Original Article

The effects of growth hormone replacement therapy on insulin, lipid profile and calcium in children with growth hormone deficiency

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Summary:

Background: Growth hormone has multiple effects on the overall form and function of growing body. Aside from these growth stimulating functions, it has marked effects on energy metabolism, it acts on fat cells to reduce the amount of stored fats, promotes protein synthesis in cells and plays a role in regulating the sugar levels in the blood.

Objective: to investigate the effect of growth hormone replacement on lipid profile, insulin level, glucose and calcium level in patients with growth hormone deficiency (GHD).

Method: A prospective study of 49 children; 37 boys and 12girls with a mean age(13.5±3.3)years attending the Children Welfare Teaching Hospital/ department of endocrinology with short stature proved to have an isolated growth hormone deficiency (other causes of short stature were excluded), with 20 healthy children as control were studied over a period of 11 months(from Oct. 2007 to Aug 2008). . Insulin level ,serum lipid ,blood glucose and serum calcium were estimated for control group and for those with isolated(GHD) prior to and post 11 months of growth hormone replacement therapy(GHRT) .

Result: Insulin levels were (8.1 µIU/L) in patients with GHD and elevated significantly to(17.4 µIU/L) after GHRT, without any unfavorable effects on blood glucose.Pre treatment lipid profile values were higher (total cholesterol T-C 4.1 mmol/L ,triglyceride TG 1.5 mmol/L ,low density lipoprotein LDL 2.5 mmol/L, very low density lipoproteins VLDL 0.7mmol/L, than the control group (T-C 3.9, TG 1, LDL 1.8, VLDL 0.5) .Significant improvement was occurred after treatment (T-C=3.6 , TG=1.2, LDL=1.6 , VLDL=0.5); while pretreatment high density lipoproteins HDL was significantly lower (1 mmol/L) than in control (1.6) which improved significantly post treatment to (1.5) mmol/L. Significant decrement of Post-treatment serum Ca mmol/L (2) noticed as compared to controls (2.3) and to its baseline values (2.2). Significant improvement of height= -3.7 and body mass index {BMI} =-1.1 Z score to-2.9and 0, 7 respectively were noticed post- treatment.

Conclusion: Several metabolic derangements are associated with (GHD) which could be managed effectively with (GHRT).

Key words: Growth hormone, insulin, lipid profile.

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Introduction:

Growth hormone (GH) is a 191-amino acid, single chain polypeptide hormone which is synthesized, stored, and secreted by the anterior pituitary. GH stimulates growth and cell reproduction. It increases the formation of bone, increases muscle mass, promotes fat breakdown (lipolysis), and stimulates the immune system [1,2]. Human GH has been used in the treatment of growth disorder in children for the last 50 years. The main therapeutic goal of GH treatment in children is the normal growth during childhood; with achievement of adult height within normal range. GH may influence metabolism and action of many substances, including other hormones and medications. GH may affect the hypothalamic-pituitary-thyroid axis, and the induction of hypothyroidism by GH treatment has been described [3]. GH also induces transient resistance to the action of insulin, this effect of GH increases circulating level of insulin but not that of glucose [4].Whoever, Particular attention has been drawn to the diabetogenic effect, because excessive GH secretion may lead to type 2 diabetes mellitus [5]. Carrol et al., 1998, suggested a predisposition for premature atherosclerosis in children with GHD (6); which was previously associated with abnormalities of lipid metabolism [7, 8,9]. This study aimed to shed a light on the metabolic effects of GH deficiency on the risk of exposing to an inflammatory disease, in addition to the monitoring of the efficacy of GH replacement therapy via the measurement of height and body mass index.

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Patients and Methods:

Among 150 patients with different causes of short stature (SS) Children and adolescents were defined as short stature cases if their heights were below the third percentile for their age and sex according to the height/age curves published by the National Center for Health Statistics (NCHS), [10] attending the department of endocrinology/Children Welfare Teaching Hospital Forty-nine children 37 boys and 12 girls aged 13.5 ± 3.3 years with isolated (GHD) after exclusion of other causes of short stature were selected to be studied and followed up over a period of 11 months. Children with multiple pituitary hormone deficiency are excluded also in order to avoid other possible influences on glucose and lipid metabolism. In order to diagnosis GHD growth hormone GH was assessed by two dynamic GH tests, blunted peak GH response < 10 ng/ml to clonidine and to glucagon tests. The study was approved by the scientific ethics committees and Informed consent was obtained from the children's parents. The patients enrolled had never received any kind of hormonal replacement therapy or drug before. . GHD children were giving GHRT (recombinant human GH rhGH) as subcutaneous once -daily dose of 0.03-0.04 mg/kg per day. A group of 20 healthy children (15 male, 5 female) with similar age and sex distribution were studied as controls. Anthropometric measurements; Height and weight were expressed in height for age Z-scor HAZ, and body mass index BMI was calculated as (weight/ (height) ^{2} - {kg}/m^2) [11,12]; Left wrist x-ray were done for bone age estimation [13] . Blood samples for (Insulin, glucose, Lipid profile, Ca) were taken from the children with GHD before the beginning of GH treatment (baseline) and after 11 months of the treatment, the same thing for their height and weight. ELISA tests for GH, insulin, and enzymatic colorimetric assay for serum lipid profile, glucose, and Ca were carried out on all studied groups. Insulin resistance was evaluated by the homeostasis model assessment insulin resistance index (HOMA-IR), applying the Matthews formula (fasting serum insulin *fasting plasma glucose/22.5) mmol/l. [14]. Statistical analysis: The statistical analysis was done by using Excel application and through the SPSS program (Statistical Package for Social Sciences), version 13. Statistical analysis was performed using Pearson chi-square test a (P value) (Sorlie, 1995) [15]. The comparison of significance (p- value) in any test

S=significant difference (p<0.05)

HS=highly significant difference (p<0.01)

NS=no significant difference (p>0.05)

Results:

Fasting serum insulin, baseline data observed in mean concentration (µIU/L) showed no significant differences among GHD patients (8.1) in comparison with controls (8.3). After treatment duration fasting serum insulin was significantly elevated among GHD patients (17.4) compared to controls (8.3) and to its baseline values (8.1) (p<0.001). Insulin resistance or HOMA-IR (1.83 ± 1.27 vs. 4.33 ± 2.38) increased in patients after treatment when compared with baseline values (P<0.001). While glycemia was unmodified (89.66 ± 6.13 vs. 93.23 ± 6.27). As shown in Table 1. lipid profile data concentrations (mmol/l) were significantly higher among GHD patients {(total cholesterol T-C=4.1), (triglyceride TG=1.5), (low density lipoprotein LDL-C=2.5), (very low density lipoprotein VLDL-C=0.7) and median value of (T-C/HDL-C=4.22), (p<0.001). Whereas mean value of serum (high density lipoprotein HDL-C was significantly lowered =1)} than in controls {(T-C=3.9), (TG=1), (LDL-C=1.8), (VLDL-C=0.5) (T-C/HDL-C=2.35) and (HDL-C=1.6)} (p<0.001). Significant improvement observed through out GHRT duration in GHD patients {(T-C=3.6), (TG=1.2), (LDL-C=1.6), (VLDL-C=0.5) (T-C/HDL-C=2.31) and (HDL-C=1.5)} compared to baseline values (p<0.001). Table 2.Ca, baseline data concentration (mmol/l) expressed as median value reveled that; baseline serum Ca was a slightly lowered (not significant) in GHD patients (2.2) than controls (2.3), this slightly lowered value was further and significantly decreased among GHD cases (2) compared to controls and to its baseline values (p<0.001). GHRT significantly improved HAZ and BMIZ in GHD patients respectively {(-2.9), (-0.7)} than it was pretreatment {(-3.7), (-1.1)}, which were significantly lowered than normal controls values {(0.2), (0.3)} (p<0.001). As shown in Table 3.

Table 1: parameters pretreatment and post treatment compared to controls

Parameter	Baseline pre treatment	Post treatment	Controls
Insulin(µIU/L)	8.1(±2.5)	17.4(±3.2)** a d	8.3(±4.7)
Fasting glycemia (mg/dl)	89.66 ± 6.13	93.23 ± 6.27	79.61 ± 17.86
Homa-IR	1.83 ± 1.27	4.33 ± 2.38** d	2.13 ± 2.66

Table 2:

Parameter	Baseline pre treatment	Post treatment	Controls
TC(mmol/l)	4.1(±4.1) ℓ a	3.6(±0.3) ** a d	3.9(±0.3)
TG(mmol/l)	1.5(±0.4)** a	1.2(±0.3) • a d	1(±0.2)
HDL-C (mmol/l)	1(±0.2)** a	1.5(±0.2) ** d	1.6(±0.3)
LDL-C (mmol/l)	2.5(±0.3)** a	1.6(±0.3) ** d	1.8(±0.5)
VLDL-C (mmol/l)	0.7(±0.2)** a	0.5(±0.1)** a d	0.5(±0.5)
TC/HDL	4.22(2.3-8.1)** a	2.31(1.75-4.11) ** d	2.35(1.55-4.1)

Table 3:

Parameter	Baseline pre treatment	Post treatment	Controls
Ca (mmol/l)	2.2(1.7-2.4)	2(1.7-2.4)** ⁿ ₫	2.3(1.9-2.6)
HAZ	-3.7(± 1.3)** ª	-2.9(±1.3) ** ⁿ ₫	0.2(±1.3)
BMIZ	-1.1(1.5)** ª	0.7(1.2)* ⁿ ₫	0.3(1.2)

*P<0.05, **P<0.001, ℓ P<0.035, • P<0.017

Data expressed as mean (SD) expect for GH, HDL/TC, Ca which are median.

ª Baseline significantly different from control.

ⁿ post treatment significantly different from control.

₫ post treatment significantly different from Baseline

Discussion:

There was no significant difference at baseline mean value for serum insulin concentration between GHD cases and controls. This is in agreement with the results of Walker et al.,; Hepatalla et al [16, 17]., whom reported that; children with GHD do not have insulin resistance at baseline. After treatment serum insulin was significantly higher in GHD cases compared to controls. This result is in agreement with Radetti et al, [18] who found a significant decrease in insulin sensitivity was detected during the first year of GH therapy. This result was also in concordant with the results of Cutfield et al. [19], who mentioned that the incidence of diabetes mellitus or impaired glucose tolerance was increased in children and adolescents receiving GH treatment. Further more the observed results are in combatable with Walker et al., Hepatulla et al. [16, 17], who reported that, short term GH-replacement was associated with development of insulin resistance and peripheral hyperinsulinemia, even if the insulin levels remained with physiological range of normal control children. This result was also in concordant with Salerno et al., [20]who observed a mild increase in insulin resistance after 2 year of GH-treatment. This result with compensation hyperinsulinemic response during treatment that may show probable tendency towards reduce insulin sensitivity as a worsen effect of GHRT i.e. contra insulin effects or may represent a compensating effect as a reflection of the anabolic process of somatic development ,and interpreted under the known physiological effects of GH, since GH possess a direct insulin antagonistic effect . Acute administration of GH causes temporary insulin like effect on glucose up take. In contrast chronic exposure to GH leads to insulin resistance, hyperglycemia and increased hepatic gluconeogenesis and glycogenolysis . The later effects may be indirectly caused by the GH induced lipolysis and elevated plasma free fatty acids that inhibit insulin activity. Previous studies concerning glucose tolerance in GHD treated children have also shown that glucose tolerance does not worsen, at the expense, however, of raised serum insulin levels (Walker et al ., Heptulla et al ., Cohen et al ., Hokken-Koelega et al [16,17,21,22]., which is an indirect sign of insulin resistance In the current study, there were significant differences in the baseline of lipid profile values between GHD cases and healthy controls with higher values of (TG, TC, LDL-C, and VLDL-C) recorded in GHD cohort. This was partially in agreement with the results of other studies; Lanes et al., [23] who found increased LDL-C levels in GHD adolescents when compared with healthy controls. Lanes et al., [24]reported that, serum TG baseline concentration was significantly elevated among GHD patients, especially in GHD adolescents, in agreement too with the results of Ciresi et al., [25]who found a significant differences between GHD children and controls in (T-C, LDL-C). Furthermore, the current results also are in concordant with Glesson et al., [26]who found that T-C/HDL-C ratio was significantly higher in GHD children than in control, as well as adverse lipid profile (abnormal) at baseline in GHD cases. The current results of abnormal baseline lipid profile in GHD patients may reflect the defective of GH lipolytic activity, in this regard it is important to note that in GHD adolescent who discontinue GH treatment at completion of linear growth, there are unfavorable effects on body composition, glucose and lipid profiles, bone mineral density, and cardiac function (Drake et al., Tauber et al., Carrol et al.,) [27, 28, 29]. The present results are in disagree with the results of other studies, which does not reported any abnormalities in lipid profiles of GHD children at base line (Boot et al.,Lanes et al., Salerno et al) [20, 30, and 31].The study results indicated improvement in all aspects of the abnormal lipid profile after 11 months of GH therapy to normal levels in healthy controls, compared to pretreatment state, with a significant reduction in (T-C, LDL-C, VLDL-C,TC/HDL-C) levels and a concomitant slight decrease in TG value, with significant rise in HDL-C value. These results are in concordant with other studies; that reported improvement in lipid profile in GHD patient after treatment. Kuromaru et al. [32] reported a decrease in fat mass, LDL-C and TC, and an increase in lean mass and HDL-C after 6 months of GH treatment. In the same regard Ciresi et al., [25]confirmed improvement in lipid profile after 12 months of GH replacement compared with baseline, with a significant reduction in T-C, LDL-C, and TG levels, and a slight improvement in HDL-C. Furthermore the post-treatment results are in agreement with Glesson et al., [26], who also reported improvement in lipid profile after GH replacement, TC/HDL-C and TG improved after 3 months, but at 12 months respectively, for LDL-C and TC.In this study, the baseline results of serum calcium mean value was slightly lowered among GHD cases compared to control, although the differences were of no statistical significance. After treatment the results revealed a significant decrease in serum calcium

value among GHD cases compared to controls. This result was in accord with Stamoyannou et al. [33],who observed a significant decrease of serum calcium in GHD children after 6 months of GHRTsince GH influences enteroendocrine cell secretion, calcium absorption Shulman, [34], as a consequence increased bone turnover and influences linear growth, skeletal maturation, and mineral metabolism. In the same context GH is known to promote water and electrolyte transport and calcium absorption; as GHR is widely distributed in gastrointestinal tract especially in the epidermal cells, suggesting that GH and GHR could play an important role in the regulation of metabolism, growth, and differentiation of gastric mucosal cells. On the other hand, the present result was in disagreement with Boot et al., [30] result who found, serum calcium remained stable during the treatment duration of GHD cases. This decrease in serum calcium in GHD patients under GHRT may reflect the increased demand of calcium during treatment, since GH influences mineral metabolism, including calcium, as essential mineral for bones building. The baseline results of BMIZ and HAZ that represent the obvious manifestation of children somatic growth, were in accord with other studies that revealed GHD short stature children have a reduced linear growth and reduced lean body mass (Hintiz et al., Elamin,) [35,36]. This reduction of BMI and HAZ in GHD cases, as a clear picture of poor growth that results from impairments of several normal GH influences on liner growth, skeletal maturation, bone turnover and mineral metabolism Stamoyannou et al. [33]. The follow up results of the current study, revealed a significant improvement in BMI and HAZ among GHD cases compared to pretreatment state, these result were in compatible with the main therapeutic goal of GHRT in GHD children. which was previously recorded in several world wide studies, that revealed, the treatment with biosynthetic GH is successful in improving adult height in children with GHD (Reiter et al.,)[37] ; i.e. the un animously summarization of all physiologic effects of GH as an active stimulator of linear growth, and as an essential for normal accrual of lean mass Hardin et al [38].In addition, this significant improvement in height and weight, were in compatible with Rriter et al.,2006; Butler, 2007, whom reported, the greatest improvement in growth is seen in the first year of treatment in GHD children[37,39]. It is clear from this study that pathological changes seen in GHD patients may be contributed to an imbalance favoring abnormal metabolic conditions due to impaired normal GH physiological functions; and this may result in an increased susceptibility for premature atherosclerosis. GHRT follow up results showed; beneficial effects of treatment in elucidating metabolic and physiological disorders associated with GHD. In addition to Trend towards increase in insulin resistance as a side effect during treatment.

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