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RESEARCH ARTICLE

New Insights in Growth Hormone Stimulation Tests Protocols

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Objective: The objective of this study was to analyze the performance of 2 stimulation tests used in the diagnosis of growth hormone deficiency. **Method**: A retrospective study was conducted on a non-random sample of 310 patients, between 2 and 20 years old, who were hospitalized in the Mureș County Hospital's Endocrinology Department and in the National Institute of Endocrinology C.I. Parhon with short stature between 2009-2015. Inclusion criteria: all subjects who underwent growth hormone stimulation tests in accordance with the national protocol. Microsoft Office Excel was used for data collection and MedCalc v 12.5 was used for statistical analysis. **Results**: From the total of 310 patients, 102 were diagnosed in Târgu Mureș and 208 in Bucharest. Sex ratio favored boys (boys:girls 1.64:1). In 173 subjects growth hormone deficiency was confirmed. For both tests the percentage of maximum response was the highest for the 60 minutes blood sample regardless if the test were positive or not. Both tests have 100% sensitivity and negative predictive value, with the highest specificity for the 60 minutes clonidine and 30 minutes insulin. The false positive rate was 60% for the insulin test and 27.2% for clonidine for Târgu Mureș sample and 86.9% for the insulin test and 62.5% for clonidine for Bucharest sample. The concordance of the 2 tests was 49.36%. **Conclusions**: Stimulating growth hormone testing has a number of limitations but is still needed in some auxological circumstances. We recommend performing the clonidine test first to exclude idiopathic short stature and then the insulin tolerance test for the diagnosis of growth hormone deficiency.

Keywords: stimulation tests, growth hormone deficiency, auxology

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Introduction

The growth and development of the child is under the strict control of the endocrine system. Since childhood, an important role is played by growth hormone-releasing hormone/ growth hormone/ insulin-like growth factor 1 (GHRH / GH / IGF1) and thyroid hormones, whereas during puberty the main role is played by sex steroid hormones [1,2]. The primary function of GH is to promote growth, being achieved mainly through IGF1. [3].

A child who is under 2.5 standard deviation (SD) for age, sex and population average height, will be classified as growth delay, while a child whose measurements exceed 2.5 SD statistically calculated average, will be diagnosed with tall stature [1,2,6,7]. In childhood, the diagnosis of growth hormone deficiency should be based on auxology, which will allow the comparison of the individual's growth model with the reference values from the growth charts [3,9-11]. In order to complete and confirm the diagnosis, static laboratory tests will be performed such as GH, IGF1, IGFBP or dynamic tests like GH stimulation tests [3,6,12]. In all cases of confirmed GH deficiency, it is mandatory to perform a magnetic resonance imaging of the pituitary gland in order to diagnose all structural anomalies associated with pituitary dysfunction [6].

Patients who will undergo GH-IGF-1-IGFBP axis evaluation belong to one of the following categories: (1) severe short stature (height <-3 DS); (2) height <-1.5 DS below the target genetic height; (3) medium stature deficit (height between -2 and -3 DS) and growth deceleration (growth velocity <-1 DS for 2 years or <-2 DS for 1 year); (4) history of brain tumor, cranial irradiation or other pituitary pathology; (5) imaging evidence of pituitary pathology [2,3,6].

Although the routine use of GH-stimulation tests is highly controversial [12,15], currently they are included in the diagnostic protocol of GH deficiency [3,6,7,10]. Stimulation tests are classified into two categories: screening tests, which include GH value after intense physical exercise, food deprivation, levodopa or clonidine stimulation, and definitive tests which include stimulation of GH secretion with insulin, arginine or glucagon [3,7]. To increase the specificity of these tests, the results of at least two of them are usually combined [3,7,10,16].

In order to establish a positive diagnosis of pituitary dwarfism, the national protocol requires the following assertions: the height deficit must be minimum 2.5 DS; stature deficit between - 2 and - 2.5 DS and the growth velocity a year before 2 DS below the average velocity for age and sex, or growth velocity in the year before at least 1.5 DS below the average for sex and age; in children with post-irradiation or postoperative acquired GH deficiency, increase in stature deficit by 0.5 DS per year; bone age should be over 2 years late; the child (generally over 3 years) must have 2 negative GH stimulation tests or 1 negative test and an IGF I value in serum below the lower

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limit of normal for age; in pubertal patients to exclude the transient GH deficiency, priming with sex steroids can be performed prior to dynamic GH testing[17].

Short stature diagnosis and treatment are quite controversial within the worldwide pediatric endocrinologists practice. Growth deficiency has a steady increase in prevalence, currently representing at least 2.5% of pediatric pathology in 3 to 16-year-old infant population. Currently, the diagnosis and treatment of growth hormone deficiency is possible in 6 centers in our country, but with some limitations and differences in GH stimulation testing.

The aim of this study was to analyze the performance of two growth hormone stimulation tests (clonidine and insulin test), by assessing the results obtained in two centers in Romania, in Târgu Mureş at the Endocrinology Clinic and in Bucharest at the National Institute of Endocrinology CI Parhon in order to optimize as much as possible the diagnostic and therapeutic protocol of this pathology.

Method

We conducted a cross-sectional study on a group of 310 patients with a suspicion of GH deficiency, aged between 2 and 20 years, admitted to the Endocrinology Clinic of Târgu Mureş and the National Institute of Endocrinology CI Parhon Bucharest, between January 2009 and October 2015.

A written informed consent was obtained for each patient included in our study. All data that was used has no personal character and it was performed according to the Helsinki Declaration. Prior to the inclusion of the patients in this study the approval from the head of both endocrinology departaments, Târgu Mureș and Bucharest, was obtained.

All children suspected with growth hormone deficiency ((1) severe short stature (height <-3 DS); (2) height <-1.5 DS below the target genetic height; (3) medium stature deficit (height between -2 and -3 DS) and growth deceleration (growth velocity <-1 DS for 2 years or <-2 DS for 1 year); (4) history of brain tumor, cranial irradiation or other pituitary pathology; (5) imaging evidence of pituitary pathology), for whom GH-stimulation tests were performed according to the national protocol, were included. Patients who presented certain genetic syndromes such as: Turner syndrome, Prader Willi, Bardet Biedl, or patients who have been small for gestational age were excluded from our study. According to the current protocol, GH deficiency is defined as GH value of <10 ng / ml during 2 GH stimulation tests (for each blood sample obtained). If IGF1 is lower than the lower limit of normal, a single dynamic test is performed.

The test protocols differ between the two centers, especially regarding blood sampling times. Therefore, in The Endocrinology Clinic from Târgu Mureş, for clonidine stimulation test, blood samples are collected to obtain a basal GH value, then the pharmacological agent is administered (Clonidine 5 mcg/kg, sau 150 mg/m^2, maxim 250 mcg) followed by sampling at 30, 60, 90 and 120 minutes. In the case of the CI Parhon Institute, the post-administration of clonidine (same dosages) blood sampling is done at 60 and 120 minutes.

For the insulin tolerance test, in Targu Mures, is used the same protocol as for clonidine, thereby blood samples are collected for basal GH monitoring and then at 30, 60, 90, 120 minutes after the administration of insulin 0.05-0.1 UI/kg i.v. în bolus. In Bucharest, after insulin (same dosage) administration sampling is done at 30 and 60 minutes.

In order to take into account the dosage of growth hormone obtained from insulin stimulation, the glucose level after insulin administration must fall to half the blood glucose fasting level or below 2.2 mmol/ l (40 mg / dl).

Data was collected using Microsoft Office Excel package, and graph pad prism was used for statistical analysis. Discrete quantitative and qualitative binary variables were used. For comparison of medians, the Mann-Whitney test was performed, chi square test for the performance of diagnostic tests and Spearman coefficient for correlation, with a significance threshold of alpha = 0.05.

Results

Of the total of 310 patients, 102 children were diagnosed in Târgu Mures and 208 in Bucharest. Gender ratio favored boys 1.64:1, accounting for a total of 193 male and 117 female patients.

Average age for Târgu Mureş group was 9 years ± 3.8 years (8.8 for girls and 9.2 for boys), of whom 59 were less than 10 years old and 43 had exceeded the average prepubertal threshold. Bone age, analyzed for each patient according to hand radiography, ranged from 1 to 15 years, the mean difference between the bone age and chronological age for the first group was 2 years.

For the Bucharest patients, the average age was 9.7 years ± 4.1 years (9.6 for girls and 9.7 for boys), 129 of them were younger than 10 years and 79 were above this age. Bone age ranged from 1 to 17.5 years with a mean difference between this and the chronological age of 3.4 years.

We compared the results obtained during the clonidine stimulation and insulin stimulation tests for each group.

For Târgu Mureş group, we had 99 patients who underwent clonidine stimulation test and 26 for whom ITT was performed. Out of the whole group, only 23 patients underwent both stimulation tests.

We noted that for the patients from Târgu Mureş the percentage of cases who had a maximum response during the stimulation tests, was the highest for the blood sample taken at 60 minutes after the administration of the pharmacological agent. More precisely for 53.53% of children we obtained the highest GH value at 60 minutes after clonidine stimulation and, at the same time of sampling, we obtained maximum GH values for 34.61% of children who underwent insulin test (Figure 1).

For the Parhon Institute group, from the 208 investigated children, 173 were stimulated with clonidine and

85 with insulin. Only 56 patients underwent both GH stimulation tests. Thus, in Figure 2 we can observe for the clonidine stimulation test, 72.25% of the patients had a maximum response at 60 minutes after the pharmacological agent administration, while 27.75% had a positive response at 120 minutes. Blood samples collected for the insulin test, pointed out that 50.58% of children had a maximum response at 60 minutes after insulin administration, and the rest of 49.42% at 30 minutes (Figure 2).

Of the whole group, for 79 subjects, both stimulation tests were performed, 39 (49.36%) were concordant, with a gender ratio favoring boys (1.4:1).Regarding the non-concordant tests, for most cases, insulin testing revealed growth hormone deficiency, while the clonidine test revealed adequate stimulation of GH (80%). The kappa index of agreement was -0.103 (95%CI -0.261-0.055, p=0.220) (Figure 3).

For both samples the performance parameters of the two tests were calculated, against the GH deficiency definition of a maximum GH value below 10ng/ml during stimulation tests. For both centers the tests have sensitivity and negative predictive value of 100%. Specificity and positive predictive value were calculated for each test separately and for each group of patients, since the test protocol differs in these two hospitals (Table I).

Also, false positive rate was calculated for each sampling moment, and for each test as a whole, by analyzing the subjects who underwent both tests. For Târgu Mureş group, clonidine at 30 minutes and insulin at 120 minutes have the highest false positive rate. In other words, if samples were taken only at these times, most of the subjects would be considered to have growth hormone deficiency when they actually had adequate stimulation at other sampling moment.

For Bucharest group, the maximum false positive rate was at 120 minutes for clonidine and 60 minutes for insulin. The false positive rates of both tests as a whole, are higher than for Târgu Mureş center, where the clonidine test has a false-positive rate of 27.27% (Table II). We calculated the number of cases that would be misdiagnosed as GH deficiency assessing how many cases were stimulated at values above 10 ng / ml only at a certain time of sampling.

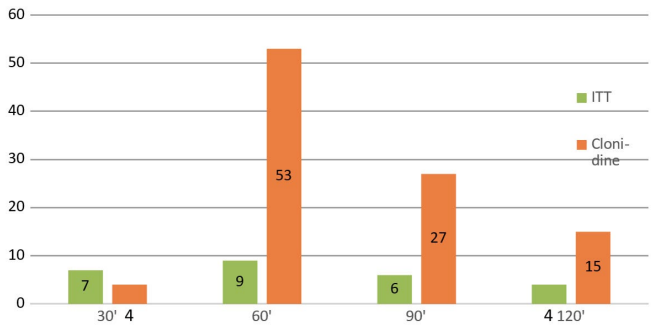

Fig. 1. Subdivision of subjects according to the maximum response of GH to the 2 tests (Târgu Mureş)

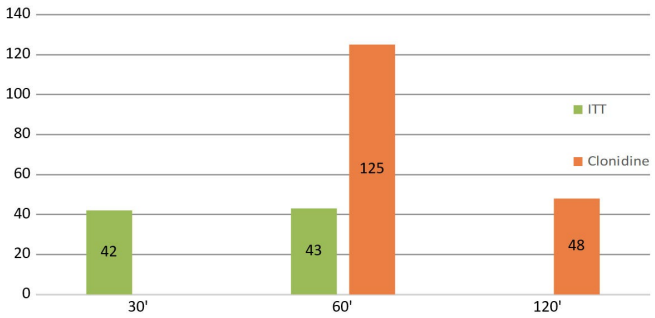

Fig. 2. Subdivision of subjects according to the maximum response of GH to the 2 tests (Buchaest)

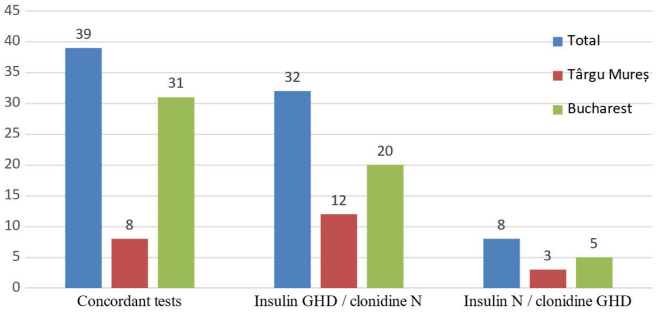

Fig. 3. The concordance of the 2 diagnostic tests

We analyzed the influence of various parameters taken into account, on the maximum response to stimulation tests. Maximum response to clonidine correlates positively with the standard deviation score for height, IGF1 and

Table I. Performance of the 2 tests

Center	Moment	Specificity	CI95%	PPV	CI95%	P
Târgu Mureş	Clonidine 30 minutes	6.82%	1.43-18.46%	57.29%	46.78-67.34%	<0.08
	Clonidine 60 minutes	86.36%	72.66-94.82%	90.16%	79.81-96.31%	<0.0001
	Clonidine 90 minutes	61.36%	45.44-75.65%	76.39%	64.9-85.63%	<0.0001
	Clonidine 120 minutes	25%	13.19-40.29%	62.5%	51.56-72.56%	<0.0001
	Insulin 30 minutes	75%	19.42-99.37%	95.83%	78.86-99.89%	0.0014
	Insulin 60 minutes	50%	6.76-93.24%	92%	73.96-99.02%	0.0171
	Insulin 90 minutes	50%	6.76-93.24%	92%	73.96-99.02%	0.0171
	Insulin 120 minutes	25%	0.63-80.58%	88.46%	69.86-97.55%	0.1481
Bucharest	Clonidine 60 minutes	89.1%	77.7-95.9	95.16	89.7-98.2	<0.0001
	Clonidine 120 minutes	18.2%	9.1-30.9	72.4	64.9-79.1	<0.0001
	Insulin 30 minutes	68.4%	43.4-87.4	92.3	84.01-97.1	<0.0001
	Insulin 60 minutes	42.1	20.2-66.1	85.7	75.9-92.6	<0.0001

negative with BMI. Maximum insulin response correlates positively with age, standard deviation score for height, and IGF1. Bone age does not correlate with the response to any of the stimulation tests (Table III).

Discussions

By analyzing the performance of the two diagnostic tests, we found that both tests had sensitivity and negative predictive value of 100%, due to the fact that the current national protocol imposes a clear cut-off for GH of 10 ng/ml. Thus we observed that in the case of Târgu Mureş, for clonidine stimulation test, the best specificity was obtained at 60 and 90 minutes blood sampling.

For Parhon Institute group, the specificity of the 60 minutes sample did not differ significantly from the Târgu Mures group, while for the 120 minutes sampling, it was significantly lower. Actually, it is worth mentioning that in case of Târgu Mureş center, for clonidine test, blood sampling at 90 minutes after the administration of the pharmacological agent, helps in diagnosing a relatively large number of children, while the blood sample taken at 30 minutes does not provide any new cases that are not further stimulated at 60 minutes. Therefore, if the elimination of the 90-minute blood sampling from the testing method can lead to over-treatment of children with growth hormone, possibly due to incomplete diagnosis, the 30 minutes blood sampling could be safely ruled out with no risk of misdiagnosing these children.

In the case of ITT, for the Târgu Mureş sample, we obtained the highest specificity for the sample taken at 30 minutes and the lowest at 120 minutes. For the Bucharest sample, the specificity of the 30-minute sample was superior to the 60 minutes one. It is not to be neglected that in Târgu Mureş clinic, the 90-minute blood sample after insulin administration diagnosed the same number of children as the 30-minute one, showing the importance of at least 3 blood samples for each test.

Test performance of these two tests has been analyzed in many other clinical trials. One of these studies reports a specificity of 79% for ITT in comparison to 85% for clonidine [22]. Another interesting aspect is that it has been shown that the specificity of the tests would improve if a lower cut-off value was used [12].

All investigations made on the whole studied group, both in Târgu Mureş and Bucharest have shown that GH deficiency is more commonly diagnosed among male patients.

The average age of diagnosis for the entire group was very close to the onset of puberty, highlighting the fact that in Romania the GH deficit is diagnosed late. Patients should be diagnosed before the age of 5 years, because the treatment results are closely related to the age when the treatment is initiated. The studies recommend to start the treatment at an early age in the prepubertal stage, the most relevant results being noticed in children younger than 4 years [6,24]. It is most reasonable to initiate postnatal growth hormone treatment when growth deficiency begins to be visible independently of the age. Therefore, favorable results have been obtained even at the age of 9 months [25].

The diagnostic tests were concordant in less than half of the analyzed results. The large number of non-concordant tests reveals that the diagnosis of pituitary dwarfism should not be based predominantly on GH stimulation test. Analyzing the correlations between anthropometric parameters and stimulation tests, we obtained statistically significant results for the clonidine test in the case of DS for BMI and IGF1. There are studies that have shown a relationship between weight, BMI and GHD. Therefore, compar-

Table II. Fals positive rate

Târgu Mureș sample		**Bucharest sample**	
Moment	Fals positive rate	Moment	Fals positive rate
Clonidine 30 minutes	93.18%	Clonidin 60 minutes	10.91%
Clonidine 60 minutes	13.63%	Clonidin 120 minutes	81.81%%
Clonidine 90 minutes	38.63%	Insulin 30 minutes	31.57%
Clonidine 120 minutes	75%	Insulin 60 minutes	57.9%
Insulin 30 minutes	25%	Insulin tolerance test	86.9%
Insulin 60 minutes	50%	Clonidin test	62.5%
Insulin 90 minutes	50%		
Insulin 120 minutes	75%		
Insulin tolerance test	60%		
Clonidin test	27.27%		

Table III. Correlation of anthropometric parameters with the maximum response to stimulation tests

	Maximum response to clonidine			**Maximum response to insulin**		
Parametre	R	95%CI	p	R	95%CI	p
SD height	0.1717	0.052-0.2865	0.0052	0.2897	0.1099-0.4509	0.0020
BA	0.1049	-0.0271-0.2334	0.1190	0.1025	-0.1011-0.2979	0.3230
DS IGF 1	0.2108	0.0886-0.3268	0.0008	0.4455	0.2871-0.5801	<0.0001
Age	-0.0598	-0.1775-0.0595	0.3257	0.4655	0.3102-0.5967	<0.0001
SD BMI	-0.1781	-0.2928-(-0.0584)	0.0038	-0.0862	-0.2644-0.0975	0.3571

Legend: SD- standard deviation; BA- Bone age; BMI- body mass index; CI- confidence interval; IGF 1- Insulin-like Growth Factor 1

ing the results of a group of children diagnosed with GH deficiency and one with an idiopathic small stature, it was showed that the BMI mean for the GH deficiency group was higher than for those in the idiopathic small stature group [26]. Another study asserts that the maximum GH value obtained from stimulation tests decreases with the increase in DS for BMI. Children who associate obesity also have a low value of endogenous GH secretion compared to normoponderal children [27].

In Romania, there are no further studies to analyze the clear differences between the protocols used for the GH stimulation tests in other reference centers.

Our proposals regarding the national protocol for GH deficiency diagnosis would be: minimum 3 blood samples for both diagnostic tests studied in order to avoid the incorrect diagnosis of this pathology or over-treatment whit growth hormone; for the clonidine test the most specific and reliable results are at 0, 60, 90 and 120 minutes, whereas for ITT is recommended to assess the 0, 30, 60, 90 minutes blood samples.

The limitations of the study were: the use of different protocols in the centers included in our study, the performance of the stimulation tests were calculated separately for each group, the results being practically difficult to compare; in ITT, there were cases included in the study group, for which the blood glucose level after insulin administration did not fall below 40 mg/dl or below half the baseline blood glucose; and the lack of data that could influence the diagnosis of GH deficiency, such as: social status, possible renal, cardiac or malabsorption disease.

Conclusions

Our study, revealed a low specificity for insulin tolerance test. During the clonidine stimulation test, the maximum specificity was obtained at 60-minutes, while in case of the insulin stimulation test, it was obtained at 30 minutes. Only half of the cases presented concordance between the two tests. BMI and DS for IFG1 significantly influence clonidine test results, whereas DS for IGF1 and age influence ITT results.

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Authors'contribution

IA – Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, writing original draft, writing review and editing

RP – Conceptualization, formal analysis, investigation, methodology, supervision

IG – Conceptualization, data curation, formal analysis, investigation, supervision

IP – Conceptualization, data curation, formal analysis, investigation, supervision, validation

Conflict of interest

None to declare.

References

1. Hermanussen M - Auxology - Studying Human Growth and Development. Stuttgart: Schweizerbart; 2013.
2. Young J - Endocrinologie, Diabetologie et Maladies Metaboliques. Massons: Elsevier; 2011.
3. Richmond EJ, Rogol AD - Growth hormone deficiency in children. Pituitary. 2008;11:115-120.
4. Paşcanu IM - Note de curs in Endocrinologie. Tg. Mureş: University Press; 2015.
5. Hoybye C, Cohen P, Hoffman AR, Ross R, Biller MK, Christiansen JS - Status of long-acting-growth hormone preparations. Growth Hormone & IGF Research. 2015;25:201-206.
6. Brook C, Clayton P, Brown R - Brook's Clinical Pediatric Endocrinology. 6th ed. Oxford: Wiley-Blackwell; 2009.
7. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM- Williams Textbook of Endocrinology. 13th ed. Philadelphia: Elsevier; 2015.
8. Luque RM, Kineman RD, Park S, Peng XD, Navarro FG, Castano JP et al. - Homologous and heterologous regulation of pituitary receptors for grelin and growth hormone-releasing hormone. Endocrinology. 2004;145:3182-3189.
9. Rogol AD, Hayden GF - Etiologies and Early Diagnosis of Short and Growth Failure in Children and Adolescents. The Journal of Pediatrics. 2014;164:S1-S14.
10. Ghigo E, Bellone J, Aimaretti G, Bellone S, Loche S, Cappa M et al - Reliability of Provocative Tests to Assess Growth Hormone Secretory Status. Study in 472 Normally Growing Children. Journal of Clinical Endocrinology and Metabolism. 1996;81:3323-3327.
11. Binder G, Huller E, Blumenstock G, Schweize R - Auxology – based cut-off values for biochemical testing of GH secretion in childhood. Growth Hormone & IGF Research. 2011;21:212-218.
12. Gandrud LM, Wilson DM - Is growth hormone stimulation testing in children still appropriate? Growth Hormone & IGF Research. 2004;14:185-194.
13. Ranke MB, Schweizer R, Lindberg A - Insulin-like growth factors as diagnostic tools in growth hormone deficiency during childhood and adolescence: the KIGS experience. Hormone Research. 2004;62:17-25.
14. Jensen RB, Jeppensen KA, Vielwerth S - Insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 as diagnostic markers of growth hormone deficiency in infancy. Hormone Research. 2005;63:15-21.
15. Wilson DM, Frane J - A brief review of the use and utility of growth hormone stimulation testing in the NCGS: Do we need to do provocative GH testing? Growth Hormone & IGF Research. 2005;15:21-25.
16. Noorisaem R, Ka YO, Eum MY, Chan JK - Growrh Hormone Response to Provocative Tess in Children with Short Stature, Chonan Med J, 2015, 51: 33-38. Chonan Med J. 2015;51:33-38.
17. Ministerul Sănătății CNdAdS. Protocoale terapeutice. 2008. http://www.ms.ro/specialisti-in-domeniul-sanatatii/#tab-id-11
18. Roland P - Hormone replacement therapy in children: The use of growth hormone and IGF-1. Best Practice & Research Clinical Edocrinology & Metabolism. 2015;29:339-352.
19. Ferguson LA - Growth Hormone Use in Children: Necessary or Designer Therapy?. Journal of Pediatric Health Care. 2010;25:24-30.
20. Hogler W, Briody J, Moore B, Pei WL, Cowell CT - Effect of growth hormone therapy and puberty on bone and body composition in children with idiopathic short stature and growth hormone deficiency. Bone. 2005;37:642-650.
21. Binay C, Simsek E, Yildirim A, Kosger P, Demiral M, Kilic Z - Growth hormone and the risk of atherosclerosis in growth. Growth Hormone & IGF Research. 2015;25:294-297.
22. Hindmarsh PC, Swift PGF - An assessment of growth hormone provocation tests. Achives of Disease in Childhood. 1995;72:362-368.
23. Bildder C, Warne JT - Assessment of short child. Pediatrics and child health. 2009;19:11.
24. Luzuriaga CT, Irigoyen MO, Cepas EC, Vazquez Salvi LA, Garcia Perez LE - Safety and efficacy of growth hormone treatament: GeNeSIS study Spain. Analesdepediatria. 2016;84:139-147.
25. Davenport ML, Crowe BJ, Travers SH, Rubin K, Ross JL, Fechner PY - Growth hormone treatment of early growth failure in toddlers with Turner syndrome: a randomized, controlled, multicentertrial. J Clin Endocrinol Metab. 2007;92:3406–3416.
26. Lee J, Yoom J, Kang MJ, Lee YA, Shin CH - Influence of body mass

index on the growth hormone response to provocative testing in short children without growth hormone deficiency. journal Korean Med Sci. 2013;28:1351-1355.

27. Stanley TL, Leitsky LL, Grinspoon SK, Misra M - Effect of Body Mass Index on Peak Growth Homone Response to Provocative Testing in Children with Short Stature. Journal of Clinical Endocrinology and Metabolism. 2009;94:4875-4881.