Growth Hormone & IGF Research 24 (2014) 150–154

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

# Corneal thickness in children with growth hormone deficiency: The effect of GH treatment

A. Ciresi [a], R. Morreale [b], S. Radellini [a], S. Cillino [b], C. Giordano [a,*]

[a] Biomedical Department of Internal and Specialistic Medicine (DIBIMIS), Section of Endocrinology, Diabetology and Metabolism, University of Palermo, Palermo, Italy
[b] Department of Experimental Biomedicine and Clinical Neuroscience, Ophthalmology Section, University of Palermo, Palermo, Italy

ARTICLE INFO

*Article history:*
Received 10 December 2013
Received in revised form 18 March 2014
Accepted 9 May 2014
Available online 24 May 2014

*Keywords:*
Growth hormone
Corneal thickness
GH treatment
GH deficiency

ABSTRACT

*Objective:* The eye represents a target site for GH action, although few data are available in patients with GH deficiency (GHD). Our aim was to evaluate central corneal thickness (CCT) and intraocular pressure (IOP) values in GHD children to assess the role played by GHD or GH treatment on these parameters.
*Design:* In 74 prepubertal GHD children (51 M, 23 F, aged 10.4 ± 2.4 years) we measured CCT and IOP before and after 12 months of treatment. A baseline evaluation was also made in 50 healthy children matched for age, gender and body mass index. The study outcome considered CCT and IOP during treatment and their correlations with biochemical and auxological data.
*Results:* No difference in CCT and IOP between GHD children at baseline and controls was found (all $p > 0.005$). GHD children after 12 months of therapy showed greater CCT (564.7 ± 13.1 μm) than both baseline values (535.7 ± 17 μm; $p < 0.001$) and control subjects (536.2 ± 12.5 μm; $p < 0.001$), with a concomitantly higher corrected mean IOP (15.6 ± 0.7 mm Hg; $p < 0.001$) than both baseline (12.5 ± 0.8 mm Hg; $p < 0.001$) and controls (12.3 ± 0.5 mm Hg; $p < 0.001$), without correlation with auxological and biochemical parameters.
*Conclusions:* 12 months of GH treatment in children with GHD, regardless of auxological and biochemical data, affect CCT and IOP. Our findings suggest careful ocular evaluation in these patients to prevent undesirable side effects during the follow-up.



## 1. Introduction

Although the intrinsic mechanism of growth hormone (GH) actions on eyes is still not fully known, it is well established that the eye represents a target site for GH action. GH may have endocrine, autocrine or paracrine roles in ocular development and growth [1]. In this connection, GH is present in the human retina and vitreous fluids [2] and Harvey et al. identified GH immunoreactivity in the retina of chicks, mice and rats, suggesting a role for GH in neurogenesis or ocular development [3–5]. The role of GH in retinal function is supported by the evidence of optic nerve and disc dysfunction in patients affected by GH deficiency (GHD) [6,7]. Many years ago it was suggested that GH might facilitate a condition of glaucoma, demonstrated by higher GH levels after intravenous arginine administration in patients with open-angle glaucoma than in control subjects, supporting the hypothesis that increased plasma GH levels may interfere with regulation of ocular pressure [8]. In addition, the importance of GH action in ocular development is demonstrated by the ocular abnormalities that can occur in patients with pituitary GH excess or deficiency [7,9–12]. Elevated intraocular levels of insulin growth factor-I (IGF-I) in acromegalic patients have previously been reported [11] while in patients with primary GH insensitivity treated with IGF-I therapy, a greater average ocular dimension, including the average corneal curvature, than that observed in untreated patients has been demonstrated, further supporting the effect of IGF-I on ocular growth [13]. The only study that performed a complete ocular evaluation, including the measurement of central corneal thickness (CCT) and intraocular pressure (IOP), in children affected by GHD already under GH-treatment, concluded that an increased CCT, probably associated with a shorter axial length, can represent a sign of a delayed growth of the eye in these patients [14]. In addition, more recently Youngster et al. showed increased IOP in GH-treated children [15]. However, to the best of our knowledge, CCT and IOP have never been prospectively assessed in GHD patients, i.e. before and after GH treatment. The aim of this study was to evaluate CCT and IOP values in children with isolated idiopathic GHD at before and after 12 months of GH therapy.

* Corresponding author at: Section of Endocrinology, Diabetology and Metabolism, Biomedical Department of Internal and Specialistic Medicine (Di.Bi.M.I.S.), University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy. Tel.: +39 091 6552109; fax: +39 091 6552123.
*E-mail address:* carla.giordano@unipa.it (C. Giordano).

http://dx.doi.org/10.1016/j.ghir.2014.05.001
1096-6374/

## 2. Materials and methods

### 2.1. Patients

For the purpose of this study, 74 consecutive children (51 males and 23 females, mean age 10.4 ± 2.4 years) affected by newly diagnosed isolated idiopathic GHD coming to the Units of Endocrinology of the University of Palermo from Jan 1st 2010 to December 31st 2012 were prospectively enrolled. Fifty healthy children, matched for age (mean age 11 ± 2.6 years), gender and body mass index (BMI), were recruited as controls among the siblings of the patients and the children of medical and paramedical personnel of the Department and their relatives.

All children evaluated were in the 1st stage of sexual development according to the criteria of Marshall and Tanner [16]. The diagnosis of GHD was established by the clinical, auxological and biochemical criteria of the GH Research Society [17]. All patients underwent IGF-I assessment, an insulin tolerance test (ITT) and a GHRH plus arginine (GHRH-Arg) test. GHD was demonstrated by the failure of GH to respond to the two stimuli, with GH peaks below 10 and 20 μg/l, respectively. The subjects with a diagnosis of GHD received GH once daily at bedtime with a pen injection system. The initial daily dose was 0.025 mg/kg. During the study, the GH dose administered was adjusted in order to maintain serum IGF-I levels within the normal range for age, with a maximum dose of 0.035 mg/kg. Children with a therapy follow-up of less than 12 months were excluded from this analysis. Similarly, children with already known ocular clinically relevant disease, severe refractive errors, or family history of ocular hypertension or glaucoma were excluded from the analysis.

### 2.2. Study design

This was an analytical, prospective study to analyze CCT and IOP and their relationship with biochemical and auxological data in GHD children. In all subjects, according to our fixed internal protocol, we measured body height (standard deviation, SD), body mass index (BMI) and bone age. We calculated the ratio between the bone age and the chronological age (normal = 1) and we showed the data as a bone/chronological age ratio. All subjects underwent ophthalmological evaluation, including measurement of CCT and IOP by applanation tonometry. GHD children were evaluated at baseline and after 12 months of GH treatment, while controls were evaluated once at baseline. The study outcome considered CCT and IOP during treatment and their correlations with biochemical and auxological data. The Institutional Ethics Committee of the University of Palermo approved this study. At the time of first observation, an informed consent for the scientific use of the data was obtained from parents. This research has followed the Tenets of the Declaration of Helsinki.

### 2.3. Ocular evaluation

CCT was measured by very high-frequency ultrasonic contact pachimetry (Pachpen Accutome 24-5100) after local anesthetic instillation, with a sound velocity of 1640 m/s and a mean accuracy of ±5 μm. The value of CCT was performed taking the average of five consecutive pachimetry measurements.

IOP was measured by means of Goldmann applanation tonometry. A single ophthalmologist performed both examinations in all children.

We showed the CCT and IOP values as the average from both eyes.

### 2.4. Hormone and biochemical assays

During the entire study period, in our centralized laboratory the GH levels were assayed by immunoradiometric assays (Radim, Pomezia, Italy), with an assay sensitivity of 0.05 μg/l. The intra-assay coefficients of variation (CV) were 2.5–3.9% and the inter-assay CV were 3.8–5.0%. Serum total IGF-I was assayed in the same laboratory with the ELISA method (OCTEIA IGF-I kit, IDS Inc., Fountain Hills, AZ, USA). The sensitivity of the method was 1.9 μg/l. The inter- and intra-assay CV values were 7–7.1 and 2.3–3.5% respectively, at IGF-I levels of 90.7–186 and 66.7–120.9 μg/l respectively. The normal ranges (males and females combined) of total IGF-I levels (μg/l) were the following: 12–108 (0–1 years); 13–100 (1–3 years); 26–280 (3–6 years); 85–230 (6–9 years); 98–404 (9–12 years); 142–525 (12–15 years); and 146–415 (15–20 years).

### 2.5. Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 was used for data analysis. Baseline characteristics were presented as mean ± standard deviation (SD) for continuous variables; rates and proportions were calculated for categorical data. Normality of distribution for quantitative variables was assessed with the Kolmogorov–Smirnov test. Differences between continuous variables were analyzed using the Mann–Whitney *U*-test, while differences between categorical variables were analyzed by using the $\chi^2$-test and Fisher's exact test, when appropriate. Differences between paired continuous variables in the GHD group (before and after 12 months of therapy) were analyzed using the Wilcoxon test. Correlations among continuous variables without normal distribution were determined using Spearman's test (non-parametric equivalent for Pearson test). A $p$ value <0.05 was considered statistically significant.

## 3. Results

All clinical and biochemical features of GHD children and control subjects are shown in Table 1.

### 3.1. GHD subjects at baseline vs. control subjects

Height, bone age, GH and IGF-I levels were significantly lower in GHD subjects than controls, as expected (Table 1). No significant difference in mean CCT values (535.7 ± 17 *vs.* 536.2 ± 12.5 μm; $p = 0.859$) was found (Fig. 1A). Similarly, no difference was found in IOP values (12.5 ± 0.8 *vs.* 12.3 ± 0.5 mm Hg; $p = 0.118$) between the two groups.

### 3.2. GHD subjects after 12 months of GH therapy vs. baseline

A significant increase in height, BMI and bone age was documented in GHD children after 12 months of therapy, as expected. Similarly, IGF-1 levels showed a significant increase (251.8 ± 100.8 *vs.* 90.34 ± 39.34; $p < 0.001$) in all GHD subjects from baseline to 12 months of therapy.

The analysis of the ocular parameters showed a significant increase in mean CCT values (564.7 ± 13.1 *vs.* 535.7 ± 17 μm; $p < 0.001$) in GHD children after 12 months of GH therapy than baseline values (Fig. 1B), with a concomitantly higher corrected mean IOP (15.6 ± 0.7 *vs.* 12.5 ± 0.8 mm Hg; $p < 0.001$).

No significant correlations among CCT at 12 months or the variation (delta) of CCT from baseline to 12 months of treatment and auxological (height SD, height velocity SD, BMI, bone age) and biochemical parameters (IGF-I SD) after 12 months or their delta were found (all $p > 0.05$; data not shown). Conversely, a significant inverse correlation was found between baseline CCT and its delta (Rho −0.656; $p < 0.001$). Grouping all children into those with lower (<the median value of 534 μm) and greater (≥the median value of 534 μm) baseline CCT, we found no significant difference in auxological and biochemical parameters (data not shown).

### 3.3. GHD subjects after 12 months of GH therapy vs. control subjects

GHD children after 12 months of therapy showed similar BMI, bone/chronological age ratio and IGF-I levels compared to control subjects (all

**Table 1**
Clinical, biochemical and ocular parameters of children affected by growth hormone deficiency (GHD) at baseline and after 12 months of GH treatment and control subjects.

| | GHD subjects at baseline (No. 74) | GHD subjects after 12 months of treatment (No. 74) | Control subjects (No. 50) | $p$ | $p^*$ | $p^{**}$ |
|---|---|---|---|---|---|---|
| | No. (%) | No. (%) | No. (%) | | | |
| Gender | | | | – | 0.752 | – |
| Males | 51 (68.9) | – | 32(64) | | | |
| Females | 23 (31.1) | – | 18(36) | | | |
| | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** | | | |
| Height (SD) | −2.12 ± 0.74 | −1.66 ± 0.73 | − 0.35 ± 0.31 | <0.001 | 0.015 | <0.001 |
| BMI (kg/m$^2$) | 17.5 ± 3.2 | 18.3 ± 3.1 | 18 ± 2.3 | <0.001 | 0.730 | 0.560 |
| Bone age (yrs) | 8.8 ± 2.9 | 10.8 ± 2.3 | 10.6 ± 2.2 | <0.001 | 0.008 | 0.629 |
| Bone/chronological age ratio | 0.79 ± 0.11 | 0.90 ± 0.06 | 0.97 ± 0.10 | <0.001 | 0.016 | 0.090 |
| IGF-I (μg/l) | 90.34 ± 39.34 | 251.8 ± 100.8 | 231.36 ± 88.72 | <0.001 | < 0.001 | 0.247 |
| Basal GH (μg/l) | 0.47 ± 0.64 | – | 4.44 ± 2.16 | – | < 0.001 | – |
| Peak GH during ITT (μg/l) | 3.15 ± 2.80 | – | 16.23 ± 5.12 | – | < 0.001 | – |
| Peak GH during GHRH plus arginine test (μg/l) | 9.32 ± 6.08 | – | 32.44 ± 8.33 | – | < 0.001 | – |
| Mean central corneal thickness (μm) | 535.7 ± 17 | 564.7 ± 13.1 | 536.2 ± 12.5 | <0.001 | 0.859 | <0.001 |
| Corrected mean intraocular pressure (mm Hg) | 12.5 ± 0.8 | 15.6 ± 0.7 | 12.3 ± 0.5 | <0.001 | 0.118 | <0.001 |

$p$ = difference between GHD subjects at baseline and GHD subjects after 12 months of treatment.
$p^*$ = difference between GHD subjects at baseline and control subjects.
$p^{**}$ = difference between GHD subjects after 12 months of treatment and control subjects.

$p > 0.005$), despite a still lower height (−1.66 ± 0.73 *vs.* −0.35 ± 0.31; $p < 0.001$).

When we compared the ocular parameters of GHD children after 12 months of therapy with those of control subjects, we found a significant difference in mean CCT (564.7 ± 13.1 *vs.* 536.2 ± 12.5 μm; $p < 0.001$) and corrected IOP (15.6 ± 0.7 *vs.* 12.3 ± 0.5 mm Hg; $p < 0.001$).

## 4. Discussion

In this study, aimed to evaluate whether CCT in GHD children is mainly determined by the condition of untreated GHD or by effects of exogenous GH, we found that 12 months of GH treatment significantly increase CCT and IOP values when compared with pre-treatment values.

We calculated correction values for IOP readings for CCT according to Doughty's meta-analysis [18]. In this connection, it is known that CCT can significantly affect IOP readings obtained using different measurement techniques, with conflicting conclusions. Normally hydrated, thicker corneas lead to higher IOP readings and thinner corneas to lower readings. Several studies in adults showed a lower CCT in some cases of normal-tension glaucoma and a higher CCT in cases of ocular hypertension [18,19]. For this reason, to determine an accurate value, IOP should always correct for CCT.

GH and IGF-I are known to be involved in ocular development [20]. The growth of the eye seems to play a role in the reduction of corneal thickness in the first years of life. Indeed, CCT in premature infants is greater than in full-term newborns and in the latter is significantly greater than in adults [21,22]. CCT in normal children from the age of 3 is similar to those reported in adults [21]. Normal subjects were found to show an average CCT of 515 ± 33 μm, with a significant decrease with age of 45 μm per decade [23]. In normal children the average CCT was found to be ranging from 529 to 555 μm [24–26], with a close correlation with values reported for adults [26]. In addition, CCT values appear stable over time and show a positive correlation with IOP [27,28].

Most of the studies performed on patients with alterations of the GH-IGF-I axis were limited to assessing the differences in the ocular parameters between GH or IGF-I-treated patients, untreated ones, and controls, without a prospective evaluation during the follow-up of treatment. Indeed, it is unclear whether the effect on the eye was caused by the GHD condition or GH treatment.

In this study, we decided to perform an ocular evaluation in GHD children before the onset of GH treatment and prospectively after 12 months, to highlight the role of the condition of hormone deficiency or GH treatment on CCT and IOP. The control group was evaluated once at baseline and this can be considered a limit of the study. However, we decided to perform the ocular evaluation in control subjects only once because the evidence that CCT in normal children, in the absence of any pathology, normally does not change over time [21].

We found that there is no difference in CCT and IOP between untreated GHD children and control subjects and this finding apparently contrasts with the few existing data in the literature [14]. Indeed, Parentin et al. showed that a greater CCT, associated with a shorter axial length, can represent a sign of delayed growth of the eye in GHD children [14,29]. However, the authors did not prospectively evaluate GHD children during GH treatment, but analyzed the ocular parameters in a group of patients already under GH treatment, and this bias could explain the different results. To reinforce this hypothesis, in our cohort of patients after 12 months of GH treatment a significant increase in CCT was observed. Therefore, GH treatment, and not the condition of GHD, seems to affect the ocular parameters evaluated. This finding is in line with the evidence that significantly higher values of CCT were found a few years ago in thirteen patients with acromegaly compared to that of the control group [9], suggesting a more important role of GH on the eye. Indeed, the effects of exogenous GH on synthesis of the extracellular matrix of sclera have been demonstrated [20]. In addition, the evidence that acromegalic patients with longer active and uncontrolled disease showed greater CCT values supported the hypothesis that GH may have stimulatory effects on the cornea as well as on other target organs. Similarly, in our patients IOP too is affected by GH treatment, in line with the data of Youngster et al., which showed an increase in mean IOP in GH treated children [15]. The hypothesis that the effect of GH on CCT is played through the rehydrating effect of GH treatment can not be ruled out [30,31].We agree with the conclusion of Youngster et al. that the clinical significance of the increase in IOP in these patients is unclear [15], as the IOP values recorded in our patients, even higher than baseline and control values, were still within the normal range [32]. Therefore, to date, the clinical consequences of the already known effect of GH on CCT and IOP, such as the risk of developing glaucoma, are likely only potential. We speculate that, based on the demonstrated effect of GH on CCT and on the effect of CCT on the IOP, the usefulness of a complete ocular evaluation, including the CCT measurement, in children who are under GH replacement treatment also for many years, is to make a correct diagnosis and any proper management of potential ocular hypertension in these patients, especially when their CCT markedly differs from the normal values. In this study children have been evaluated for a follow-up of only 12 months, showing an increase in CCT and consequently in IOP, although it remains in the normal range. However, with these data in mind, a longer period of GH therapy could probably further increases these values. In addition,

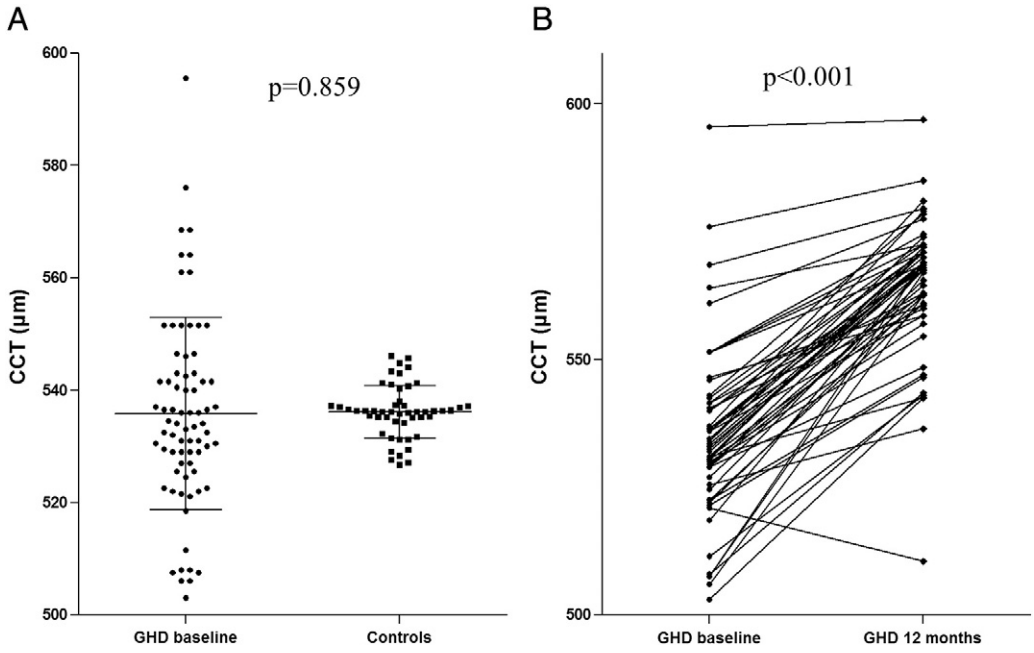


**Fig. 1.** Difference in mean central corneal thickness (CCT) among children with growth hormone deficiency (GHD) at baseline, before the start of GH treatment, and control subjects (1A) and difference in CCT before and after 12 months of GH treatment in GHD children (1B).

if these are the data of a population of children without a family history of ocular hypertension or overt glaucoma, we can speculate that a full ocular assessment should be especially done in case where there is a positive family history.

The absence of correlation between CCT and biochemical data could be explained with the evidence that all subjects enrolled in this study underwent a similar GH dose, between 0.025 to 0.035 mg/kg during the study, in order to maintain serum IGF-I levels within the normal range. Prospective large-scale studies aiming to consider the possible role of different GH doses on CCT changes could better clarify the effect of GH on corneal thickness. In addition, it would be interesting to perform a re-evaluation of ocular parameters after the discontinuation of GH to understand whether the abovementioned changes in CCT and IOP are reversible or not. For this reason, we will plan a careful ocular examination in all children after the discontinuation of therapy. Instead, the baseline CCT value seems to be a determinant for how the cornea reacts to GH replacement therapy. Curiously, children with lower CCT at baseline showed a greater increase in CCT after 12 months of GH therapy although this finding, in our opinion, does not seem to have a great clinical relevance. In fact, we found no significant difference in auxological or biochemical parameters between GHD children with lower and greater baseline CCT.

In conclusion, our data demonstrated that 12 months of GH treatment in children with GHD, regardless of auxological and biochemical data, affect corneal thickness and IOP. With this in mind, our findings suggest careful ocular evaluation in GHD children during GH treatment, with CCT and IOP measurements, to prevent the potential risk of undesirable side effects during the follow-up.

## Conflict of interest statement

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

## Author statement

The authors hereby confirm that neither the manuscript nor any part of it has been published or is being considered for publication elsewhere. By signing this letter each of us acknowledges that he or she participated sufficiently in the work to take public responsibility for its content.

## Acknowledgment

A special thanks to Dr. Daniele Monreale, who died after having brilliantly worked to the realization of this study.

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