# CHANGES IN BODY COMPOSITION AND LIPID PROFILE IN GROWTH HORMONE DEFICIENT CHILDREN DURING GROWTH HORMONE TREATMENT

Thesis

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# التغيرات فى تكوين الجسم وتوزيع الدهون فى الأطفال المرضى بنقص هرمون النمو أثناء العلاج بهرمون النمو

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# Introduction

Physiologic effects of growth hormone (GH) extend beyond the stimulation of linear growth during childhood and adolescence. These effects include building and sustaining lean body mass, facilitating the utilization of fat mass for energy needs, and maintaining bone mineral density. These non growth effects of GH appear to be important throughout life. Children and adults with severe GHD demonstrate marked reduction in lean body mass, increases in percent body fat, and subnormal bone mineral density. Replacement of GH attenuates these abnormalities, though it remains unknown whether it does so completely ***(Aaron et al., 2000)***.

Growth hormone deficiency (GHD) is associated with an accumulation of abdominal visceral fat which is linked to reduced insulin sensitivity and increased serum lipid concentrations in children, GH therapy accelerates lean tissue accrual especially water and protein compartments but has a smaller effect on reducing fat mass ***(Roemmich et al., 2001).***

There are contrasting reports about the occurrence of cardiovascular risk factors in children with GHD, some have found hypercholesterolemia whereas others have not ***(Gleeson et al., 2002).***

## Aim of the work

This study aims at elucidating the short term changes in body composition and fat distribution in GHD children during growth hormone treatment. Concomitant changes in lipid profile will also be studied.

# Contents

# List of Abbreviations

| | | |
|---|---|---|
| ACTH | : | Adrenocorticotrophic hormone |
| ALS | : | Acid labile subunit |
| AMP | : | Adenosine monophosphate |
| ATP | : | Adenosine triphosphate |
| ATT | : | Arginine tolernce test |
| BIH | : | Benign intracranial hypertension |
| BMC | : | Bone mineral content |
| BMD | : | Bone mineral density |
| BMI | : | Body mass index |
| cAMP | : | Cyclic adenosine monophosphate |
| CDC | : | Centers for Disease Control |
| CE | : | Cholesterol esterase |
| CNS | : | Central nervous system |
| CT Scanning | : | Computerized tomographic scanning |
| DEXA | : | Dual energy x-ray absorptiometry |
| EEG | : | Electroencephalogram |
| FFAs | : | Free fatty acids |
| GH | : | Growth hormone |
| GHD | : | Growth hormone deficiency |
| GHRH | : | Growth hormone releasing hormone |
| GHRPs | : | Growth hormone releasing peptides |
| HDLC | : | High density lipoprotein cholesterol |
| hGH | : | Human growth hormone |
| HSDS | : | Height standard deviation score |

| | | |
|---|---|---|
| HSL | : | Hormone sensitive lipase |
| Ht. | : | Height |
| IGFBp | : | Insulin like growth factor binding proteins |
| IGFs | : | Insulin like growth factors |
| IGHD | : | Idiopathic growth hormone deficiency |
| IM | : | Intramuscular |
| ITT | : | Insulin tolerance test |
| LDLC | : | Low density lipoprotein cholesterol |
| LpL | : | Lipoprotein lipase |
| MPHD | : | Multiple anterior pituitary hormone deficiency |
| MRI | : | Magnetic resonance imaging |
| NAD | : | Necotinamide adenine dinucleotide |
| NADH | : | Reduced Necotinamide adenine dinucleotide |
| PRL | : | Prolactin |
| Prop-1 | : | Prophet of pit-1 |
| rhGH | : | Recombinant human growth hormone |
| Rph | : | Rathke's pauch homeobox |
| SC | : | Subcutaneous |
| SD | : | Standard deviation |
| SDS | : | Standard deviation score |
| SGA | : | Small for gestational age |
| SS | : | Somatostatin |
| TC | : | Total cholesterol |
| TG | : | Triglycerids |
| TSH | : | Thyroid stimulating hormone |
| WSDS | : | Weight standard deviation score |
| Wt | : | Weight |

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## Discussion

The physiologic effects of growth hormone (GH) extend beyond stimulation of linear growth during childhood and adolescence. These effects include building and sustaining lean body mass, facilitating the utilization of fat mass for energy needs and maintaining bone mineral density. These non growth effects of GH appear to be important throughout life. Children and adults with severe growth hormone deficiency (GHD) demonstrate marked reductions in lean body mass, increases in body fat percent, and subnormal bone mineral density. Replacement of GH attenuates these abnormalities, though it remains unknown whether or not it does so completely ***(Aaron et al, 2000).***

There are contrasting reports about the occurrence of cardiovascular risk factors in children with GHD, some have found hypercholesterolemia, whereas others have not ***(Gleeson et al., 2002).***

This study was conducted on twelve children with GHD (8 males and 4 females) and ten (7 males and 3 femalesl) apparently healthy children as a control group. The aim of this work was to evaluate the effect of GH on body composition in those patients over a period of six months. This was done by

measuring lean tissue percent, fat tissue percent and bone mineral density Z-score using DEXA (dual energy x-ray absorptiometry) before and after six months of GH therapy in patients and once in the control group.

Our study also aimed to evaluate the effect of GH on lipid profile by measuring total cholesterol (TC), high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC) and triglycerides (TG) over the same period.

The mean age of GHD patients was 12.9 ± 3.6 years. And the mean bone age SDS was 0.03 ± 0.04, while the mean statural age was 8.8 ± 3.1 years.

The control group was matched with patients as regards sex and statural age. They were chosen from sibs of GHD patients, their height and weight were within normal limits ± 2 SD from mean for age and sex. The mean age of the control group was 9.7 ± 2.5 years.

In a study done to evaluate the effect of GH on body composition and fat distribution in six GHD prepubertal children during GH therapy, ***Roemmich and Coworkers, (2001)*** found significant increase in height SDS from –1.4 ± 0.5 before treatment to –0.9 ± 0.5 after 6 months of treatment

($p<0.001$) and weight from 35.7 ± 3.4 before treatment to 40.1±3.9 after six months of growth hormone therapy ($p<0.001$).

***Wolfgang et al., (2005)*** demonstrated gaining in height SDS ($p \leq 0.003$) and weight SDS ( $p \leq 0.003$) in GHD children treated with human growth hormone (hGH) for 2 years. Also ***Sas et al., (2000)*** found that height SDS increased significantly during GH treatment of GHD children ($p< 0.001$). Also significant increase of height SDS of 0.42 ± 0.16 ($p= 0.03$) was also found by ***Grotel et al., (2005)*** in the group treated with hGH over a period of 2 years.

In our study we found a significant increase in height SDS from a mean ± SD of -4.09±1.61 before treatment to -3.49±1.49 six months after GH therapy with a gain of 0.5 SD ($p=0.002$) while there was no significant difference in weight SDS or weight for height centile.

In our patients a redistribution of lean and fat tissue occurred on GH therapy with no net increase in body weight. This could be attributed to nutritional status as all our patients come from a low socioeconomic class.

Also, in our study there was no significant increase in body mass index (SDS).

In accordance to our study ***Wolfgang et al., (2005)*** found no significant changes in body mass index (SDS).

While in discordance to our study, ***Sas et al., (2000)*** demonstrated a significant increase in body mass index (SDS) from -0.8 ± 1.4 before treatment to -0.2 ± 1.4 after 6 years of growth hormone therapy and this increase in body mass index can be explained by the longer duration of growth hormone therapy, as our patients were treated for 6 months only while the patients in **sas et al., (2000)** study were treated for 6 years.

In this study we found a statistically significant decrease in hip and waist circumference with a mean ± SD decrease in waist circumference from 62.25 ± 8.06 cm to 59.08 ± 8.58 cm (p=0.002), and a mean decrease in hip circumference from 71.21 ± 9.77 cm to 67.81 ± 9.69 cm (p=0.002).

In a study done by ***Boguszwski, (2005)*** on 18 GH deficient adults revealed a statically significant decrease in waist circumference of -1.84 ± 3.31cm (p = 0.03) occurred after one year of GH therapy.

In discordance to our study ***Roemmich et al., (2001)*** study on six prepubertal children with GH deficiency revealed a statistically significant increase of waist circumference from

28.1 ± 1.2 cm to 30.4 ± 1.3 cm (p= 0.03) and hip circumference from 21.8 ± 0.8 cm to 22.7 ± 0.9 cm (p= 0.04) after one year of GH therapy.

Our study revealed that total cholesterol (TC), triglycerides (TG) and low density lipoprotein cholesterol (LDLC) significantly decreased after six months of GH treatment while high density lipoprotein cholesterol (HDLC) significantly increased with mean ± SD for TC from 185.00 ± 56.93 mg/dl to 169.17± 54.58 mg/dl, TG from 123.58 ± 66 mg/dl to 62.25 ± 23.03 mg/dl, HDLC from 41.75 ± 19.87 mg/dl to 68.33 ± 14.90 mg/dl LDLC from 124.67 ± 34.06 mg/dl to 98.92 ± 28.90 mg/dl.

Also, our study revealed no statistically significant difference before and after treatment as regards TC SDS but the increase in HDLC SDS and the decrease in LDLC SDS and TG SDS was statistically significant ($p < 0.05$).

***Sas et al., (2000)*** concluded that during 6 years of GH therapy TC, LDLC and other atherogenic indexes significantly decreased, whereas HDLC remained unchanged with mean ± SD change of TC from 181.3 ± 33.3 mg/dl to 166.5 ± 25.9 mg/dl, LDLC from 147.3 ± 29.6 mg/dl to 129.6 ± 33.3 mg/dl and HDLC from 51.8 ± 11.1 mg/dl to 46.2 ± 11.1 mg/dl.

Also, ***Roemmich et al., (2001)*** found that serum cholesterol concentration decreased in a GH deficient group from baseline to 6 months on GH therapy whereas triglyceride concentration was unchanged.

In another study, a statistically significant decrease in LDLC ($p < 0.04$) and LDLC: HDLC ratio occurred after 12 months of GH therapy ***(Louis et al., 2003).***

***Bojuszewski et al., (2005)*** performed a study to prove that one year of GH replacement therapy improves body composition, bone mineral density and lipid profile of GHD adults. Their study revealed that HDLC and TG didn't change significantly with therapy, while there was a statistically significant reduction in TC from 190 $\pm$ 36.3 mg/dl to 171.93 $\pm$ 39.6 mg/dl ($p= 0.003$) and LDLC from 130.3 $\pm$ 36 mg/dl to 108.57 $\pm$ 36.3 mg/dl ($p = 0.004$).

***Kamel et al., (2000)*** found no significant effect on lipid profile in obese prepupertal children a part from a transient decrease in LDLC after 6 weeks of GH treatment.

As regards body composition, our study revealed a significant increase in lean tissue percent with a mean $\pm$ SD increase from 74.67 $\pm$ 12.36 % to 79.50 $\pm$ 10.32 % ($p = 0.002$) in patients after a period of six months GH therapy. When