Effects of Growth Hormone (GH)Therapy on Free Thyroxine (FT4) And Thyroid Stimulating Hormone (TSH) Concentration in Children

Mosleh Jabari[1*], Abdulrahman Sami Mirza[2], Ahmad Hany Tatwany[2], Khalaf Mohammed Alkhalaf[2], Ahmed Hamoud Alotaibi[2] , Mouath Mohammed Alrajhi[2], Hassan Al-Shehri[1], Abdullah Al-Faris[3], Mohammed Al-Sayed[3]

[1] Department of Pediatrics, College of Medicine, Al-Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia.
[2] Medical Students, College of Medicine, Al-Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia.
[3] Department of Pediatrics, Security Forces Hospital, Riyadh, Saudi Arabia.

ABSTRACT

Introduction: Several studies found that growth hormone therapy affects many hormonal pathways in the body, for instance causing a decrease in FT4 levels over time, which might eventually lead to the development of central hypothyroidism.

Materials and methods: A retrospective chart review study was conducted in Security Forces Hospital, Riyadh, Saudi Arabia. 149 patients diagnosed with short stature receiving growth hormone therapy from both genders were recruited 91 males and 57 females. Data were collected from patients at the base line and a subsequent follow up visit. Demographic data were also collected such as height, weight, and subsequently body mass index was calculated.

Results: the major finding is a negative correlation between the duration of treatment and decrease in Free thyroxin (T4) at the follow up visit (P = 0.006). TSH levels did not differ significantly between baseline and follow up (P > 0.05) as medians seem comparable to each other.

Conclusion: The duration of growth hormone therapy seems to be associated with a lower T4 levels at the follow up visits. Growth hormone therapy has no significant effects on either TSH or BMI.

Key Words: homone, thyroxine (FT4), Children.

eIJPPR 2017; 7(4):13-17

HOW TO CITE THIS ARTICLE: Mosleh Jabari, Abdulrahman Sami Mirza, Ahmad Hany Tatwany, Khalaf Mohammed Alkhalaf, Ahmed Hamoud Alotaibi , Mouath Mohammed Alrajhi, Hassan Al-Shehri, Abdullah Al-Faris, Mohammed Al-Sayed. (2017). "Effects of Growth Hormone (GH)Therapy on Free Thyroxine (FT4) And Thyroid Stimulating Hormone (TSH) Concentration in Children" , *International Journal of Pharmaceutical and Phytopharmacological Research, 7*(4), pp.13-17.

INTRODUCTION

Central Hypothyroidism is a thyroid disorder characterized by inadequate stimulation by thyroid-stimulating hormone (TSH) due to pituitary or hypothalamic dysfunction. Central hypothyroidism is about 1000-fold rarer than primary hypothyroidism, estimated to occur in 1: 20,000 to 1: 80,000 in the general populatio n [1]. Central hypothyroidism can be caused by genetic defects, tumours or it can be iatrogenic. Some of the drugs that may cause central hypothyroidism are growth hormone therapy, glucocorticoids, and somatostatin therapy [2].

Growth hormone (GH) also known as somatotropin is used as the replacement treatment for children with growth hormone deficiency. It is normally secreted by

Corresponding author: Mosleh Jabari
Address: Department of Pediatrics, College of Medicine, Al-Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia
e-mail ✉ dr.mus888@hotmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 06 December 2016; **Revised:** 11 June 2017; **Accepted:** 24 June 2017

anterior pituitary cells called somatotrophs, and it stimulates the growth of tissues of the body [1].

One of the leading causes of Central Hypothyroidism is drug related, and that is the primary objective of our research to find if there is a correlation between thyroid gland, free thyroxine (FT4), and thyroid stimulating hormone (TSH), and the intake of growth hormone (GH) therapy in children.

Clinical studies on the effect of growth hormone (GH) on thyroid function in patients with GH deficiency are growing. Further, most of published observations has no glance about incidence, nor the relevance at Saudi Arabia or the Middle Eastern countries. The aim of our study is to estimate the incidence of clinically relevant hypothyroidism in pediatric patients receiving GH therapy.

To find whether the same results would be manifested in Saudi Arabia, growth hormone treatment affects must be observed. Concerning our research, a significant negative correlation between the duration of growth hormone treatment and the decrease in free thyroxine levels (FT4). With the results, we can verify that growth hormone treatment can play a key role in the hormonal secretions of the free thyroxine by the thyroid gland. Further explanations will be presented in the methods, results, discussion, and conclusion.

METHODOLOGY

Study design

This was a retrospective chart review study conducted at Security Forces Hospital in Riyadh, Saudi Arabia. The study involved 149 patients who were on growth hormone therapy. Data were collected from patients at base line and at a subsequent follow up visit. Demographic data were also collected from patients such as height, weight and subsequently, body mass index was calculated. Patients' profiles were in electronic form and were recorded previously. All the patients were diagnosed with short stature and none of them had pituitary gland disorders or taking drugs, which may interfere with GH or the thyroid gland function.

Statistical analysis

Analysis software is R studio version 3.2. Differences in Free T4 and TSH between baseline visit and follow up visit were compared by paired t-test or Wilcoxon rank sum test as appropriate according to normality of the data. This was done to show if there was any significant difference change in their levels, which may indicate an effect related to growth hormone. Appropriate histograms were plotted to determine whether normality assumption was met. The difference was stratified by age, gender, and body mass index to consider the effect of these variables that may have on the TSH and Free T4 level. Correlation coefficients were also calculated to assess the relation of the change in TSH levels and Free T4 with age, body mass index, and duration of follow up as continuous variables. Spearman (or Pearson correlation coefficient was used as appropriate. Mcnemar test was used to assess proportions of individuals with TSH above upper limit (0.5 – 5) or T4 levels below lower limit (10 -26 pmol/L)

RESULTS

Demographics for the included patients at base line is shown in Table 1.

Table 1. Demographics of the patients included in the current case-series study

Age (years)	6.3 [4 – 9.5]
BMI (Kg/m²)	15.88 [13.88 – 16.39]
Weight (Kg)	17 [13 – 23]
Gender	
Male	97 (65.5%)
Female	51 (34.5%)
Free T4 at baseline (pmol/L)	15.9 [14.8 – 17.3]
TSH at baseline	2.24 [1.71 – 3.65]
Follow up duration (years)	3 [2 – 5 years]

Data is shown as mean [Inter Quartile Range] for continuous variables and as count (Percentage) for categorical variables

Data show that the average age for the included children was 6.3 years with an interquartile range of 4 -9.5. None of the children was obese (BMI <25 Kg/m2). Most of the children were males (65.5%). The median follow up period was 3 years with an interquartile range of 2 to 5 years.

Free T4 data were missed in 10% of the patients at base line and 34% of the patients at the follow up.

There was no significant difference between T4 levels at base line and T4 at the follow up visit (Table 2). Although there was a trend towards decrease in Free T4 level (mean levels were lower by 0.12 at follow up but 95% C.I did not confirm such as an association [-0.58 – 035]. Regarding TSH level, there was no significant difference between TSH levels at baseline and TSH levels at follow up, although there was a trend towards an increase in TSH levels in males and females, but it did not reach statistical significance (P > 0.05).

Table 2. Comparison of T4 and TSH levels

	Total		
	Baseline	Follow up visit	P value
Free T4 (pmol/L)	15.99 (2.11)	16.02 (2.49)	0.61
TSH	2.76 (1.87)	2.93 (2.16)	0.37
Females			
Free T4 (pmol/L)	15.95 (2.08)	16.69 (2.74)	0.029**
TSH	2.88 (2.19)	3.33 (2.95)	0.21
Males			
Free T4 (pmol/L)	16.01 (2.13)	15.58 (2.21)	0.27
TSH	2.7 (1.68)	2.72 (1.58)	0.93

Data is shown as mean (SD)

Interestingly, there was a significant difference in free thyroxin levels in females (Table.2) where free T4 was higher in the follow up visit by 0.82 pmol/l (95% C.I -1.53 to 0.1). However, this was not accompanied by a notable change in TSH. This is illustrated in Figure 2. There was no significant difference in TSH, Free T4 levels between baseline and follow up in males (Table.2)

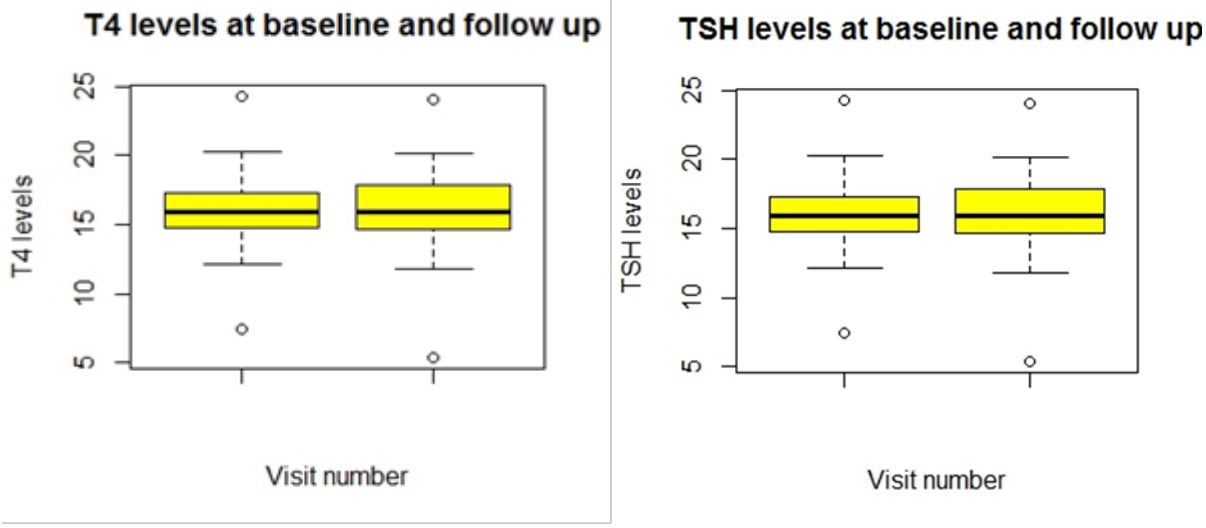

Figure 1. Association between TSH and T4 levels at baseline and follow up

Figure1 shows that T4 and TSH levels did not differ significantly between baseline and follow up (P > 0.05) as medians seem comparable to each other.

Correlation

There was no correlation between the weight of the children and difference in T4 and TSH at two visits (P > 0.05). Moreover, there was no significant correlation between age or body mass index with either T4 or TSH. P values were greater than 0.05 for all tests.

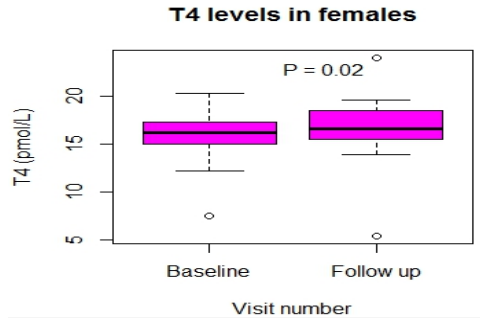

Figure 2. Association between T4 levels at baseline and follow up in females

On the other hand, by looking at data from another point of view, Mcnemar test was performed to determine if the proportion on individuals with TSH and Free T4 levels above normal limit changed significantly after follow up. Patients with Free T4 levels above normal limit, although higher at the follow up did not change significantly (P = 0.6). All patients had TSH below upper normal level and none of them had TSH above upper normal level at follow up.

Another interesting finding was a negative correlation between duration and Free thyroxin (T4) at the follow up visit (P = 0.006). This is an interesting finding as it may indicate that growth hormone can cause a decrease in T4 levels and this effect is related to the duration of GH therapy. This is illustrated in the following table.

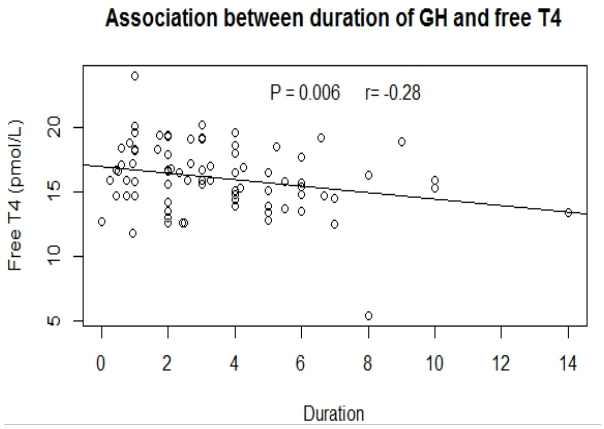

Figure 3. Correlation between free T4 levels and Duration of follow up in years

DISCUSSION

As known in previous literature growth hormone treatment can cause the incidence of developing central hypothyroidism, or somehow might affect the levels of thyroid stimulating hormone (TSH) or the free thyroxine (FT4).

FT4

Through the administration of GH, duration of therapy increased. The data conducted by this study provide a strong correlation that free T4 level was decreased according to the duration of follow up in years , as shown in figure 3 (P=0.006). This significant value illustrates that the more the patient is on growth

hormone, the lower the FT4 levels will get, other studies confirm the same results. [3-6]

From another viewpoint, males' FT4 levels as indicated in table 2 showed a slight reduction in FT4 levels between the baseline and follow up. Nevertheless, the mean is still within the normal range according to the British Thyroid Foundation [7], therefore, it does not indicate the development of central hypothyroidism. Similar study support our findings [6], on the other hand, another study presented 17 children who developed hypothyroidism [5].

On the other hand, conversely and surprisingly, an unexpected increase in free T4 levels in females oppose our hypothesis (table2). No literature found with similar findings, therefore, a suggested reason is the high rate of missing data of FT4 in the follow up visits as it was calculated to be 34% .

TSH

Another hormone that is of our concern is the TSH as it is the main hormone for stimulating the thyroid gland. It was hypothesized that GH treatment can lead to an increase in TSH levels, conversely many studies found no changes that is of any significance. Nevertheless, different studies had conflicting results as most of them reviled a non-significant slight increase (table2) or slight decrease in TSH(4-6,8,9).

Other

As to age, height, weight, and BMI nothing significant in their relation to hormones levels were found, which is somehow expected as many studies showed no concern regarding demographic data while the rest indicated nothing significant [4][4].

Limitations

The study was conducted at a single center; thus, results cannot be generalized in Saudi Arabia. Data were collected from an electronic patient's profiles that are self-entered. Moreover, 34% of FT4 follow up visits were missing.

CONCLUSION

The duration of growth hormone therapy seems to be associated with a lower T4 levels at the follow up visit. On the contrary, growth hormone seems to be associated with a slight increase in T4 levels in females only. Also, growth hormone therapy has no significant effects on neither TSH nor BMI. The incidence of central hypothyroidism during the GH therapy in children with growth hormone deficiency should be taken into account when starting GH treatment.

REFERENCES

[1] Persani L. Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges. The Journal of Clinical Endocrinology & Metabolism. 2012 Jul 31;97(9):3068-78.

[2] Gupta, V., & Lee, M. (2011, July). Central hypothyroidism. Indeian Journal of Endocrinology & Metabolism. S99–S106. doi: 10.4103/2230-8210.83337

[3] Căpraru, O., & Paşcanu, I. (2014). Thyroid function during the first year of recombinant human growth hormone therapy in short stature children. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi., 118(2), 307–14. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25076692

[4] Jørgensen, J., Pedersen, S., Laurberg, P., Weeke, J., Skakkebaek, N., & Christiansen, J. (1989). Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine-substituted central hypothyroidism. The Journal of clinical endocrinology and metabolism., 69(6), 1127–32. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2685007

[5] Moayeri, H., Hemati, A., Bidad, K., & Dalili, H. (2015). Effects Of Growth Hormone Replacement Therapy On Thyroid Function Tests In Growth Hormone Deficient Children. Acta Medica Iranica, 46(6), 473–476. Retrieved From Http://Acta.Tums.Ac.Ir/Index.Php/Acta/Article/View/3522

[6] Smyczynska, J., Hilczer, M., Stawerska, R., & Lewinski, A. (2010). Thyroid function in children with growth hormone (GH) deficiency during the initial phase of GH replacement therapy - clinical implications. , 3, . Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858102/

[7] Foundation, B. T. (2016). Thyroid function tests. Retrieved January 5, 2017, from http://www.btf-thyroid.org/information/quick-guides/97-thyroid-function-tests

[8] Giavoli, C., Porretti, S., Ferrante, E., Cappiello, V., Ronchi, C., Travaglini, P., … Beck-Peccoz, P. (2004). Recombinant hGH replacement therapy and the hypothalamus-pituitary-thyroid axis in children with GH deficiency: When should we be concerned about the occurrence of central hypothyroidism? Clinical endocrinology., 59(6), 806–10. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14974926

[9] Seminara, S., Stagi, S., Candura, L., Scrivano, M., Lenzi, L., Nanni, L., … Chiarelli, F. (2005). Changes of thyroid function during long-term hGH therapy in GHD children. A possible relationship with catch-up growth? Hormone

and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme., 37(12), 751–6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/16372229