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# Assessing The Potential of Somatotrophic Hormone/Growth Hormone for Craniofacial Development: A Systematic Review

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## Abstract

**Aim:** To assess the potential of growth hormone / somatotrophic hormone for craniofacial development. **Methods:** A literature review was performed using PubMed, google scholar, science direct, Wiley online library, Cochrane library, and MeSH "GROWTH HORMONE AND CRANIOFACIAL DEVELOPMENT". The mesh terms were altered in the search engine accordingly to Prisma guidelines. **Results:** 3 out of 4 articles positively impacted craniofacial development. Growth hormone also showed increased somatic growth (body height) and overall skeletal maturation. Growth hormone is a potential regulator of bone homeostasis and also stimulates osteoclastic activity. Short-term growth hormone therapy showed increased longitudinal and angular measurements while linear measurements were normal except for cranial base length and anterior face height. Long-term growth hormone therapy resulted in acromegalic features. Ceasing the growth hormone before completion of the full growth resulted in a 'catch down' of the development. Growth hormone showed an increase in the extremities, especially the feet. Growth hormone can also improve facial profile in retrognathic patients without causing facial disharmony. **Conclusion:** In the available literature, the administration of growth hormone is effective in craniofacial development. It is possible by showing an increase in the angular measurement and longitudinal measurement.

**Keywords**

Cranial base size, Craniofacial development, Growth hormone, Maturation.

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## INTRODUCTION:

Growth hormone, a peptide hormone induced and oozed by the somatotroph cells of the anterior hypophysis, has notable effects on bone growth and bone metabolism. Craniofacial development of an individual comprises the interaction of hormones, environment, and genes regulating growth as well as bone metabolism [1]. Growth Hormone therapy

plays a pivot role and gives the impression of being to elicit varying responses in the craniofacial region. It alters the growth site with endochondral ossification and has likely to regulate odontogenesis, bone modelling and remodelling.

Literature about craniofacial development gives the idea that growth hormone deficiency out-turn into an immature facial appearance [8]. Growth Hormone administration exhibits the significance of facial convexity decrease, mandibular length increase, and posterior facial height increases [2]. Growth Hormone can promote facial profile in retrognathic patients and does not manifest facial disharmony, although extremity growth, particularly feet, can take place [12]. Hyper and hyposecretion of growth hormone in the course of development might lead to gigantism and dwarfism, respectively.

The length and depth of the face are likely to be insignificant for the child's age, with the face keeping up child-like convexity in growth hormone-deficient patients. Growth Hormone regulates cartilage formation [3]. Growth hormone is a chief regulator of bone homeostasis. The somatomedin theory institutes the concept that growth hormone stimulates skeletal growth by restoring insulin-like growth factor-1(IGF-1). This stimulates longitudinal bone growth in an endocrine manner [4].

Deficiencies during childhood lead to the fall of the growth of the maxilla and the mandible. Dental development /eruption is also compromised [5]. As craniofacial structures progress from intramembranous together with endochondral ossification, some variation in growth hormone production may act on them by firsthand or secondarily action (GH/IGF-1 AXIS) [6]. Progression of dentition is an integral part of craniofacial maturation. As dental progression is mildly set-backed, occlusal characteristics have been investigated in individuals with growth hormone deficiency [7].

Growth hormone was put in place to stimulate young preadipocytes, whereas insulin-like growth factor-1 (IGF-1) stimulated cells at a late stage of progression. The growth hormone receptor (GHR) has been recognized in the hypertrophic zone of the cartilage that evolves into a secondary ossification centre. "Maturity gradient'' is unique for the growth of the human craniofacial complex [16].

In the cranial bones, bone growth in the first place takes place at the epiphyseal growth plates. Cranial bone growth arises from the differentiation and proliferation of chondrocytes. Growth hormone affects these chondrocytes but primarily controls this function through insulin-like growth factor-1 (IGF). Growth hormone further triggers osteoclast activity and differentiation, as a consequence contribute to bone resorption [9]. Insulin-like growth factor-1 (IGF-1) is induced under growth hormone control in the liver and as soon as in the cartilage.

Dentition and its development are a chief part of craniofacial development [14]. Growth hormone is worthwhile on nasal, maxillary, mandibular, and humerus length [17]. Maxilla has a noteworthy reduction which brings about retrognathic maxilla, but the mandible is routinely altered [10]. In females, the anterior cranial base looks normal, on the other hand, the posterior cranial base length appears short; males, on the contrary, reveal an overall general deduction in cranial base size. The basis of short stature may be genetic or pathologic. The pathologic factor may be postnatal malnutrition, gastrointestinal disease, long-standing infection, endocrine factor (such as Growth hormone deficiency), chromosomal abnormalities, and genetic syndromes [7]. Decreased overbite and class 2 jaw relationships exist [11].

Growth hormone appears to end in excessive head circumference growth [18]. Excluding the body height, the mechanisms regulating craniofacial growth and development are complex interplay uniting genes, hormones, nutrition, and epigenetic factors that gives the cranial bone its final morphology [7]. Growth hormone was unable to normalize the craniofacial features related to X chromosome deficiency [13].

**OBJECTIVES:**

To assess the potential of growth hormone for craniofacial development

**MATERIALS AND METHODS:**

Randomized controlled trials with the intervention were included in this study.

**ELIGIBILITY CRITERIA:**

**Inclusion criteria**

Full-text articles

Randomized controlled trails

**Exclusion criteria**

Studies without administration of growth hormone were excluded

Articles that don’t include human or animal trials.

**SEARCH STRATEGY:**

The results of growth hormone for craniofacial growth are published based on the original articles and paperwork in databases such as PubMed, google scholar, science direct, Wiley online library, and Cochrane library. A literature search to obtain data was done using MeSH terms "GROWTH HORMONE AND CRANIOFACIAL DEVELOPMENT".

The mesh terms were changed in the search engine accordingly to Prisma guidelines when the results went too many or too less.

**FIGURE1: FLOW DIAGRAM SHOWING THE NUMBER OF STUDIES IDENTIFIED, SCREENED, AND ASSESSED FOR ELIGIBILITY INCLUDED IN THE SYSTEMATIC REVIEW**

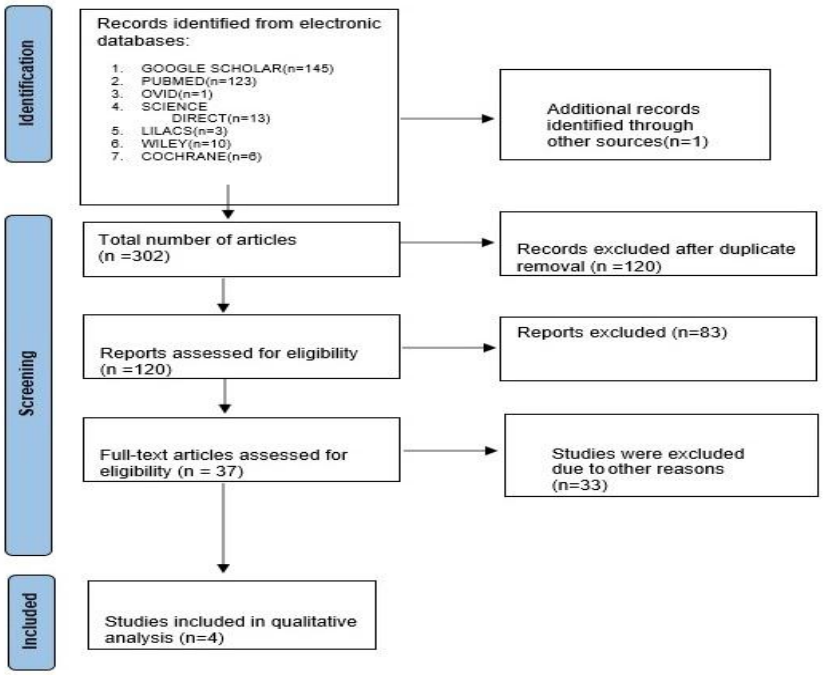


**Figure 1 shows a flow chart expressing the number of studies identified, screened, assessed for eligibility, and included in a systematic review.**

**RESULTS:**

The search contains 302 articles, and 4 were assessed among these articles. Three tables were included; Figure 1 depicts a flow diagram of the study identified, screened, assessed for eligibility, excluded, and included for the review.

**TABLE 1: CHARACTERISTICS OF INTERVENTIONS IN THE STUDY**

| AUTHOR NAME | YEAR | SAMPLE SIZE | AGE RANGE | INTERVENTIONS |
|---|---|---|---|---|
| G. Cantu et al. [8] | 2004 | 40patients (21males and 19 females) | 5-18 | Administration of growth hormone in doses of 0.3mg/kg/week s.c. 3-6 times per week |
| H Kjellberg et al. [15] | 2007 | 46 boys | 7-21 | Test group: Injected daily with 33 or 67µg GH/kg body weight/day<br>Control group: For comparing the sagittal cephalograms |
| German omar rami-yanez et al [6] | 2005 | 42 mice (3 different genetically altered groups) | NA | Administered with growth hormone |
| Minoyo Funatsu et al [10] | 2005 | 57(33 boys; 24 girls) | 4.5-16.7 | growth hormone is given as short-term and long-term therapy |

**Table 1 depicts the characteristics of the studies chosen for the systematic review. The following characteristics were studied: Name of the author, year of study, sample number including their details such as gender, age range, and the interventions. Studies were randomized controlled trials.**

**TABLE 2: CHARACTERISTICS OF OUTCOME AND EFFECT MEASURES**

| AUTHOR NAME | YEAR | EFFECT MEASURE | RESULTS |
|---|---|---|---|
| G. Cantu et al. [8] | 2004 | Skeletal maturation was evaluated from a hand-wrist radiograph using the FELS method | Growth hormone has not so much as of a positive result on bony craniofacial growth than that on somatic growth or overall skeletal maturation |
| H. Kjellberg et al. [15] | 2007 | Tracings were digitized, and analysis was conducted using a computer program | Growth hormone treatment brought an overall increase in the growth of the craniofacial skeleton |
| German omar rami-yanez et al [6] | 2005 | The radiographic images were scanned with the help of a Bio-Rad GS-700 imaging densitometer, and the landmarks were determined on the computerized pictures. The measurements were made on-screen images using pre-calibrated morphometric analyzer software | Longitudinal measurements: Showed a notable increase in craniofacial length, upper face height, and mandibular corpus length<br>Angular measurements: The significant difference in only two of the four angles |
| Minoyo Funatsu et al. [10] | 2005 | A cephalometric radiograph and hand-wrist radiograph were obtained. A wide-opening lateral cephalometric radiograph was obtained to identify the mandibular condyle. | Long-term growth hormone therapy showed an increase in the growth of the craniofacial skeleton, peculiarily in the maxilla and mandibular ramus. |

**Table 2 shows the following characteristics: name of the author, year of the study, effect measures used in the craniofacial measurement, and the results following it.**

**TABLE 3: CHARACTERISTICS OF BIAS IN VARIOUS STUDIES THAT WERE TAKEN FOR REVIEW**

| AUTHOR NAME | RANDOM SEQUENCE GENERATION | ALLOTMENT CONCEALMENT | BLINDING OF OUTCOME | INCOMPLETE OUTCOME | SELECTIVE BIAS | OTHER BIAS |
|---|---|---|---|---|---|---|
| G. Cantu et al. [8] | + | - | + | - | - | - |
| H. Kjellberg et al [15] | + | + | + | - | - | - |
| German omar rami-yanez et al [6] | + | - | + | - | - | - |
| Minoyo Funatsu et al [10] | + | - | + | - | - | - |

**+: low risk of bias; -: high risk of bias; ?: unclear risk of bias**

**Table 3 shows the bias analysis of the studies included, which were categorized as high risk of bias, low risk of bias, and unclear risk of bias.**

**DISCUSSION:**

In this systematic review, 4 studies have been considered for assessing the potential of somatotrophic hormone/ growth hormone for craniofacial development. Growth hormone administration is taken into consideration. Craniofacial measurements were evaluated using a

cephalometric radiograph, wide-opening cephalometric radiograph, and computer programs.

G. Cantu et al (2004) carried out a randomized controlled trial with 40 children with growth hormone deficiency. The sample was categorized into three groups based on the duration of the replacement therapy, which has a group of 13 untreated children compared with 13 children who received short-term therapy and 13 children who received long-term therapy. Growth hormone must be administered in dose of 0.3 mg/kg/week s.c. 3-6 times per week. The untreated patients were delayed in height by roughly 3.8 standard units. The treated children showed notable growth and maturation. Further, there was no significant effect on dental maturation and cranial bone development.

H. Kjellberg et al (2007) carried out a randomized controlled trial with 46 boys. 25 boys were classified as growth hormone deficient, and 21 boys as idiopathic short stature. The boys were injected daily with 33 or 67µg/kg body weight/day. During therapy, an increase in growth was detected, especially facial growth in an anterior direction. Withdrawal of growth hormone before completion of growth showed 'catch-down' growth of the craniofacial component. Long-term growth hormone therapy can be associated with acromegalic features such as an increase in mandibular size. Linear measurements were normal except for cranial base length and anterior face height. Growth hormone administration does not improve angular measurement. High-dose administration (100mg/kg/day) increased body height.

German Omar rami-Yanez et al (2005) carried out a randomized controlled trial with 3 different models of mice: GH excess(giant), dwarf GH antagonist(dwarf-ant), and dwarf GH receptor knockout(dwarf-KO). The giant mice longitudinal measurement made visible a significant increase in craniofacial length, upper face height, and mandibular corpus length. At the same time, these distances were significantly reduced in dwarf-ant and dwarf-KO mice. Angular measurements manifested a significant difference between only two or four angles. The A-N/N-Ba angle and angle of the mandible expressed a substantial increase in giant mice. Conversely, there was significant down growth in dwarf-ant and dwarf-KO. A rise in growth hormone increased the mitotic activity but lagged the cartilage cell maturation.

Minoyo Funatsu et al (2005) carried out a randomized controlled trial with 57 patients (33 boys and 24 girls) with an age range of 4.5-16.7 with growth hormone deficiency and divided into three groups: untreated, short-term therapy group, and long-term therapy group. The SD score for N-Me in the long-term therapy group was significantly less when correlated to that of the short-term therapy group. N-ANS, A'-Ptm', Cd-Go, and the SD score of the long-term therapy group were significantly greater than that of the untreated group. Growth hormones step up cartilage growth and intramembranous bone growth. Growth hormones also play an important role in longitudinal bone growth. Growth hormone accelerates to catch up with the development of the cranial bone, which enhances the occlusion and facial profile.

**CONCLUSION:**

The result of the study suggested that growth hormone plays an important role in craniofacial development. Mainly, growth hormone accelerated somatic growth more than that craniofacial growth. It showed an effective increase in body height. The size of the craniofacial structures and their angular relationships are directly related to the growth hormone status. More prognathic growth pattern and anterior rotation of the mandible was seen. Growth hormone showed a significant role in angular and linear measurements by improving the facial profile, thereby developing occlusion.

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