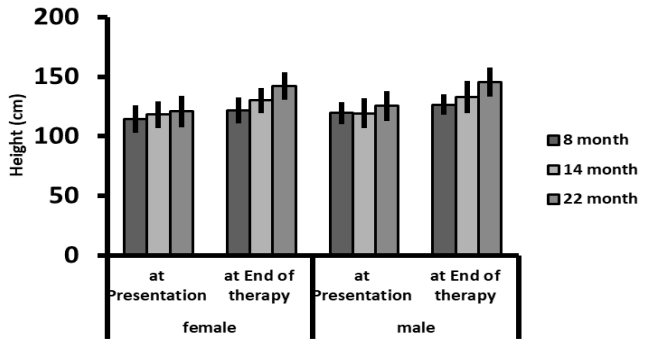

Figure. 4. *Children averaged height (cm) at presentation and after therapy.*

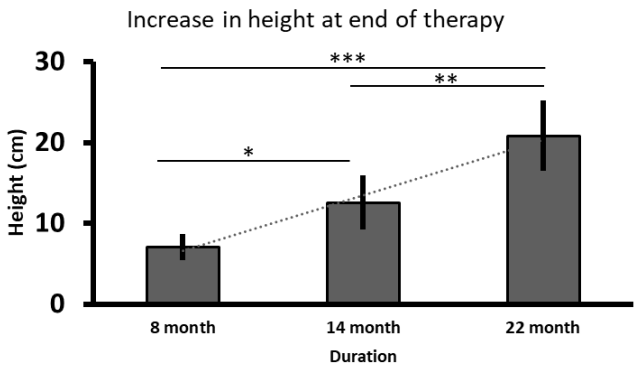

Figure. 5. *The height difference between mean presentation height and mean at the end of therapy height in all study participants. *, p-value < 0.05; **, p-value < 0.01; *** p-value < 0.001 using Dunnett's one way ANOVA.*

Table 1. *Demographic representation of the study variables.*

		Treatment duration (months)		
		8 (n=25)	**14 (n=59)**	**22 (n=45)**
Age (years)	(mean ± SD)	8.56 ± 2.28	9.01 ± 2.29	10.43 ±2.65
Gender	*male*	n = 10 (40 %)	n = 26 (44.06%)	n = 15 (33.4%)
	female	n = 15 (60 %)	n = 33 (55.9%)	n = 30 (66.6%)

be vindicated in short-stature children unless there are contraindications [2]. Objectively this study aimed to assess the impact of rhGH therapy duration on the increase of subjects' height at the end of therapy (8 months, 14 months and 22 months). We Adjusted the duration of therapy to the clinical follow-up. Once desired length is reached based on the growth chart; the treatment is stopped while follow-up continues until reaching a year beyond the time target height.

Although the duration of growth hormone therapy has been a controversial approach for many years, recent data suggest that GH therapy plays a significant role in bone mineralization and body lean mass [9-11] together with improving risk factors for cardiac problems such as taming lipid profile [10,12,13]. These benefits have recommended the life-long use of GH therapy in susceptible individuals.

The findings of our study indicated that children's bone age and height increased in accordance with the extension of therapy duration. Similar results were obtained by Ross et al. 2011[14]. Briefly, the height outcomes in patients with Turner Syndrome on GH therapy were measured following a short-term period (1 year), long-term period (less than 3 years) and extended period (more than 3 years) and authors found that 62.3 % of the patients on continuous therapy for more than 3 years achieved a normal population range of standard deviation scores highlighting the importance of long-term therapy commenced early after diagnosis. Another study revealed a significant difference in height scores between short-term therapy (less than 5 years) and long-term rhGH therapy (more than 5 years) with normalization of bone age at uniformity with their age [15]. Supporting our finding is a meta-analysis study of 21 studies indicating a significant increase in height following the 1-year treatment period when compared to the control group. The effect on height was further improved following the second year of therapy and the final adult height [16]. Moreover, a recent Korean observational study conducted on patients with growth hormone deficiency and idiopathic short stature documented an increase in height standard deviation score from that of the baseline in response to GH therapy [17].

GH assay was monitored during therapy and a trend of declining with treatment duration was reported in our study. The pulsatile nature of the growth hormone secretion makes the diagnosis of hormone deficiency difficult. Other factors also affect hormone secretion such as an individual's age, gender, genetic background and body mass. Hence, diagnosis cannot rely on a single random hormone measure. Also, it has been suggested that the GH stimulation test can be omitted in patients with short stature. This is particularly applicable in places where GH stimulation test is not available as in some countries of the Middle East, where patients have to queue long before getting the test and starting therapy. The delay of treatment may be harmful when bone maturation is completed. In certain situations, such as isolated GH deficiency, it has been claimed that the initial GH stimulation test has minimum impact on the continuation of the therapy and that the GH stimulation test needs to be performed repeatedly at eighteen years [18]. Moreover, although the GH stimulation test can aid in guiding GH dosing, weight-based or body surface area-based dosing is recommended in addition to physician and institution decisions [19-23]. Being multifactorial, the short stature has been improved with the addition of Citicoline used in this study. Other coexisted conditions were treated individually, such as thyroid disorders.

Regarding our study design, we acknowledge the impact of conducting a retrospective study in imposing the limitation of missing valuable data essential for robust study outcomes. A need for prospective studies investigating the effect of GH stimulation test treatment commencement and duration, especially in individuals with the normal test.

Conclusion.

This study provides evidence of the effect of long-term 22-month GH therapy on bone age and body height both in male and female children involved in the study. Further prospective studies are required to assess the effect of the GH stimulation test on GH therapy.

REFERENCES

1. Nath P, Kumar J, Rahman SH, et al. Short Stature: Evaluation and Management. Medicine Update. 2013:626-631.
2. Cohen P, Rogol AD, Deal CL, et al. 2007 ISS Consensus Workshop participants. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European

Society for Paediatric Endocrinology Workshop. The Journal of Clinical Endocrinology & Metabolism. 2008;93:4210-4217.
3. Reed ML, Merriam GR, Kargi AY. Adult growth hormone deficiency–benefits, side effects, and risks of growth hormone replacement. Frontiers in endocrinology. 2013;4:64.
4. Lam WF, Hau WL, Lam TS. Evaluation of referrals for genetic investigation of short stature in Hong Kong. Chinese medical journal. 2002;115:607-611.
5. Al-Zubaidi MA, Al-Shuwailli SH, Abd KQ. Effect of growth hormone therapy on Iraqi children with growth hormone deficiency. Curr Pediatr Res. 2021;25:1051-1055.
6. AlZubaidi MA, Saleh MM, Jawad ZM. Causes of short stature in Iraqi hospital-based study patients. Journal of the Faculty of Medicine Baghdad. 2017;59:221-225.
7. Cavallo F, Mohn A, Chiarelli F, et al. Evaluation of bone age in children: A mini review. Frontiers in Pediatrics. 2021;9:580314.
8. Harris M, Hofman PL, Cutfield WS. Growth hormone treatment in children. Pediatric Drugs. 2004;6:93-106.
9. Saggese GI, Baroncelli GI, Bertelloni SI, et al. The effect of long-term growth hormone (GH) treatment on bone mineral density in children with GH deficiency. Role of GH in the attainment of peak bone mass. The Journal of Clinical Endocrinology & Metabolism. 1996;81:3077-3083.
10. Underwood LE, Attie KM, Baptista J, Genentech Collaborative Study Group. Growth hormone (GH) dose-response in young adults with childhood-onset GH deficiency: a two-year, multicenter, multiple-dose, placebo-controlled study. The Journal of Clinical Endocrinology & Metabolism. 2003;88:5273-5280.
11. Boguszewski CL, Meister LH, Zaninelli DC, et al. One year of GH replacement therapy with a fixed low-dose regimen improves the body composition, bone mineral density and lipid profile of GH-deficient adults. European Journal of Endocrinology. 2005;152:67-75.
12. Colao A, Di Somma C, Pivonello R, et al. The cardiovascular risk of adult GH deficiency (GHD) improved after GH replacement and worsened in untreated GHD: a 12-month prospective study. The Journal of Clinical Endocrinology & Metabolism. 2002;87:1088-1093.
13. Lanes R, Paoli M, Carrillo E, et al. Cardiovascular risk of young growth-hormone-deficient adolescents. Hormone Research in Paediatrics. 2003;60:291-296.
14. Ross J, Lee PA, Gut R, et al. Impact of age and duration of growth hormone therapy in children with Turner syndrome. Hormone research in paediatrics. 2011;76:392-399.
15. Nwosu BU, Jasmin G, Parajuli S, et al. Long-term GH Therapy Does Not Advance Skeletal Maturation in Children and Adolescents. Journal of the Endocrine Society. 2021;5:bvab036.
16. Paltoglou G, Dimitropoulos I, Kourlaba G, et al. The effect of treatment with recombinant human growth hormone (rhGH) on linear growth and adult height in children with idiopathic short stature (ISS): a systematic review and meta-analysis. Journal of Pediatric Endocrinology and Metabolism. 2020;33:1577-1588.
17. Rhie YJ, Yoo JH, Choi JH, et al. Long-term safety and effectiveness of growth hormone therapy in Korean children with growth disorders: 5-year results of LG Growth Study. PloS one. 2019;14:e0216927.
18. Molitch ME, Clemmons DR, Malozowski S, et al. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology & Metabolism. 2011;96:1587-1609.
19. Root AW, Dana K, Lippe B. Treatment of growth hormone-deficient infants with recombinant human growth hormone to near-adult height: patterns of growth. Hormone Research in Paediatrics. 2011;75:276-283.
20. Gjikopulli A, GRIMCI L, Kollcaku L, et al. Final height in children with idiopathic growth hormone deficiency treated with growth hormone: Albanian experience. Current Health Sciences Journal. 2015;41:22.
21. Mauras N, Attie KM, Reiter EO, et al. High dose recombinant human growth hormone (GH) treatment of GH-deficient patients in puberty increases near-final height: a randomized, multicenter trial. The Journal of Clinical Endocrinology & Metabolism. 2000;85:3653-3660.
22. De Luca F, Maghnie M, Arrigo T, et al. Final height outcome of growth hormone-deficient patients treated since less than five years of age. Acta Paediatrica (Oslo, Norway: 1992). 1996;85:1167-1171.
23. Juul A, Bernasconi S, Clayton PE, et al. European audit of current practice in diagnosis and treatment of childhood growth hormone deficiency. Hormone Research in Paediatrics. 2002;58:233-241.