

## ACROMEGALY AND TEETH

**Mihaela Jana Tuculina<sup>1</sup>, Ionela Teodora Dascălu<sup>1</sup>, Oana Andreea Diaconu<sup>1</sup>, Adina Turcu<sup>1</sup>, Andreea Nicola<sup>1</sup>, Sanda Mihaela Popescu<sup>1</sup>, Cristian Petcu<sup>1</sup>, Ruxandra Voinea Georgescu<sup>2</sup>, Anda Dumitrascu<sup>3</sup>, Mara Carsote<sup>4</sup>**

1. University of Medicine and Pharmacy of Craiova, Faculty of Dentistry, 2-4 Petru Rareș Str., 200349, Craiova, Romania
2. University Titu Maiorescu of Bucharest, Faculty of Dental Medicine, 67A Gheorghe Petrascu Str., 031593, Bucharest, Romania
3. C.I. Parhon National Institute of Endocrinology, Bucharest, Romania
4. Carol Davila University of Medicine and Pharmacy & C.I. Parhon National Institute of Endocrinology, Bucharest, Romania

Correspondent author:

Ruxandra Voinea Georgescu - ruxi0372@yahoo.com

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### Abstract

Acromegaly, a GH (Growth Hormone) excess – related condition, has co-morbidities varying from cardio-metabolic events, sleep apnea, osteoporotic fractures, and oncologic risk especially of colonic cancer up to oral, facial and dental anomalies. We aim to briefly revise oro-dental status in acromegalic patients through a multidisciplinary perspective. This is a review of literature. Because of GH and IGF1 (Insulin-like Growth Factor) actions, a wide area of anomalies are registered, for example, mandibular protrusion, widening of maxillary, increased spaces between teeth, malocclusion, thick lips, all of them causing functional impairment and facial appearance changes. Oro-facial manifestations are among earliest signs; however, the acromegaly phenotype is recognizable after more than a decade of biochemical exposure to GH excess (unrecognized, untreated and/or uncontrolled acromegaly). The mentioned anomalies require a specialized team of medical dentists, and orthodontists, as well as otorhinolaryngology practitioners in addition to endocrinologists. Mandibular ramus has a larger height in acromegaly, main characteristic being increased L1/MP (labial inclination of mandibular central incisors) which might function as a discriminator parameter from non-acromegalic malocclusion. Some individuals might experience gingivitis, moderate chronic periodontitis or bulky oral bony outgrowths according to AcroDent study. Another consistent chapter of dental and periodontal complications is provided by the presence of secondary diabetes mellitus in acromegalic patients, a “sweet” complication that is controlled at the point when GH excess is controlled, due to hyperglycemic effect of GH and associated insulin resistance. An additional perspective on facial bones is related to GH excess – induced bone remodeling pattern that delays some dental procedures since acromegaly stabilization is mandatory first. Incrementally, the delay of dental intervention limits the dental management, finally requiring prosthetic approach. In the meantime, increased bone turnover associates anomalies of skeleton micro-architecture and increased osteoporotic fracture risk. High bone turnover should be taken into consideration when planning implant surgery. Awareness among dentists and orthodontists is essential to early recognition of acromegaly and its complications in order to improve the outcome. A close collaboration with endocrinologists is required.

**Key words:** acromegaly, teeth, GH, IGF1, pituitary tumor, dental, oral, jaw, mandibular protrusion, maxillary, malocclusion, diabetes mellitus

## Introduction

Acromegaly, a GH (Growth Hormone) excess – related condition is mostly related to a pituitary tumor causing complications due to abnormal GH - IGF1 (Insulin-like Growth Factor) axes or to the anatomic features of the hypophyseal tumor mass, a disease that is either an isolated neoplasia or a syndrome – related neoplasia (like multiple endocrine neoplasia type 1 syndrome or Carney syndrome). (1-5) Co-morbidities vary from cardio-metabolic events, sleep apnea, osteoporotic fractures, and oncologic risk especially of colonic cancer up to skin, oral, facial and dental anomalies. (1-5)

## Aim

We aim to briefly introduce practical aspects concerning oro-dental status in acromegalic patients through a multidisciplinary perspective.

## Method

This is a review of literature. The inclusion criteria are: full length, original, English language articles published in international indexed databases (mostly PubMed); the research words are a combination of “acromegaly” and “teeth” (or “dental” or “oral”). A number of 50 references is cited.

## General data

### *Oral and facial anomalies in acromegaly*

Because of GH and IGF1 actions, a wide area of anomalies are registered, for example, at the level of the jaw (overgrowing of mandibular bone, prognathism), widening of maxillary, increased spaces between teeth (tooth separation or diastema), malocclusion (with increased gonial angle), thick lips, all of them causing functional impairment and facial appearance changes (even exceptional enlargement of parotid gland). (6,7) Oro-facial manifestations are among earliest signs; however, the acromegaly phenotype is recognizable after more than a decade of

biochemical exposure to GH excess (unrecognized, untreated and/or uncontrolled acromegaly). (8) The real prevalence in acromegalic population of full blown clinically manifested or subtle oro-facial-dental anomalies is still an open issue, many of them being under-diagnosed; also, the paucity of controlled studies concerning this particular matter deprives us of trans-disciplinary specific data. (1-8) The mentioned anomalies require a specialized team of medical dentists, and orthodontists, as well as otorhinolaryngology practitioners in addition to endocrinologists. (1-8) (Figure 1) This comes as part of the multidisciplinary team which is mandatory to assess and follow the potential multi-organ complications of prolonged tumor – related somatotropin excess in human body. (9,10) Notably, under adequate control of acromegaly, which includes hypophysectomy, medical therapy (with one drug of combine regimes underling dopamine agonists, somatostatin analogues and GH receptor blockers) or even radiotherapy, the cardio-metabolic parameters may improve, soft tissue anomalies may reverse, while bone involvement is typically irreversible. (11,12) In controlled acromegaly, additional specific therapy for malocclusion might be useful, for instance, reestablishing the occlusal vertical height up to 1 cm increase has been reported (13) Bone augmentation/regeneration procedures are applicable only if pituitary tumor – associated hormonal imbalance is controlled. (14) A correlation between malocclusion and GH excess – related respiratory and sleep anomalies has also been suggested. (15)

### *Clinical studies*

A telematics - based study on 426 participants (dentists and orthodontists) included a questionnaire with oro-dental aspects in acromegalic individuals plus a tele-X-ray (lateral incidence) of the skull; the

results showed that, on one hand, dentists recognized more often mandibular and lips anomalies, while, on the other hand, orthodontists observed more frequently the facial soft tissue changes, also, paying more attention to general changes during follow-up (based on serial photos), and identified more often tongue enlargement and sleep apnea; generally, one in ten physicians had at least one acromegalic patient or suspected at least one individual to have the condition. (16)

A retrospective study on 37 persons with acromegaly analyzed the mandibular protrusion and dental morphology based on cephalometry and face profilogram (*versus* individuals with C-III malocclusion without acromegaly); the results revealed that mandibular ramus had a larger height in acromegaly, main characteristic being increased L1/MP (labial inclination of mandibular central incisors) which might function as a discriminator parameter. (17)

AcroDent study assessed IGF1/GH levels in relationship with oral and dental status, based on AcroQoL questionnaire, stomatology assessment and X-Ray evaluations; 16 out of 29 subjects with active acromegaly (mean age of 59 years) had gingivitis, 18 out of 29 patients had moderate chronic periodontitis, 11 out of 29 individuals had bulky OBO (oral bony outgrowths). (18)

A single centric study on 145 acromegalic patients showed that 80% had oro-dental anomalies that were recognized rather after the first 2 years since acromegaly diagnostic than within first 24 months, including thick tongue – 57%, diastema - 42%, mandibular enlargement - 24% and prognathism - 22%; specific dental management was heterogeneous like correction of teeth (based on orthodontal and surgical procedures) – 2.1%, prostheses – 3.4%, dental implants – 9%, dental crowns – 16%. (19)

### ***Secondary diabetes mellitus and oral health***

As mentioned, acromegaly associates multiple dental anomalies which raised the question whether acromegaly is a “dental disease”. (20) Another consistent chapter of dental and periodontal elements is provided by the presence of secondary diabetes mellitus in acromegalic patients, a “sweet” complication that is controlled at the point when GH excess is controlled. (21,22,23) Secondary diabetes mellitus is a typical comorbidity in acromegaly due to hyperglycemic effect of GH and associated insulin resistance. (24,25) (Figure 1)

Impaired glucose profile is associated with periodontal disease; it seems that the co-presence of diabetes rather than abnormally high GH/IGF1 is correlated with worsening of periodontal health, possible through an associated higher cytokine status. (26,27) Also, associated hypogonadism due to pituitary macroadenoma might be a supplementary contributor to periodontal disease. (28) Glycated hemoglobin A1c, as a reflection of 3-month glycaemia, is reduced under specific medication with somatostatin analogues, especially first generation, thus an improvement of periodontal malady is expected. (29,30,31)

### ***Skeleton involvement***

Understanding the oral anomalies that include mandibular and maxillary bones changes is part of a large class of effects concerning GH excess and skeleton and joints. (32,33,34) Prolonged GH overproduction upregulates FGF23 (Fibroblast Growth Factor) – alpha Klotho system expression, a multi-factorial effect that also takes into account the renal function and vitamin D - parathormone status. (35,36,37) A controlled study from 2021 in 35 acromegalic patients identified that age and body composition are independent predictors of bone mineral density as assessed through central DXA (Dual-Energy X-Ray Absorptiometry), while IGF1 levels

are correlated with bone formation marker osteocalcin in active disease. (38) The GH excess – induced bone remodeling pattern delays some dental procedures which require the acromegaly stabilization first. (39) Incrementally, the delay of dental intervention limits the dental management, finally requiring prosthetic approach. (40) In the meantime, increased bone turnover associates anomalies of skeleton micro-architecture and increased osteoporotic fracture risk. (41,42,43) High bone turnover (which is reflected by increased bone turnover markers) should be taken into consideration when planning implant surgery. (44,45) (Figure 1)

## Discussion

**Conflict of interest: none**

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Particular aspects in oro-dental area are registered in patients with GH excess at early age, namely gigantism, as seen in patients with *AIP* mutations or syndromes like Beckwith Wiedemann, also including neonatal hypoglycemia, omphalocele, adrenal tumors like adrenocortical carcinoma. (46,47) Macro-glossia requires tongue reduction procedures to prevent malocclusion. (48,49,50)

## Conclusion

Awareness among dentists and orthodontists is essential to early recognition of acromegaly and its complications in order to improve the outcome. A close collaboration with endocrinologists is required. Specialized multidisciplinary teams represent an advantage in this particular matter.

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**Figure 1. Operating landscape behind acromegaly and dental/facial status. GH-IGF1 excess causes dental anomalies (malocclusion, diastema), soft tissue enlargement (thick lips), periodontal disease (which is particularly aggravated by secondary diabetes mellitus) and facial osseous changes (widening of maxillary, overgrowing of mandibular bone) which are part of GH-IGF1 – related bone remodeling reset (Abbreviations: GH = Growth Hormone, IGF1 = Insulin-like Growth Factor, HgA1c = glycated hemoglobin) (see references 1-45)**

